The effect of gestational diabetes mellitus on maternal and child health

Maleesa Pathirana

B. Med Sci., B. Health Med Sci (Hons)

Supervisors

Prof. Claire Roberts and Dr. Prabha Andraweera

Adelaide Medical School

Discipline of Obstetrics and Gynaecology

The University of Adelaide

2022

Table of Contents

Abstract

Introduction: Gestational diabetes mellitus (GDM) affects 1 in 7 pregnancies globally. Development of GDM can be influenced by antenatal factors, such as maternal BMI, metabolic syndrome and poor mental health. Furthermore, previous research suggests that GDM increases the risk of diabetes and coronary heart disease to the mother and child and is associated with impaired neurodevelopment in the child. Therefore, greater understanding of the lifestyle factors which influence GDM development, the trajectory of cardiovascular risk factor appearance in women and children and assessing neurodevelopment in the child will aid intervention strategies that can significantly reduce the risk of chronic disease later in life.

Methods: This thesis includes a comprehensive series of systematic reviews and meta-analyses to identify the cardiovascular risk factors seen in women with a history of GDM and their offspring exposed to GDM *in utero.* To complement the review series, an observational follow-up study of the Screening Tests to Predict Poor Outcomes of Pregnancy (STOP) cohort was undertaken with women and children being recruited at 3 years postpartum. The original STOP study recruited 1,363 nulliparous women from 2015 to 2018 primarily from the Lyell McEwin Hospital in South Australia. This hospital services patients from the Northern Adelaide region which statistically has some of the worst chronic health outcomes in metropolitan Australia due to significant socioeconomic disadvantage in the community. The follow-up study consisted of hemodynamic and metabolic assessments that were undertaken to determine the prevalence of cardiometabolic risk factors three years postpartum in women with a history of GDM 3 years later, and to determine whether the children also exhibited any cardiovascular risk factors or measures of poor neurodevelopment at 3 years of age.

Results: The systematic review and meta-analysis series identified that women who have a history of GDM have an increase in blood pressure, BMI lipids, serum glucose, and serum insulin and are at a higher risk of metabolic syndrome than those without a history of GDM.

Children exposed to GDM *in utero* exhibited higher blood pressure, BMI z-score, blood glucose and risk of metabolic syndrome than those who were not exposed to GDM *in utero.* Women with a history of GDM who breastfed had reduced serum glucose and reduced risk of type II diabetes mellitus than those who did not.

In the original STOP study, there was no difference in history of depression in women who developed GDM compared to those who did not. The latter comprised women with uncomplicated pregnancies, and one or more of the following complications: gestational hypertension, preeclampsia, and delivery of a preterm infant and/or a small for gestational age infant. A total of 281 women-children dyads attended a 3 year follow-up appointment. There were no significant differences in cardiometabolic variables between women with a history of GDM and those without a history of GDM at 3 years postpartum, nor in their offspring exposed to GDM *in utero* compared to unexposed offspring, when adjusted for BMI and socioeconomic index (SEI). Breastfeeding for at least 6 months postpartum provided some protection against cardiovascular risk factors in all women in the cohort at 3 years postpartum but this was attenuated by maternal BMI in first trimester and socioeconomic index. Anthropometric and hemodynamic outcomes were not different between children who were breastfed for at least 6 months compared to those who were not. Within the group of women with at least one pregnancy complication in their index pregnancy and their *in utero* exposed children, breastfeeding or being breastfed until at least 6 months old, was some protection against cardiovascular risk factors. Children who were exposed to GDM *in utero* had significantly reduced communication, gross motor and problem-solving skills than those who were not exposed to GDM *in utero,* even after adjustment for maternal history of depression during pregnancy. Three year old females who were exposed to GDM *in utero* appeared to be less able at problem solving than exposed males.

Conclusion: Based on the systematic review and meta-analyses conducted, women with a history of GDM are likely to exhibit an increase in conventional cardiovascular risk factors later in life. However, in our smaller cohort, this was not completely evident in women with a history of GDM at 3 years postpartum. Much of this association is largely mediated by covariates including SEI in this socioeconomically disadvantaged community. Breastfeeding may confer some protection to women with GDM but further studies are warranted to assess this association. Exposure to GDM *in utero* promotes an increase in some cardiovascular risk factors in the literature but this was not evident in our cohort. However, children who were exposed to GDM *in utero* appear to have impaired neurodevelopment. Interventions in pre-conception and in early pregnancy that target obesity may significantly reduce the risk of GDM and associated cardiovascular risk factors in the early years after delivery for both women and their children.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time. I acknowledge the support I have received for my research through the provision of a University of Adelaide Faculty of Health and Medical Sciences Divisional Scholarship.

Signed _____

Maleesa Melanie Pathirana

Acknowledgments

I would first like to acknowledge the incredible work and support of my supervisors, Prof. Claire Roberts and Dr. Prabha Andraweera. I am fortunate to have been mentored by such powerful, intelligent women who are working hard to improve the lives of women and children.

Claire, a key lesson you have taught me our passion for research is for the health of women and children. You made sure I was doing a project that was not only important, but enjoyable. You allowed me to put my foot in the door to my career and for that I am very grateful.

Prabha, thank you for your constant support in every step of my PhD journey. There has never been a question I have asked that you have not been able to help me with! Without you this thesis would not have been written, thank you!

I would also like to acknowledge the mentorship and guidance I have received from A/Prof Margaret Arstall and Prof. Gus Dekker. Your clinical and patient centred perspective into research is something I value and has helped me grow as a researcher. Thank you to Dr Zohra Lassi and Dr Anna Ali for working with me to create important reviews to publish.

A special acknowledgment to Emily Aldridge for being my saviour at the Lyell McEwin. I am so fortunate to have been side by side together during our PhDs, and to have eaten lots of sweet treats with you along the way.

I would like to thank all the past and present members of the Pregnancy, Health and Beyond group, who have provided me with feedback and support throughout my PhD. I must acknowledge the assistance of Shalem, who has significantly helped me with the database for the STOP follow-up and with all of my statistical analysis. Thank you to my honours students Jade and Maddie for helping me complete the 3 year follow-up and bringing well needed

optimism to my final months of my PhD! Thank you also to the Cardiology research team at the Lyell McEwin Hospital who I have had the pleasure of working with the past three years.

This research would not have been possible without the mothers and children of the STOP study. Thank you all for generously giving up your time to participate in the follow-up study.

I would like to acknowledge the financial support I received during my candidature from The University of Adelaide Faculty of Health and Medical Sciences. I would like to thank the Robinson Research Institute, Adelaide Medical School and The Hospital Research Foundation for the support I have received, including in regard to funding for conference travel.

Thank you to my friends (both high school, undergrad Medical Science, and Kmart) who have always been such an amazing support system throughout my PhD. Of course, I have to acknowledge the love I received from my pets (past and current), Biscuit, Blue and Bella. You all have provided me with so much support, love and motivation.

Thank you to my partner Nathan, for being such a pivotal pillar during my journey. Thank you to my family, Dilrini, Neil, Sujith (Buzzy), Catherine, Chanelle and Summer. I love you all so much, you always lift me up and push me to be the best person I can be. A special acknowledgment to my mother Dilrini, whose love for academia, research and cups of tea has been instilled in me. My path would not be shaped without your guidance.

Publications arising from this thesis

Chapter 3: Published in 2021 – Reviews in Endocrine and Metabolic Disorders
Pathirana MM, Lassi Z, Ali A, Arstall M, Roberts CT, Andraweera PH. Cardiovascular risk factors in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2021;22(4):729-761. doi:10.1007/s11154-020-09587-0

Chapter 4: Published in 2020 – Journal of Developmental Origins of Health and Disease
Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis. *J Dev Orig Health Dis*. 2020;11(6):599-616. doi:10.1017/S2040174419000850

Chapter 5: Published in 2020 – Journal of Developmental Origins of Health and Disease
Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Author response: cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis. *J Dev Orig Health Dis*. 2020;11(3):244-245. doi:10.1017/S2040174420000185

Chapter 6: Accepted for publication 2022 – Journal of Developmental Origins of Health and Disease

Chapter 7: Published in 2021 – Endocrine
Pathirana MM, Lassi ZS, Ali A, Arstall MA, Roberts CT, Andraweera PH. Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis. *Endocrine*. 2021;71(2):310-320. doi:10.1007/s12020-020-02492-1

Chapter 8: Published in 2021 – Journal of Human Lactation
Pathirana MM, Ali A, Lassi ZS, Arstall MA, Roberts CT, Andraweera PH. Protective Influence of Breastfeeding on Cardiovascular Risk Factors in Women With Previous Gestational Diabetes Mellitus and Their Children: A Systematic Review and Meta-Analysis [published online ahead of print, 2021 Oct 5]. *J Hum Lact*. 2021;8903344211034779. doi:10.1177/08903344211034779

Chapter 9: Submitted for publication – Journal of Diabetes Research

Chapter 10: Submitted for publication – Acta Diabetologica

Chapter 11: Submitted for publication – International Breastfeeding Journal

Chapter 12: Submitted for publication – Paediatric Research

Publications to which I contributed towards the course of my PhD

Aldridge E, **Pathirana MM,** Wittwer M. Sierp S, Leemaqz SY, Roberts CT, Dekker G, Arstall MA. Prevalence of metabolic syndrome in women after maternal complications of pregnancy: an observational cohort analysis. *Accepted in Frontiers in Cardiovascular Medicine (online ahead of print)* https://doi.org/10.3389/fcvm.2022.853851

Aldridge E**, Pathirana MM,** Wittwer M. Sierp S, Leemaqz SY, Roberts CT, Dekker G, Arstall MA. Effectiveness of a nurse practitioner-led cardiovascular prevention clinic at reduction of metabolic syndrome following maternal complications of pregnancy: a preliminary analysis (*under review).*

Aldridge E, **Pathirana MM,** Leemaqz SY, Roberts CT, Arstall MA, Schubert K.O, Dekker G, Depression and anxiety screening scores of women with and without metabolic syndrome six months after complications of pregnancy *(under review).*

Andraweera PH., Plummer MD, Garrett A, Leemaqz S, Wittwer MR, Aldridge E, **Pathirana MM,** Dekker GA, Roberts CT, Arstall MA. Early pregnancy cardio metabolic risk factors and the prevalence of metabolic syndrome 10 years after the first pregnancy *(under review).*

Andraweera PH, Lassi ZS, **Pathirana MM,** Plummer MD, Dekker GA, Roberts CT, Arstall MA. Pregnancy complications and cardiovascular disease risk perception: A qualitative study *(under review).*

Andraweera PH, Lassi ZS, **Pathirana MM,** Ali A, Dekker GA, Roberts CT, Arstall MA. Offspring size at birth and maternal risk for cardiovascular disease: a systematic review and meta-analysis *(under review).*

Andraweera PH, **Pathirana MM,** Gamage A, Lassi ZL, Ali A, Wittwer MR, Aldridge E, Roberts CT, Arstall MA. Gestational hypertension and the risk of cardiovascular disease in women and offspring: a systematic review and meta-analysis *(in prep)*

Andraweera PH, **Pathirana MM,** Lassi ZS, Roberts CT, Arstall MA. Interpregnancy interval and the risk of cardiovascular disease: A systematic review and meta-analysis (in prep)

Khoja A, Andraweera PH, Lassi ZS, Zheng M, **Pathirana MM,** Ali A, Aldridge E, Wittwer MR, Chaudhuri DD, Tavella R, Arstall A. Risk factors for premature coronary artery disease (PCAD) in adults: a systematic review protocol. Accepted in F1000 Research: doi:10.12688/f1000research.74926.1

Khoja A, Andraweera PH, Lassi ZS, Zheng M, **Pathirana MM,** Ali A, Aldridge E, Wittwer MR, Chaudhuri DD, Tavella R, Arstall A. Risk factors for premature coronary artery disease (PCAD) between males and females: a systematic review and meta-analysis *(in prep)*

Khoja A, Andraweera PH, Lassi ZS, Zheng M, **Pathirana MM,** Ali A, Aldridge E, Wittwer MR, Chaudhuri DD, Tavella R, Arstall A. Differences in risk factors for premature coronary artery disease (PCAD) and coronary artery disease (CAD). A systematic review and meta-analysis. *(in prep)*

Presentations

Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to GDM *in utero:* a systematic review and meta-analysis. *Accepted for oral presentation –Australian Society of Medical Research South Australian Conference, Adelaide, 2019.*

Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to GDM *in utero:* a systematic review and meta-analysis. *Accepted for poster presentation and invited speaker for trainee symposium– DoHAD International Conference 2019, Melbourne, Australia.*

Pathirana MM, Ali A, Lassi ZS, Arstall MA, Roberts CT, Andraweera PH. Protective effect of breastfeeding on cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: A systematic review and meta-analysis. *Accepted for poster presentation, DoHAD ANZ Trainee Virtual Conference, 2020.*

Pathirana MM, Lassi ZS, Ali A, Arstall MA, Roberts CT, Andraweera PH. Cardiovascular risk factors in women with previous gestational diabetes mellitus: a systematic review and meta-analysis. *Accepted for poster presentation. Endocrine Society Australia Virtual Conference 2020.*

Pathirana MM, Lassi ZS, Ali A, Arstall MA, Roberts CT, Andraweera PH. Cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: a systematic review and meta-analysis. *Accepted for poster presentation. Florey Postgraduate Conference, The University of Adelaide, 2020.*

Pathirana MM, Lassi ZS, Ali A, Arstall MA, Roberts CT, Andraweera PH. Cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: a

systematic review and meta-analysis. *Accepted for poster presentation. Robinson Research Institute Symposium, November 2019.*

Pathirana MM, Lassi ZS, Ali A, Arstall MA, Roberts CT, Andraweera PH. Cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: a systematic review and meta-analysis. *Presentation at NALHN Research Meeting November Edition, 2019, Lyell McEwin Hospital.*

List of tables and figures

List of supplementary tables and figures

SECTION 1: Introduction and context of thesis

Chapter 1

1. Introduction

1.1. Summary

This introduction is a literature review of gestational diabetes mellitus (GDM) and how it affects maternal and child health postpartum. This review covers prevalence and pathophysiology of GDM and its relation with maternal metabolic syndrome, cardiovascular disease and antenatal mental health. This is followed by a review of on the developmental origins of health and disease (DOHaD), which underpins the association between GDM exposure *in utero* and subsequent poor chronic health in offspring later in life. There is discussion of exposure to GDM *in utero* and the risk of cardiovascular disease later in life, followed by a review of the literature on how breastfeeding may confer as a protective measure for both women with a history of GDM and their children exposed *in utero.* This is followed by discussion of the association between exposure to GDM *in utero* and poor neurodevelopment in offspring, and the literature spanning whether there are sex specific differences seen in these offspring. Following this is an explanation of the context of this thesis, introducing the Screening Tests to Predict Poor Outcomes of Pregnancy [1] study and the observational 3 year follow-up of the women and children in this study to explore the gaps in literature underpinning the review.

1.2. Prevalence and definition of gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is the fastest growing diabetes condition in Australia, affecting 15% of all pregnancies[2]. It is defined as diabetes first diagnosed during pregnancy [3]. It is thought that 1 in 7 pregnancies globally are affected by GDM[4]. In Australia, GDM is diagnosed between 24-28 weeks' gestation. However, prior risk factors in women such as obesity, known impaired glucose metabolism, history of gestational diabetes, Asian/Hispanic ethnicity and familial history of T2DM or having a mother or sister with a history of GDM warrant early screening[5].

The prevalence of GDM in Australia has grown significantly between 1994-1996 and 2000-2002 by approximately 12% each year. In 2008, an observational multicentre study of over 25,000 pregnant women with GDM was conducted (the Hyperglycaemia and Adverse Pregnancy Outcomes, HAPO study) [6]. This study observed that maternal glucose levels in third trimester that were below the diagnostic threshold for GDM were associated with adverse maternal and neonatal outcomes, including primary caesarean delivery, neonatal hypoglycaemia and elevated cord blood serum c-peptide levels[6]. This led to a change in the diagnostic criteria for GDM (Table 1.2.1), which is expected to result in an increase in the number of women diagnosed with GDM.

Table 1.2-1 Plasma glucose values (75g oral glucose tolerance test) used in the diagnosis of GDM in the Australian Diabetes in Pregnancy Study (2011) and International Association of Diabetes in Pregnancy study (IADPSG).

OGTT test	ADIPS 2011 criteria	IADPSG criteria
Fasting	>5.5mmol/L	>5.1mmol/L
1-h	-	>10.0mmol/L
2-h	>7.8mmol/L	>8.5mmol/L

*ADIPS - Australian Diabetes in Pregnancy Study; IADPSG – International Association of Diabetes in Pregnancy Study Group

1.3. Pathophysiology

GDM represents glucose intolerance first diagnosed in pregnancy, and the underlying mechanism is elevated insulin resistance without sufficient compensatory insulin secretion [7]. Placental hormones in pregnancy promote a diabetogenic state, whereby relative insulin resistance enables sufficient glucose transfer from the mother via the placenta to the growing fetus. The placenta and decidua secrete prolactin and promotes β-cell expansion[8]. If a woman's pancreatic function cannot adjust to this diabetogenic state, it leads to elevated blood glucose levels and thus development of GDM[7]. The inability of the pancreas to compensate

by increasing insulin secretion reflects an individual's pre-disposition to impaired β-cell function that was not apparent pre-pregnancy[9]. Differences in β-cell function may also dictate the severity of GDM. Other factors may also contribute to the pathogenesis of GDM. Insulin resistance is regulated by placental hormones such as placental growth hormone, and human placental lactogen[10] .Within normal physiological levels, these hormones stimulate insulin resistance and pancreatic β-cell expansion, particularly in the second half of pregnancy. However, aberrant secretion of these hormones may promote cellular insulin resistance and thus maternal hyperglycaemia[10, 11].

1.4. Inflammatory markers of insulin resistance

Insulin resistance is the key inflammatory process that underpins GDM, and it is influenced by different inflammatory markers that are highly involved in obese, pre-diabetic and diabetic states. Tumour necrosis factor alpha (TNF-α) is a pro-inflammatory mediator which induces tissue specific inflammation through activation of oxidative stress[12]. It is heavily involved in reduction of glucose transporter type 4 (GLUT4), which is involved in insulin regulated glucose transfer in tissues such as adipocytes and skeletal muscle[13]. It decreases oxidation of fatty acids and elevation in plasma free fatty acid levels[14]. In individuals with obesity, TNF-α is elevated in the hepatocytes and adipocytes and is thought to promote obesity induced insulin resistance[12, 15]. TNF-α causes inflammation of the pancreatic islets and subsequent apoptosis of the β-cells[16].

Leptin is an adipo-cytokine involved in satiety and energy expenditure through direct signalling to the hypothalamus[12]. It has a major role in insulin and glucose regulation, maintaining normal triglyceride levels in adipocytes [17], and influences pancreatic β-cell secretion[18]. In individuals with obesity, leptin resistance causes dysregulation of insulin leading to excess secretion of triglycerides into the bloodstream [19].

Adiponectin is an adipose specific protein, with a myriad of roles involving insulin sensitisation [20]. It is thought that adiponectin increases fatty acid oxidation and decreases triglyceride build up in skeletal muscle. Through AMP-kinase activated protein (AMPK), adiponectin is able to stimulate β-cell function and promote glucose uptake[21]. Women who are obese and overweight in pregnancy have reduced adiponectin levels, inversely correlating with insulin resistance[22], which is in contrast to the inflammatory markers previously mentioned.

Dysregulation of the above inflammatory markers is associated with development of both GDM and insulin resistance [23] [24, 25]. During pregnancy, there is placental and systemic regulation of adipokines in order to promote insulin resistance and increased glucose transfer to the fetus via the placenta[7]. It has been shown that genes regulating lipid transport and inflammation are highly expressed in the placenta of women with GDM[26]. Therefore, obesity, in conjunction with regulatory placental hormones, can contribute to inflammation and increasing insulin resistance. If β-cell function is already impaired, then this can result in increased blood glucose and GDM [9]. In some cases, glucose levels will return to prenatal levels after delivery and the diabetogenic state is alleviated. However, due to the impairment of β-cell function, there may be long-lasting effects on maternal metabolic health[27].

1.5. Cardiovascular disease and metabolic syndrome

Cardiovascular disease (CVD) is a significant health problem and leading cause of mortality due to non-communicable diseases. In Australia, it is one of the most prevalent diseases and has caused approximately 26% of all deaths[28]. There are many modifiable risk factors for CVD, including smoking, unhealthy diet, being overweight/obese and lack of exercise[29]. All of these risk factors increase the risk of developing metabolic syndrome (MetS), a cluster of metabolic conditions that increases the risk of CVD, stroke and diabetes. The International Diabetes Federation (IDF)[30] has defined MetS as the presence of central adiposity (defined by waist

circumference which are ethnic specific (for women of all ethnicities, this is ≥80cm) and/or an obese BMI ≥30kg/m^2) and at least two of the following:

- Raised systolic blood pressure ≥130mmHg or diastolic blood pressure >80mmHg or the treatment of previously diagnosed hypertension
- Raised serum triglycerides ≥1.7mmol/L or being on treatment for increased triglycerides
- Raised fasting plasma glucose ≥5.6mmol/L or previously diagnosed type 2 diabetes mellitus
- Reduced HDL cholesterol ≤1.29mmol/L

Obesity is a risk factor for both GDM and CVD. There is an established relationship between weight gain and insulin resistance, which has been demonstrated by studies that have assessed increased adipose tissue growth and subsequent insulin resistance. Adipocyte hypertrophy as occurs with weight gain promotes insulin resistance [31]. This is due to elevated blood sugar and dyslipidaemia in obesity that promotes an increase of free fatty acids and inflammatory markers (i.e. leptin, TNF-a) and a significant decrease in anti-inflammatory markers such as adiponectin[32]. These pro-inflammatory markers induce tissue specific inflammation, leading to development of insulin resistance and β-cell dysfunction. Metabolic syndrome is promoted by the same dysregulation of inflammatory and anti-inflammatory markers and is associated with insulin resistance[33].

1.6. GDM and cardiovascular disease

A study by Bellamy *et al.* (2014) has shown that women with previous GDM have a 7.5-fold increased risk of developing Type 2 Diabetes Mellitus (T2DM) after pregnancy. Approximately 50% of women with GDM will develop T2DM within one year postpartum[34]. This is due to damage to pancreatic β-cells after a GDM pregnancy[7]. In a meta-analysis by

Kramer at al. (2019) based on more than one million participants, women with GDM have a 2-fold increased risk of developing CVD, and this is irrespective of disease progression to T2DM[35]. We conducted a comprehensive systematic review and meta-analyses (published in 2020) on cardiovascular risk factors in women with a history of GDM, which demonstrated that there is an increase in all conventional cardiovascular risk factors (i.e. systolic and diastolic blood pressure, BMI, lipids, serum glucose, serum insulin) in these women[36]. This review comprises chapter 3 of this thesis.

1.7. Depression and anxiety

Major depressive disorder (MDD) is defined as at least a two week period of low mood or loss of interest or pleasure, associated with at least five main symptoms: appetite or weight change, psychomotor changes (i.e. slowed speech, thought, movement), fatigue or decrease in energy, sense of worthlessness or guilt, helplessness or hopelessness, inability to make decisions or concentrate, recurrent thoughts of death or suicide[37]. Generalized anxiety disorder [38] is often seen in parallel with other chronic and mental health disorders, and is associated with recurring intrusive thoughts or concerns and physical symptoms that may also be present such as sweating, trembling, dizziness or a rapid heart beat[37].

1.7.1. Perinatal depression and anxiety and the effect on pregnancy

Depression affects 20% of young mothers in Australia, while 50% of women report being diagnosed with depression in the perinatal period (i.e. during pregnancy and up to their child's first birthday)[39]. Significant predictors of antenatal depression include stressful life events (e.g. history of abuse), low social support and low income [39, 40]. Risk factors for antenatal depression (i.e. depression in pregnancy) include psychological disorders/current depression, stress and/or low social support during pregnancy [41]. These risk factors are seen commonly in communities with low socioeconomic status [42]. Psychosocial risk factors, along with metabolic risk factors

seen in such populations including poor diet, drug and alcohol use will promote inflammation and stress in the mother.

1.7.2. Antenatal depression and the risk of GDM

There is a known bi-directional association between T2DM and MDD, which is thought to be mediated by hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA). The HPA promotes an increase in cortisol and inflammatory markers that lead to systemic insulin resistance [43]. Therefore, pre-disposition to depression may increase insulin resistance during pregnancy and further increase the risk of GDM.

1.8. The fetal origins of adult disease hypothesis

Pregnancy complications, such as GDM, are now known to have significant health implications for the offspring. The fetal origins of adult disease (FOAD) was first conceptualised by David Barker who, when assessing midwifery records of 16,000 individuals born in Hertfordshire from 1911 to 1930, found that that low weight, head circumference and ponderal index recorded at birth were associated with increased risk of coronary heart disease in adulthood[44]. The data from this cohort revealed that poor fetal growth was associated with hypertension, CAD and insulin resistance in adulthood. Analysis of data from the Dutch Famine in 1944-1945, which recorded a nutritional intake of pregnant women being reduced to 1000 calories or less, found that offspring *in utero* that were exposed to calorie restriction in mid or late gestation were lighter than those who were exposed in early gestation[45]. The mothers who were malnourished in mid or late pregnancy had reduced glucose tolerance, and those exposed to famine during early pregnancy had dyslipidaemia and higher BMI later[45]. Barker proposed that those "starved" *in utero* were more likely to become overweight and therefore develop diabetes and cardiovascular problems later in life[45]. This association has been shown in generational and biobank studies of middle aged adults, such as the Birth Gene [46] study with data from over 180,000 participants in 49 studies, whereby those who were born with a low birth weight were

at greater risk of T2DM and coronary artery disease[38, 47]. This work underpins the developmental origins of health and disease (DOHAD) hypothesis, which states that external influences on the intrauterine environment at critical stages of fetal growth have significant consequences on later life health, from infancy and throughout life[48]. The FOAD theory evolved to DoHAD allowing a broader focus on preconception and the first 1000, sometimes 2000 days of development rather than purely the prenatal period.

1.8.1. Gestational diabetes mellitus in the context of DoHAD

The concept of DoHAD has transitioned from the effect of undernutrition *in utero* on later life health and expanded to consider all intrauterine exposures, including the effect of GDM and obesity on offspring health later in life. Elevated maternal insulin resistance during GDM allows for increased transplacental transfer of glucose to the growing fetus[49]. Based on the DOHaD hypothesis, exposure to an adverse intrauterine environment (i.e. excess nutrients) promotes activation of genes as a compensatory mechanism.[48]. In studies of Native American Pima populations, children who were exposed to a hyperglycaemic environment *in utero* have elevated blood glucose comparative to their siblings who were exposed to a normoglycemic environment[50]. A study by Coles *et al.* (2020) found that children as young as 3 years of age who were exposed to GDM *in utero* were more likely to be insulin resistant based on the Homeostatic Model of Insulin Resistance (HOMA-IR), than those who were not [51]. Therefore, while increased fetal β-cell activity was advantageous *in utero,* it may promote reduced β-cell capacity compared to those born to a normoglycemic pregnancy, which could lead to development of chronic metabolic diseases later in life.

1.9. Exposure to GDM *in utero* and risk of cardiovascular disease later in life

In a systematic review and meta-analysis from 2012, Aceti *et al.* showed that systolic blood pressure was 1.88mmHg higher in offspring exposed to GDM *in utero* compared to controls (95% CI 0.00-2.77)[52]. This finding is particularly important, as it has been shown in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, that having arterial stiffness during adolescence (17-24 years old) tracks into adulthood 7 years later[53]. It is important to assess whether elevated blood pressure and increased stiffness are detected within a few years after birth and if this influences elevated blood pressure during this adolescent period and later in life. Children who are born to mothers who are diabetic are more likely to have impaired glucose tolerance and develop type II diabetes mellitus in early adolescence[54]. Furthermore, obesity has been seen in children as early as 2 years of age in those exposed to GDM *in utero*[55]. This is likely to contribute to poor metabolic health later in life and increase the risk of developing metabolic syndrome and CVD. Data from the PREOBE cohort have shown that maternal diabetic disorders have a significant effect on maternal cord blood metabolites such as elevated hexoses (primarily glucose) and L-asparagine and L-aspartic acid, which are associated with insulin resistance and hyperglycaemia during pregnancy[56].

We conducted a comprehensive systematic review and meta-analysis (published in 2020) on cardiovascular risk factors in children exposed to GDM *in utero.* This review showed that systolic blood pressure, BMI z-score and serum glucose are significantly higher in those exposed to GDM *in utero* than those who were not. This paper comprises chapter 4. The fifth chapter of this thesis is a comprehensive systematic review and meta-analysis on metabolic syndrome in women with a history of GDM and among children exposed to GDM *in utero.* This review found that children who are exposed to GDM *in utero* are more likely to develop metabolic syndrome.

1.10. Breastfeeding as a protective measure for cardiovascular disease in mothers and children

Breastfeeding is considered the best form of infant nutrition, whereby World Health Organization recommends at least 6 months of exclusive breastfeeding from the baby's birth[57]. Breastmilk is composed of macronutrients, micronutrients, hormones, digestive enzymes and immune cells that support all facets of infant growth[58]. It has been shown that breastfeeding reduces the risk of chronic diseases in women such as type II diabetes mellitus, obesity and cardiovascular disease[59]. Furthermore, children who are exclusively breastfed as early as <3 months postpartum are less likely to be obese[60]. Therefore, breastfeeding may affect the risk of developing type II diabetes and cardiovascular disease in mothers and offspring exposed to GDM *in utero,* later in life. Our systematic review and meta-analysis was published in 2021 assessing the effect of breastfeeding on cardiovascular risk factors in both women and children. It was found that women with a history of GDM who breastfed had significantly lower serum glucose and lower risk of developing T2DM than women who did not breastfeed. This paper comprises chapter 7 of this thesis.

1.11. Exposure to GDM *in utero* and neurodevelopment in the offspring

During late gestation, major fetal neural networks affecting behaviour, emotion, structural development of neurons, dendritic arborisation and synaptogenesis develop. During normal gestation, docosahexaenoic acid, a major component of brain cell membranes and myelin, is taken up by the placenta and transferred for fetal neural development[61]. In a healthy pregnancy, cord blood DHA is elevated while maternal DHA is decreased. However, in a diabetic pregnancy, maternal-fetal transfer of DHA is altered, as it is significantly lower in cord blood of the babies exposed to *GDM in utero* compared to those who are not [62, 63]. This is thought to be due to down regulation of peroxisome proliferator activated receptor (PPAR)-alpha in the placenta in a GDM pregnancy, a nuclear receptor that promotes fatty acid metabolism such as

omega-3 fatty acids[64]. Therefore reduced PPAR- α may contribute to reduced placental transfer of DHA[63]. Furthermore, a hyperglycaemic environment *in utero* is thought to inhibit dendritic arborisation in the fetal brain [65, 66]. There is evidence to suggest that those exposed to GDM *in utero* are at a higher risk of having poor neurodevelopment, impaired brain function and mental disorders later in life than those who were not exposed[67, 68]

There is emerging, but scant, evidence on the effect of fetal sex on different cognitive areas in the brain in those exposed to GDM *in utero.* Alves *et al.* (2020) found evidence that pre-pregnancy BMI was associated with total hippocampal volume in boys, but not girls, at age 7-11 years old[69]. There is evidence from one study showing that children exposed to GDM *in utero* had reduced radial thickness in a small region of the hippocampus corresponding to the CA1 subfield. This association between GDM and reduced volume in this region was seen in boys only, but attenuated after controlling for age[70].

Chapter 2

2. Context of thesis

2.1. The STOP study cohort

The Screening Tests to Predict Poor Outcomes of Pregnancy [1] study began recruitment in March 2015 at the Lyell McEwin Hospital and the Women's and Children's Hospital in South Australia. Majority of participants were recruited at the Lyell McEwin Hospital, which serves a population with one of the lowest socioeconomic status scores in metropolitan Australia[71]. It has high rates of chronic disease, such as of obesity, cardiovascular disease and mental health disorders [72]. Recruitment ended in December 2017, with a total of 1,383 nulliparous pregnant women, their partners and babies recruited. Detailed information was collected at 9-16 weeks' and 34 weeks' gestation and following delivery of the baby. The maternal data includes demography, medical history, fertility history, information on previous pregnancies, diet, exercise, work, smoking, intake of alcohol and recreational drugs, measures of stress, anxiety and depression. Physical measurements including height, weight, waist and hip circumference, BMI and haemodynamic measurements were performed. Women were screened for gestational diabetes at 28 weeks' gestation by a 75g Oral Glucose Tolerance Test (OGTT). Data collected at birth included newborn weight, length, arm circumference, birthweight centile, and complications during the neonatal period and type of feeding at discharge from hospital. A sample of cord blood and/or saliva was collected at birth.

The STOP study complements the Screening Outcomes of Pregnancy Endpoints (SCOPE) study, an international multicentre prospective cohort study aimed to develop screening tests to predict the development of pregnancy complications. The Adelaide arm of the SCOPE cohort was also recruited at the Lyell McEwin Hospital. The data collected reflected the socioeconomic status of the population, showing higher rates of obesity, smoking, poor quality diet and pregnancy complications compared to the national average. This cohort has been

described previously[73]. Women in Adelaide were followed up 8-10 years after delivery of their SCOPE baby, showing that those with hypertensive disorder of pregnancy (HDP) had higher BMI and blood pressure compared to controls. The children of these pregnancies also showed significantly higher augmentation indices (i.e. a marker of arterial stiffness) compared to those born to controls[74]. Children who were born after a preeclamptic pregnancy had poorer executive functioning, and those born small for gestational age had poorer working memory compared to controls of uncomplicated pregnancies[75]. The SCOPE follow-up showed evidence of impaired cardiovascular function in women who developed pregnancy complications, and poorer metabolic health and neurodevelopmental outcomes in their offspring. However, SCOPE and many other prospective cohort studies did not examine the associations between pregnancy and health parameters at an earlier follow-up. Information collected earlier may be particularly useful because it may identify women and children who could benefit from early intervention and changes in lifestyle and health management.

In this thesis, systematic reviews and meta-analyses on long term consequences of GDM in women and their children were performed. In addition, STOP women and children were followed up at 3 years after the STOP pregnancy.

2.2. Hypothesis and aims

Based on evidence in the literature, we hypothesise that:

- Risk factors for CVD and metabolic disease will be increased within a few years after pregnancy among women who experienced GDM compared to those who did not.
- Women with poor mental health status (i.e. depression, anxiety, high perceived stress) are more likely to develop GDM
- Offspring of GDM pregnancies will demonstrate an adverse anthropometric and hemodynamic profile compared to those who were not exposed to GDM *in utero*

- Offspring of women who experience GDM will demonstrate poorer neurodevelopment and cognitive function compared to those who were born to a non-GDM pregnancy
- Breastfeeding will result in reductions in cardiovascular disease risk factors in both the mother and children exposed to pregnancy complications, including GDM.

The aims of this thesis are:

1. To investigate the association between gestational diabetes mellitus and risk of cardiovascular disease in women with previous GDM;
2. To determine if there is an association between poor mental health outcomes (i.e. depression, anxiety, perceived stress on the risk of developing GDM;
3. To investigate the association between exposure to GDM *in utero* and poor anthropometric and hemodynamic outcomes, as early as age 3 years;
4. To determine if exposure to GDM *in utero* influences cognition, behaviour and neurodevelopment in offspring at 3 years of age;
5. To ascertain if there is a protective effect of breastfeeding on cardiovascular risk factors in both women and children exposed to pregnancy complications *in utero*

SECTION 2: Systematic review and meta-analyses series

This section encompasses the series of systematic reviews and meta-analyses completed investigating cardiovascular risk factors in women with a history of GDM and children exposed to GDM *in utero.* All reviews have been published, therefore the methodology sections across chapters may be repetitive.

Chapter 3

3. Cardiovascular risk factors in women exposed to gestational diabetes mellitus: A systematic review and meta-analysis

Maleesa M Pathirana, Zohra Lassi, Anna Ali, Margaret Arstall, Claire T Roberts, Prabha H Andraweera

3.1. Statement of Authorship

Title of Paper	Cardiovascular risk factors in women with a history of GDM: a systematic review and meta-analysis
Publication Status	Published – 2021
Publication Details	**Pathirana MM,** Lassi Z, Ali A, Arstall M, Roberts CT, Andraweera PH. Cardiovascular risk factors in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. Rev Endocr Metab Disord. 2021 Dec;22(4):729-761. doi: 10.1007/s11154-020-09587-0. Epub 2020 Oct 27. PMID: 33106997.

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Acquiring data, knowledge, analysis, drafting
Overall Percentage (%)	70%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Zohra S Lassi	
Contribution to the Paper	Conceptualisation, acquiring data, analysis, drafting	
Signature		**Date 14 Feb 2022**

Name of Co-Author	Anna Ali
Contribution to the Paper	Acquiring data, analysis
Signature	**Date 14 Feb 2022**

Name of Co-Author	Margaret Arstall
Contribution to the Paper	Conception, knowledge, drafting
Signature	**Date 28/02/2022**

Name of Co-Author	Claire Roberts
Contribution to the Paper	Conception, knowledge, drafting
Signature	**Date 28/02/2022**

Name of Co-Author	Prabha Andraweera
Contribution to the Paper	Conception, acquiring data, knowledge, drafting
Signature	**Date 28/02/2022**

3.2. Abstract

Aims: This systematic review and meta-analysis aimed to synthesize evidence on conventional cardiovascular disease (CVD) risk factors among women with previous Gestational Diabetes Mellitus (GDM).

Methods: The review protocol is registered with PROSPERO (CRD42019118149). PubMed, CINAHL, SCOPUS, and EMBASE databases were searched. Studies reporting on CVD risk factors in women with previous GDM compared to women without previous GDM were selected.

Results: A total of 139 studies were eligible, of which 93 were included in the meta-analyses. Women with previous GDM have significantly higher systolic blood pressure (2.47mmHg 95% CI 1.74 to 3.40, n=48, 50,118 participants) diastolic blood pressure (1.89mmHg 95% CI 1.32 to 2.46, n=48, 49,495 participants), BMI (1.54 kg/m^2 95% CI 1.32 to 2.46, n=78, 255,308 participants), total cholesterol (0.26 SMD 95% CI 0.15 to 0.37, n=48, 38,561 participants), LDL cholesterol (0.19 SMD 95% CI 0.08 to 0.30, n=44, 16,980 participants), triglycerides (0.56 SMD 95% CI 0.42 to 0.70, n=46 , 13,175 participants), glucose (0.69 SMD 95% CI 0.56 to 0.81, n=55, 127,900 participants), insulin (0.41 SMD 95% CI 0.23 to 0.59, n=32, 8,881 participants) and significantly lower HDL cholesterol (-0.28 SMD 95% CI -0.39 to -0.16, n=56, 35,882 participants), compared to women without previous GDM. The increased blood pressure, total cholesterol, triglycerides and glucose are seen as early as <1 year postpartum.

Conclusions/interpretation: Women with previous GDM have a higher risk of CVD based on significant increases in conventional risk factors. Some risk factors are seen as early as <1 year postpartum. Women with GDM may benefit from early screening to identify modifiable CVD risk factors.

3.3. Introduction

Cardiovascular disease (CVD) is a major global health burden. There are 17.9 million deaths annually, accounting for 31% of global mortality[76]. CVD is also a leading cause of death in women[77]. Research over the past decade has shown an association between the major pregnancy complications including preeclampsia, intrauterine growth restriction, preterm birth and gestational diabetes mellitus and increased risk of CVD, with each pregnancy complication incurring a 2-fold increased risk of developing CVD later in life[78].

Gestational diabetes mellitus (GDM) is defined as glucose intolerance, which is first recognised in pregnancy, hence different from both type I and type II diabetes mellitus. GDM is estimated to affect one in seven pregnancies[79]. Women with previous GDM are more likely to be obese, have dyslipidaemia and hypertension postpartum[78]. These women have an approximately seven-fold increased risk of developing type II diabetes mellitus (T2DM) later in life[34]. The definition of GDM changed in 2013, following a study by the Hyperglycaemia Adverse Pregnancy Outcomes (HAPO) cohort, which showed that adverse perinatal outcomes were seen even in women whose glycaemic levels were below the conventional GDM criteria [80]. This meant that women, who were not diagnosed with GDM based on previous guidelines, were still at risk for these adverse outcomes. With the implication of the new international guidelines for GDM, the rate of women classified as having GDM is expected to increase.

A recent meta-analysis by Kramer *et al.* (2019) based on more than a million participants, showed that women with GDM have a 2-fold increased risk of developing CVD, irrespective of the disease progression of T2DM[35]. Thus, impaired glucose tolerance postpartum does not appear to be the only cardiovascular risk factor in women who experience GDM to warrant screening for CVD. A major mechanism that underlies the risk of CVD is metabolic syndrome, which is a collection of vascular derangements including obesity, dyslipidaemia, insulin resistance and hypertension[81]. Therefore, early identification of these modifiable risk factors is

pertinent in order to offer targeted interventions/lifestyle modification advice to reduce the subsequent risk for CVD. It has been shown that minimal decreases in risk factors including systolic blood pressure, total cholesterol and adiposity can significantly reduce the risk of ischemic heart disease later in life [82, 83].

There has not been a systematic review and meta-analysis that has comprehensively evaluated all conventional CVD risk factors simultaneously in women with previous GDM, and none that has assessed the timeline of development of risk factors for CVD. This is particularly important as Kramer *et al.* (2019) showed an association between previous GDM and increased risk of CVD events as early as one year postpartum[81].

Therefore, our primary aim was to conduct a systematic review and meta-analysis on the association between GDM and major risk factors for CVD including blood pressure (BP), body mass index (BMI), fasting glucose, insulin and lipids using data from all eligible studies. Our secondary aim was to assess the risk factor profile based on the time elapsed postpartum at which assessments were conducted.

3.4. Methods

3.4.1. Search strategy

All studies describing the association between GDM and risk factors for CVD in women were identified by searching the following electronic databases: PubMed, CINAHL, SCOPUS and EMBASE with an end of search date of 5th November 2018. Subsequently, we updated the literature search to include all relevant articles published until 10th Jan 2020. The search was conducted by ZL. The review protocol is registered in PROSPERO (CRD42019118149).

The review was undertaken with reference to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[84]. The search strategy was as follows**:** ("gestational diabetes*" OR "pregnancy induced diabetes" OR "diabetic pregnancy") AND (pregnan* OR mother OR women OR woman) AND ("blood pressure" OR diabetes OR cardiovascular OR metabolic OR hypertension OR BMI or "body mass index" OR obesity OR overweight OR lipids OR lipid OR cholesterol OR triglyceride* OR glucose OR insulin OR vascular).

We included case-control studies, cross-sectional and cohort studies. Previous systematic reviews and meta-analyses on closely related topics, and references from eligible studies were checked for additional studies. All identified studies were assessed for relevance by four authors (MP, PA, AA, ZL). Data were independently extracted by two authors (MP, AA). Discrepancies were resolved by discussion with ZL and PA.

3.4.2. Inclusion criteria

Studies were selected if they compared CVD risk factors in women with a previous history of GDM compared to women with no history of GDM. We included studies that defined GDM based on the International Association of Diabetes and Pregnancy Study

Groups (IADPSG)[85]. However, since the diagnostic criteria have been revised recently, we included studies that used prior recommended diagnostic criteria of GDM including the 1999 World Health Organization definition, and other regional definitions. The definitions of GDM of included studies are detailed in Table 1. Studies that did not include a definition of GDM, those that did not define the case and control groups and those that compared women with GDM to another risk group were excluded.

Data were extracted independently and in duplicate for outcomes, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), lipid levels (total cholesterol, low density lipoprotein (LDL) high density lipoprotein (HDL), and triglycerides), blood glucose, and fasting insulin. We analysed all studies collectively as an overall analysis, and subsequently stratified into subgroups based on the time of follow up postpartum as: <1 year, 1-5 years, 5-10 years and 10+ years from the index pregnancy. Studies that did not provide details on when the follow up assessment was conducted, were only included in the overall analysis. When the same cohort was assessed at multiple times postpartum, the study with the largest sample size was used in the overall analysis and in the relevant subgroup analyses. When outcome measures of the same cohort at one follow up time point were reported in multiple publications, the one with the largest sample size was used in the overall analysis.

We considered studies published in English, and studies that could be translated to English. We contacted authors via email to obtain missing data and clarifications when required. We included abstracts of cohort studies, but only abstracts which provided data for relevant outcomes were included in the meta-analysis and non-meta-analysis table (Supplementary Table 3.8.1).

3.4.3. Statistical analysis

The following data were collected from each included study: definition of GDM, time of postpartum follow up (number of years since index pregnancy), number of cases (those who experienced GDM) and controls (those who did not experience GDM), child birthweight, and gestational age at delivery of cases and controls, and data on the variables considered in any adjusted analyses/variables used to match cases with controls.

The meta-analysis was performed using RevMan software (Review Manager Version 5.3) based on an inverse variance method. As per protocol, the random-effects model was selected to account for the differences in diagnostic criteria of GDM. For each outcome measure, unadjusted mean and standard deviation (SD) were used in meta-analyses. When mean and SD were not reported, Standard Error of Mean (SEM) was converted to SD using RevMan software. The Standard Mean Difference (SMD) was used when the outcome was measured in different units across studies and Mean Difference (MD) when units were consistent.

Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the Chi^2 P value was less than 0.1. The studies that reported on outcome measures using median and IQR are detailed in Supplementary Table 3.1. To assess publication bias, funnel plots were used for the primary outcomes. The methodological quality was assessed using the Newcastle - Ottawa Quality Assessment Scale (NOS) and graphically illustrated in the supplementary data (Supplementary Figure 1)[86]. Sensitivity analyses were performed to evaluate heterogeneity for outcomes after excluding low quality studies (i.e. scored 1-3 on the NOS) and excluding abstracts that were included in the meta-analyses.

3.5. Results

3.5.1. Search results

The literature search identified 12,248 articles. Four hundred and thirteen (413) articles were eligible for full text review. Of these, 139 were included in the review and 93 were included in the meta-analyses. The reasons for excluding 274 studies are detailed in Figure 3.5.1-1. We contacted 24 authors for additional data; we received a 17% response rate (n=4 studies). Of the included studies, 33 were of high quality (scored 7-8), 79 were of moderate quality (scored 4-6), and 28 were of low quality (scored 1-3) (Supplementary Table 3.8-2). The results of the overall meta-analyses for all CVD risk factors in women with previous GDM compared to those without previous GDM are shown in Table 3.5.7-2.

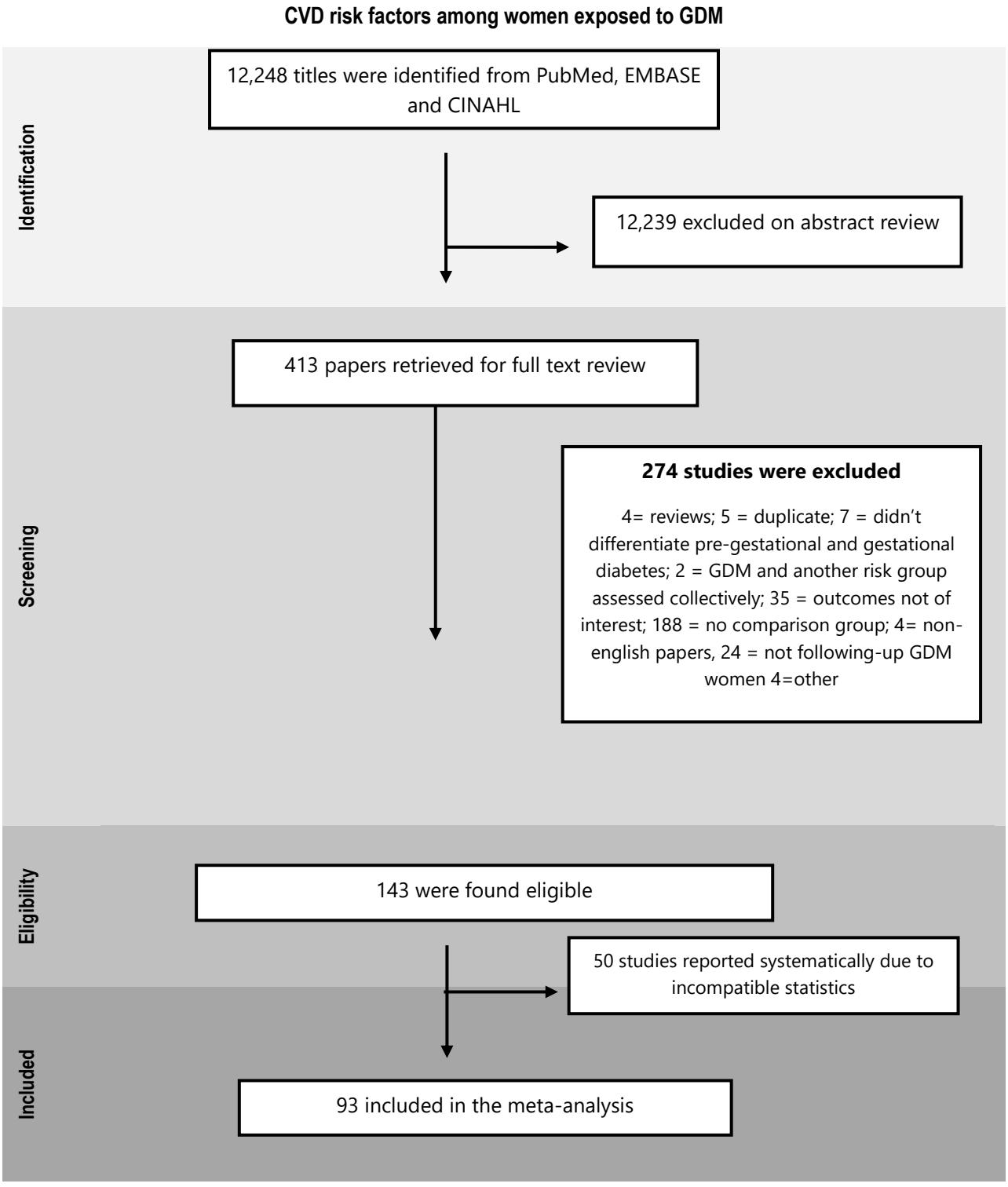


Figure 3.5.1.1 Flow Chart of Study Selection

Table 3.5.1-1 Included Studies in Systematic Review and Meta-Analysis

Author and year	Study design	Country	Exposed/ Definition of GDM (n=)	Non-exposed (n=)	Birthweight of offspring cases/controls (g)	Parity cases/ controls	Gestational age of delivery cases/control	Years follow up postpartum	Outcome measure considered	Adjusted analysis CVD outcomes
< 1 year postpartum										
Albareda 2004	Prospective	Spain	696/50g, 1h GCT-	70	**NR**	446/694 (64.3)	**NR**	6 weeks and 5 year	Blood pressure BMI, Serum Lipids Blood Glucose Insulin	Independent predictors of GDM: previous hyperglycaemia, 4 abnormal values in diagnostic OGTT or overt diabetes during pregnancy, 2h blood glucose

										in diagnostic OGTT 11/7mmol/L, gestational age at diagnosis, pre-pregnancy BMI. Accumulates to 49.3% risk of diabetes in GDM women
Anastasiou 1998	Case-control	Greece	33/ADA	19	**NR**	*Mean (SD)* Normal: 1.6 ±0.6, Non-obese: 1.4 ±0.6, Obese:1.7 ±0.8	**NR**	3-6 months	Serum Lipids	Endothelium dependant dilation not associated with diagnosis of GDM

Berglund 2016	Cohort	Spain	331/ NDDG or IDF	132	**NR**	Parity>1 (n=): Normal weight: 55 Overweight: 24 Obese: 28 GDM:35	**NR**	At birth	BMI	**NR**
Bowes 1996	Prospective	UK	7/75g OGTT 2h blood glucose > 9 mmol/1.	5	**NR**	**NR**	*Mean (SD)* 30.9 + 0.8	2-3 months	BMI Blood glucose Fasting Plasma Insulin	**NR**
Bozkurt 2010 - abstract (2)	Cross-sectional	Italy	62/ 4th International Workshop conference on GDM	29	**NR**	**NR**	**NR**	3–6 months	BMI, Triglycerides	**NR**

Bozkurt 2012 (2)	Cross-sectional	Vienna	54/4th International Workshop conference on GDM	**29**	**NR**	**NR**	**NR**	3–6 months	Blood pressure, Triglycerides, Blood Glucose	**NR**
Cellina 1983	Observational Cohort	Italy	20/ O'Sullivan and Mahan	**15**	**NR**	**NR**	**NR**	5 weeks	Blood pressure	**NR**
Chan 1992	Retrospective	UK	15/ 75g OGTT: 120 minutes venous plasma glucose >7.8 mmol/l.	15	**NR**	**NR**	**NR**	60 and 120 minutes after delivery	Serum insulin Glucose	**NR**
Davis 1999	Cross-sectional	USA	21/medical records	39	**NR**	**NR**	**NR**	3-18 months	Blood pressure BMI Serum Lipids Blood glucose Fasting Insulin	MANOVA adjusting for insulin metabolic syndrome variables - all significant for

										glucose sum, triglycerides, BMI and diastolic BP.
Eroglu 2006	Prospective	Turkey	36/ Abnormal 3h 100g OGTT at 24–28 weeks' gestation	33	Cases: 3308±401, Control:3334 ± 373	Parity: Cases: 1.3±0.7 Control: 1.4±0.	**NR**	10–15 months after delivery	BMI, Serum Lipids Blood glucose, Fasting insulin	**NR**
Ferrada 2007	Case-control	Chile	58/GDM definition not explained	58	**NR**	**NR**	**NR**	End of puerperal period	Blood pressure, BMI Serum Lipids	**NR**
Friere 2006	Cross-sectional	Brazil	13/ Carpenter and Coustan.	13	**NR**	**NR**	**NR**	8 weeks	Blood pressure BMI	**NR**
Homko 2001	Cross-sectional	USA	7/ Carpenter and Coustan	8	**NR**	**NR**	**NR**	3 months postpartum	Blood Glucose Fasting insulin	**NR**

Kjos 1991	Prospective	USA	6-12 weeks (n=1340), 1 year (n=157)/ NDDG (1979)	6-12 week (n=43) 1 year (n=36)	**NR**	Mean (SD): GDM 3 (2)/ Control: 3 (2)	**NR**	6-12 weeks,	BMI Serum Lipids	Women with DM had significantly elevated TG and reduced HDL than those who remained non-diabetic.
Ko 1999	Case-control	Hong Kong	19/ 75g OGTT	10	**NR**	**NR**	**NR**	6 weeks	Blood pressure BMI, SBP, DBP, Serum Lipids Blood Glucose Fasting Plasma Insulin (uU/mL)	GDM women had significantly higher risk of developing obesity, hypertension, hypercholesterolemia, dyslipidaemia,

										diabetes, and IGT (after excluding those with DM)
Lee 2008	Cross-sectional	Korea	620/ NDDG after two step OGTT	868	**NR**	**NR**	**NR**	Median 2.1 years	Blood Pressure BMI Serum Lipids Blood glucose	Logistic regression: T2DM risk higher for women with GDM risk compared to general population (stratified by race status). GDM status interpedently and significantly

										associated with diabetes development (3.7-fold increase risk)
Lee 2015	Cross-sectional	Korea	36/75g oral glucose tolerance test (OGTT)	19	**NR**	**NR**	**NR**	6–8 weeks after delivery,	Blood Pressure BMI Serum Lipids Blood glucose Fasting Insulin	Multiple regression: b-cell function significantly associated with parental diabetes history and waist-hip ratio after adjustment for age, BMI, BP and visceral adiposity in

										previous GDM women
Maghbooli 2010	Case-control	Iran	92/50g O'Sullivan and Mahan criteria after two step OGCT	100	**NR**	1.4 +/- 0.03 0.38 +/- 0.59	**NR**	6-12 weeks	Serum Lipids Blood glucose	**NR**
McLachlan 2005	Case-control	Australia	19/ 75-g OGTT (ADIPS)	19	**NR**	**NR**	**NR**	3–6 weeks	BMI, Blood glucose	**NR**
Morbiducci 2009 (1)	Methodology study	Italy	122/ Not specified	19	**NR**	**NR**	**NR**	4-6 months	BMI	**NR**
Noujah 2017	Population Based Cohort Study	Iran	176/ IADPSG criteria, or medical records	86	**NR**	**NR**	**NR**	6-12 weeks	Serum Lipids	Univariate analysis – pre-pregnancy BMI > 35 and GDM history in first relatives

										associated with dyslipidaemia in GDM women. Multivariate analysis showed significance for BMI > 25 only
Noujah 2018	Population Based Prospective Cohort Study	Iran	176/ IADPSG criteria, or medical records	86	**NR**	**NR**	**NR**	6-12 weeks	Blood pressure BMI, Blood Glucose	Backward linear regression - gravidity > 2, pre-pregnancy overweight or obesity, systolic BP, and metformin

										or insulin use in pregnancy risk factors for MetS in univariate analysis.
Pacini 2012 (2)	Retrospective	Austria	104/Not specified	35	**NR**	**NR**	**NR**	6 months	BMI (kg/m2), Blood Glucose Fasting Plasma Insulin	**NR**
Retnakaran 2009*	Observational Study	Canada	137/NDDG (1979)	259	**NR**	Nulliparous: (GDM 50.4%/CON: 46.7%)	*Median (IQR)* 29 (28-31)/30(28-32)	3 months	BMI Blood Glucose	Meta-regression analysis –IR postpartum associated with adiponectin levels in pregnancy

										after adjustment for various covariates
Retnakaran 2010*	Observational Study	Canada	107/NDDG (1979)	73	**NR**	**NR**	**NR**	3 months	Blood Pressure BMI Blood Glucose	AUC associated with total cholesterol, LDL, HDL, triglycerides in adjusted model for age ethnicity and diabetes history
Retnakaran 2010*	Prospective observational Study	Canada	136/NDDG (1979)	87	**NR**	**NR**	34.4 (4.3)/ 34.0 (4.4)	3 months	Blood Pressure BMI	Multiple linear regression: GDM was negative

										predictor of change in beta cell function between 3-12 months postpartum, after adjustment for age, ethnicity, familial history of diabetes, breastfeeding and b-cell function.
Retnakaran 2011*	Observational Study	Canada	137/NDDG (1979)	259	**NR**	**NR**	**NR**	3 months	Blood Pressure BMI Serum Lipids	Multiple linear regression performed for effect on adiponectin in

										metabolic status in GDM women adjusted for various covariates.
Roca-Rodrigeuz 2012*	Case-control	Spain	41/NDDG (1979)	21	**NR**	**NR**	**NR**	≤1 year	Blood Pressure BMI, Serum Lipids Blood glucose Fasting plasma insulin	Changes at 3 and 12 months postpartum not significant after adjusting for waist circumference, weight, insulin sensitivity and b-cell function adjusted for baseline values.

Roca-Rodrigeuz 2014*	Case-control	Spain	41/NDDG (1979)	21	**NR**	**NR**	**NR**	≤1 year	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Relationship between AUC glucose and lipids adjusted for age, ethnicity and familial diabetes.
Sartore 2011	Retrospective cohort	Italy	21/Carpenter and Coustan (1982)	21	**NR**	**NR**	**NR**	6 months	Serum Lipids, Blood Glucose	Adjusted p-value reported, specified for age and waist circumference (based on Kruskall Wallis test)
Seck 2018	Case-control	Sengal	20/ Not specified	20	**NR**	**NR**	**NR**	After delivery	Serum Lipids Blood Glucose	**NA**

Sokup 2012*	Prospective cohort	Poland	85/ WHO 1999	40	**NR**	**NR**	**NR**	2-24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Sokup 2012*	Prospective cohort	Poland	125/WHO 1999	40	**NR**	**NR**	**NR**	2-24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Shen 2018	Observational Study	China	1263/WHO 1999	705	**NR**	**NR**	**NR**	3.65	Serum Lipids, Blood Glucose	NR
Shen 2019	Observational Study	China	1263/WHO 1999	705	**NR**	**NR**	**NR**	3.65	Serum Lipids, Blood Glucose	Women with GDM had higher risk of postpartum metabolic syndrome by

										NCEP ATPIII criteria (2.79, 95% CI 2.00 to 3.89) even with adjustment for various covariates: (central obesity hypertriglyceridemia, high blood pressure, low HDL cholesterol hyperglycaemia

Sung 2008	Cohort	South Korea	140/ Third International Workshop Conference on GDM	17	**NR**	**NR**	**NR**	2 months	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Todoric 2012	Retrospective	Austria	10/Universal GDM Screening	6	**NR**	**NR**	**NR**	6-12 weeks	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Adjusted p-values for BMI: Fasting plasma glucose (mmol/L): p=0.000; TC (mmol/L): p=0.9940; HDL-C (mmol/L) p=0.0027, LDL-C p=0.4022; TG p=0.0006

										Fasting plasma glucose: HDL-C p=0.0049, TG p= <0.0001
Tura 2006 (2)	Prospective cohort	Austria	24/4th Workshop Conference on GDM	23	**NR**	Mean (SE) 1.26 (0.11)/1.48 (0.18)	**NR**	4-6 months	BMI, Blood glucose Fasting plasma insulin	**NR**
Ueland 2018	Population based prospective cohort study	Norway	48/ IADPSG 2010	225	**NR**	**NR**	**NR**	5 years	Blood Pressure BMI	Adiponectin significantly lower in women with GDM than controls even after adjustment for BMI, age, parity, diabetes

										in family and C- Reactive Protein
Vitoratos 2001	Retrospective	Greece	24/ Carpenter and Coustan (1982)	19	**NR**	**NR**	Case: 38.6 (38-39.5)/ Control39.4 (39-40)	6 weeks	BMI	**NR**
Wang 2019	Retrospective	China	30/ 75g OGTT	15	3,445.67/ 3,362.85	**NR**	**NR**	After delivery	BMI	**NA**
Weisnagel 2013 abstract	Abstract	Canada	20/ Not reported	27	**NR**	**NR**	**NR**	2 months	Total cholesterol, HDL, Triglyceride, Fasting glucose, Fasting Insulin (not specified)	**NR**
Winzer 2004 (1)	Cross-sectional	Austria	89/4th Workshop Conference of	**19**	**NR**	**NR**	**NR**	3 months	BMI Serum Lipids	Adiponectin unadjusted is negatively

			Gestational Diabetes						Blood glucose Fasting plasma insulin	associated with fasting glucose, triglycerides and positively associated with HDL cholesterol in pGDM and healthy control subjects, this correlation stays after adjustment for BFM, WHR and SI
Zajdenverg 2014	Cross-sectional analysis	Brazil	25/ADA criteria	20	**NR**	2.3 (1.22)/ 2.4 (1.4)	**NR**	≤ 1 year	Blood Pressure BMI Serum Lipids	**NR**

									Blood glucose	
1-5 years postpartum										
Akinci 2008	Cross-sectional	Turkey	46/ 50g-OGTT, ADA	30	**NR**	**NR**	**NR**	3 years	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Multiple regression analysis: Plasma PAI-1 antigen significantly correlated with BMI fasting and post load glucose, total cholesterol, triglyceride, HDL and LDL.
Akinci 2011*	Cross-sectional	Turkey	195/ 50g-OGTT, ADA	71	**NR**	**NR**	**NR**	3 years	Blood Pressure BMI Serum Lipids	No association was seen between pre-pregnancy

									Blood glucose Fasting plasma insulin	obesity (BMI >30 kg/m2) and postpartum diabetes association was weak, controlled for age, parity and gestational week at the diagnosis of GDM.
Akini 2011*	Cross-sectional case–control study	Turkey	128/ 50g OGTT, ADA	67	**NR**	**NR**	**NR**	3 years	Serum Lipids Blood glucose Fasting plasma insulin	**NR**

Akini 2013*	Prospective	Turkey	141/ 50 g OGTT, ADA	49	**NR**	**NR**	**NR**	3 years	Serum Lipids Blood glucose Fasting plasma insulin	Fasting glucose, post-load glucose - separate models run along with age, postpartum duration, smoking, BMI, waist circumference and HOMA index.
Albareda 2003 (3)	Prospective	Spain	696/ 50g, 1h glucose challenge test	70	**NR**	**NR**	**NR**	6 weeks and 5 year	Blood Glucose	Independent predictors of GDM: previous hyperglycaemia, 4 abnormal values in

										diagnostic OGTT or overt diabetes during pregnancy, 2h blood glucose in diagnostic OGTT 11/7mmol/L, gestational age at diagnosis, pre-pregnancy BMI. Accumulates to 49.3% risk of diabetes in GDM women

Albareda (3)	Prospective	Spain	262/50-g, 1h glucose challenge test	66	**NR**	**NR**	**NR**	5 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Logistic regression: Metabolic syndrome significantly associated with all independent variables age, GDM/control status, obesity were independent variables. Second model included HOMA-IR, insulin

										secretion and resistance
Banerjee 2012	Prospective	UK	8/75g OGTT at 28 weeks pregnancy - WHO defined GDM (Fasting glucose >7mmol/L or 2h >7.8 mmol/L)	8	**NR**	**NR**	**NR**	2 years	Blood Pressure BMI Serum Lipids Blood glucose	BMI directly correlated with arterial stiffness, inversely related to maximum endothelium dependant and independent dilation
Bently Lewis 2015*	Cohort	USA	96/ Carpenter Coustan criteria	96	Normal GT: 3455±464, GDM:3571±525	Nulliparous: GDM: 245 (47.0). Multiparous GDM: 273 (52.4)	≥37 weeks	4.1 years	Blood Pressure BMI Serum Lipids	**NR**

Bently Lewis 2016^^*	Cohort	USA	51/ Carpenter Coustan criteria	1810	Same as 2015	Same as 2015	≥37 weeks	4.1 years	Blood Pressure BMI	Risk of essential hypertension higher in women with GDM adjusted for demographic (age, race gravidity, parity) + clinical features (SBP, BMI, GWG, BW and GA percentile) + SES (smoking status, breastfeeding

										as discharge, marital status, education years)
Cocilovo 1990	Cohort	Italy	41/ 3h OGTT O'Sullivan criteria.	25	**NR**	**NR**	**NR**	1 year	BMI	**NR**
Davenport 201	Prospective	Canada	10/ Canadian Diabetes Association	10	**NR**	**NR**	**NR**	2 months postpartum	Blood Pressure BMI Serum Lipids	**NR**
Davis 1999	Cross-sectional	USA	21/medical records	39	**NR**	**NR**	**NR**	3-18 months	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	MANOVA 2: Insulin and metabolic syndrome variables - all significant adjusting for glucose sum, triglycerides,

										BMI and diastolic BP. MACOVA: Insulin metabolic variables, significant for glucose, triglycerides, BMI and diastolic blood pressure
Demir 2016	Cohort study	Turkey	80/Carpenter Coustan criteria;	40	**NR**	**NR**	**NR**	**3-4 years**	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Eroglu 2006	Prospective	Turkey	36/ 3h 100g OGTT	33	3308±401/ 3334±373	1.3±0.7/ 1.4±0.	**NR**	10–15 months after delivery	BMI Serum Lipids	**NR**

			O'Sullivan and Mahan						Blood glucose Fasting plasma insulin	
Fakhrzadeh 2012	Retrospective	Iran	O'Sullivan and Mahan	20	**NR**	1.45±0.76/ 1.95 ± 1.05	**NR**	4 years	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Logistic regression -. Stratified analysis showed association of CVD with GDM was only seen among women with BMI > 25, but only women with BMI < 30 accounted for the increased risk.

Hakkariainen 2015**	Hospital register base cohort study	Finland	489/ Fasting, 1h, 2h capillary whole blood glucose values 4.8, 10.0 and 8.7mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1h and 2h respectively after Sept 2001	385	**NR**	**NR**	**NR**	≤5	BMI Blood glucose Fasting plasma insulin	**NR**

Hakkariaine n 2016**	Hospital register base cohort study	Finland	489/ Fasting, 1h, 2h capillary whole blood glucose values 4.8, 10.0 and 8.7mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1h and 2h respectively after Sept 2001	385	GDM (1) 3637±571, GDM (2) 3671±531/ Control: 3581±571	Primiparity (%): GDM (1) 35.9 (2) 37.9/ 54.7	Days: GDM (1) 278±10 (2) 278±10/ Control279±11	≤5	Blood Pressure BMI Serum Lipids Blood glucose	**NR**

Hu 1998	Cross-sectional	Sweden	17/ 75g OGTT capillary blood glucose > 9 mmol/UL	20	**NR**	**NR**	**NR**	2	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Kjos 1991	Prospective cohort	USA	6-12 weeks (n=1340), 1 year (n=157)/ NDDG (1979)	6-12 week (n=43) 1 year (n=36)	Not reported	3 (2)/ 3 (2)	Not reported	1	BMI Serum Lipids,	N/A
Kousta 2003	Retrospective	UK	34/ 75g-OGTT, WHO (1999)	44	**NR**	Median (IQR) 2 (1-3)/ 2 (1-3)	**NR**	2 years	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Krishnaveni 2007	Prospective cohort	India	35/ Diagnosis made based on Carpenter and Coustan criteria	489	**NR**	Parity 2+ :GDM: NGT: 1 (9%) IGT: 2 (18%) DM:3 (23%)	30 weeks	>5 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**

						No GDM: NGT:65 (16%) IGT:14 (19%)DM: 4 (50%)				
Levka 2015*	Prospective Cohort	Norway	50(IADPSG) and 31 (WHO) /IADPSG and WHO 1999	234 (IADPSG) and 253 (WHO)	Mean (SD): IADPSG: 3832 (530)/ 3588 (502) WHO: 3740 (455)/ 3640 (520)	Primipara (%) IADPSG: 44%/60% WHO: 60.0%/48.6	Median (IQR): IADPSG: 40.4 (39.0-41.3)/ 40.4 (39.3-41.1)	5	Blood Pressure Serum Lipids	Adjusted p-value for age, smoking frequency and BMI HDL-C (mmol/L) **p=0.058** LDL-C (mmol/L) p=0.405 TG (mmol/L) p=0.261 Multivariate

										analysis: Pulse Wave Velocity at 5 years is associated with age, GDM systolic blood pressure. TG/HDL-C ratio is associated with BMI, GDM status, SBP
Levka 2016*	Prospective Cohort	Norway	50(IADPSG) and 31 (WHO) /IADPSG and WHO 1999	234 (IADPSG) and 253 (WHO)	**NR**	IADPSG: 6 (12.0)/26 (11.1) WHO: 6 (19.3)/26 (10.3)	**NR**	5	Blood Pressure BMI	**NR**

Levka 2017*	Prospective Cohort	Norway	50(IADPSG) and 31 (WHO) /IADPSG and WHO 1999	234 (IADPSG) and 253 (WHO)	**NR**	IADPSG: 6 (12.0)/26 (11.1) WHO: 6 (19.3)/26 (10.3)	**NR**	**5**	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Univariate analysis showed LDL at 5 years postpartum negatively associated with insulin sensitivity and resistance, b-cell function
Lim 2007	Cohort	Korea	81/ Third International Workshop-Conference on GDM	**17**	**NR**	**NR**	**NR**	1 year	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	

Madarasz 2009	Retrospective	Hungary	68/WHO 1985	39	**NR**	**NR**	**NR**	**3.5**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Adjusted p-value specified for age and BMI: Systolic blood pressure p= 0.40 Diastolic blood pressure **p=0.017** HDL-C: p=0.68 LDL-C: p=0.18
Magenheim (2010) - Abstract	Prospective	Germany	66/Not specified	26	**NR**	Cases with Normal Glucose: 2.5 ± 1.4, Cases with IGT: 2.7 ± 1.3	**NR**	38.2(5.4)	BMI	**NR**

						Control 2.3 ± 1.2,				
Mai 2014	Case-control	China	190/ ADA 2004	80	**NR**	*Mean (SD)* 2.5 (1.8)/2.6 (1.9)	**NR**	2.5	Blood Pressure Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Noctor 2015**	Prospective Cohort study (Based on Noctor 2013)	Ireland	265/ modified WHO 1999 (based on Noctor 2016)	378	**NR**	**NR**	**NR**	≤3	Blood Pressure BMI Serum Lipids Blood glucose	BMI > 30, first degree relative with GDM, macrosomic baby in previous pregnancy associated with GDM

Noctor 2016**	Prospective Cohort study (Based on Noctor 2013)	Ireland	270/WHO 1999	388	**NR**	**NR**	**NR**	≤3	Blood Pressure BMI Serum Lipids Blood glucose	Abnormal glucose tolerance at any time 5 years postpartum associated with fasting glucose, 1-h glucose values on pregnancy OGTT, and family history of diabetes. BMI >30 at follow-up associated with abnormal

										glucose tolerance
Ozuguz 2011	Prospective case control	Turkey	61/Carpenter and Coustan (1982)	40	**NR**	*Mean (SD)* 2.63 (1.36)/ 2.64 (1.13)	*Mean (SD)* 26.23 (1.73)/26.54 (1.81)	1	Serum Lipids Blood glucose Fasting plasma insulin	
Perrson 2015	Retrospective	Sweden	111/Not reported	333	**NR**	*Mean (SD)* 1.3 (0.8)/1.3 (1.3)	**NR**	4	BMI	**NR**
Pimenta 2004	Prospective	Brazil	20/ NDDG (1979)	20	**NR**	Median (IQR): 2 (1)/ 2 (2)	**NR**	5	Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Prikoszovic h 2011	Retrospective	Austria	23/Fourth Workshop Conference of Gestational Diabetes	8	**NR**	**NR**	**NR**	3 to 5	BMI Serum Lipids Blood glucose Fasting plasma insulin	Adjustment for Body Fat Mass attenuated after adjusting for HDL-C in pGDM

										compared to control
Rauito 2014	Multicentre Prospective cohort	Finland	115/Medical records	150	**NR**	**NR**	**NR**	**1**	Blood Pressure BMI Serum Lipids	Adjusted p-value for age, outcome variable and BMI at baseline
Retnakaran 2010*	Observational Study	Canada	107/NDDG (1979)	Not reported	**NR**	**NR**	**NR**	3 months	Blood Pressure BMI Blood glucose	Area under curve associated with total cholesterol, LDL, HDL, triglycerides in adjusted model for age ethnicity and

										diabetes history
Ruksasakul 2016	Case control	Thailand	56/Carpenter and Coustan (2007)	51	**NR**	**NR**	**NR**	≤3	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Metabolic syndrome associated significantly with BMI >25 and age > 35, but not previous GDM
Ryan 1995	Cross-sectional	Canada	14/ Hospital based definition	14	**NR**	**NR**	**NR**	≤4.9	BMI Blood glucose	**NR**
Shen 2018	Observational Study	China	1263/WHO 1999	705	**NR**	**NR**	**NR**	3	BMI Blood Glucose	pGDM women have 13.fold multivariable adjusted risk for diabetes

Sokup 2012^	Prospective cohort	Poland	85/ WHO 1999	40	**NR**	**NR**	**NR**	2-24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	Adjusted p-values for BMI reported
Sokup 2012^	Prospective cohort	**Poland**	125/WHO 1999	40	**NR**	**NR**	**NR**	2-24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	hsCRP associated with BMI, serum e-selectin associated with TG, Serum TC and HDL associated with LDL
Stuebe 2011	Longitudinal cohort	USA	16/ Carpenter and Coustan	461	**NR**	*(n=)*GDM P1= 7; P2= 6, P3= 3/ CON:	**NR**	3	BMI Serum Lipids	Adjusted analyses performed for

						P1=131; P2=227; P3+= 112			Blood glucose Fasting plasma insulin	age, parity, race, parental history of diabetes and maternal BMI at 3 years postpartum
Verma 2002	Prospective cohort	USA	58/Carpenter and Coustan modification of NDDG	51	**NR**	P1 (n=) 42/49 P2 (n=) 64/52 >= P3 (n=) 23 (22)/16 (16)	**NR**	4 to 5	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Risk of developing MetS in subsequent 2 years was 26 times higher in women with GDM with PPO (cumulative HR: 1.3) compared to controls

										without PPO (cumulative HR: 0.05)
Vigneault 2015	Retrospective	Canada	216/Medical Records	83	**NR**	Normal Weight *(Mean (SD))* 2.14 (0.89)/2.12 (0.13) Overweight 1.93 (0.11)/2.38 (0.17) Obese: 3.57 (0.25)/2.85 (0.51)	**NR**	≤4	BMI Blood glucose Fasting plasma insulin	**NR**

Vilmi-Kerala 2016	Cross-sectional	Finland	120/ Finnish Current Guidelines (2013)	120	**NR**	Nulliparous: (GDM 23 (19.2%)/CON: 23 (19.2%)	**NR**	≤4	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Previous GDM is not an important influencing factor for the primary outcome measurements in study.
Wang 2015	Cross-sectional	China	48/ ADA (2013)	48	**NR**	**NR**	**NR**	**1**	Blood Pressure BMI Serum Lipids	**NR**
Winhofer 2013* (1)	Prospective Longitudinal Follow-Up	Austria	62/ ADA (based on Tura 2008)	10	**NR**	**NR**	**NR**	5	Blood Pressure BMI Serum Lipids	pGDM group had increased waist circumference , HBA1C and increased fasting glucose

										but was attenuated after adjusting for BMI (Values not shown)
Winhofer 2013 abstract* (1)	Longitudinal Follow-Up	Austria	43/ADA (based on Tura 2008)	10	**NR**	**NR**	**NR**	5	HDL-C (mg/dl),	**NR**
Winhofer 2014* (1)	Prospective longitudinal follow-up	Austria	45/ (ADA based on Tura 2008)	18	**NR**	**NR**	**NR**	5	BMI Blood Glucose	**NR**
Winzer 2004 (1)	Cross sectional	Austria	89/4th Workshop Conference of Gestational Diabetes	19	**NR**	**NR**	**NR**	1	BMI Serum Lipids Blood glucose Fasting plasma insulin	Fasting glucose adjusted Mean: 89.00/82.33 - adjusted for waist

										circumference Mean: 89.93/81.36 - adjusted for body fat mass
Xiang 2012	Abstract Longitudinal	USA	76/Based on medical records (Watanabe 2007)	88	**NR**	**NR**	**NR**	≤5	BMI	Plasma glucose and insulin not significantly different between GDM and controls for adjusted values (Adjusted age, age at first pregnancy, baseline percentage

										body fat, baseline calorie intake and physical activity, additional pregnancy).
Xiong 2013	Case control	USA	19/ACOG	20	**NR**	Nulliparous *(n=)*: 2 (10.5%)/ 4(20%) Multiparous(n=): 17 (89.5%) 16 (80.0%)	**NR**	1.9	Blood glucose Fasting plasma insulin	**NR**
Xiang 2013	Observational longitudinal	USA	93/ Based on medical records	142	**NR**	*Mean (SD)* 3.1(1.3)/2.9 (1.2)	**NR**	>10	BMI Fasting plasma glucose	**NR**

									Fasting plasma insulin	
5-10 years postpartum										
Ajala 2011 (abstract)	Cohort	UK	n=95/ GDM diagnosis not specified	Not specified (total n=95)	**NR**	**NR**	**NR**	10	Blood Pressure BMI Serum Lipids	**NR**
Ajala 2015	Cohort	Canada	90/ Canadian Diabetes Association	59	**NR**	**NR**	**NR**	4 to 10 year	BMI Serum Lipids Blood glucose	After controlling for adiposity, BP, lipids, CRP glycaemic status did not contribute to vascular function.
Benjamin 1993	Case-control	India	47/O'Sullivan and Mahan	47	**NR**	*Mean:* GDM, 3.2 Non GDM: 3.4	**NR**	9 years	BMI	**NR**

Bian 2000	Retrospective	China	45/ >2 abnormal FPG > 5.8 mmol/L, at 1 hour > 10.6 mmol/L, at 2 hours > 9.2 mmol/L, at 3 hours > 8. 1 mmol/L.	**39**	**NR**	**NR**	**NR**	5-10 years	Rate of T2DM	T2DM is higher in GDM women with antepartum BMI < 25kgm/2 and >25kg/m2
Bo 2007	Cohort	Italy	82/ 50g GCT Carpenter and Coustan	113	**NR**	*Mean:* Control: 1.6 GDM: 1.9	**NR**	6.5year	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Multiple regression analysis showed e-selectin, ICAM-1, IL-6 and hsCRP associated with Mean IMT

										after adjustment for BMI, waist circumference, blood pressure and blood glucose
Caliskan 2014	Case-control	Turkey	62/ Medical history	33	**NR**	**NR**	**NR**	6 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Carotid intima medial thickness (cIMT), total cholesterol, BMI, HBA1C, and HOMA-IR independently correlated with epicardial fat thickness

Da 2016 (Abstract)	Retrospective	Poland	199/ Based on OGTT values (not specified further)	50	**NR**	**NR**	**NR**	5-12 years	BMI Serum Lipids Blood glucose	**NR**
Donhorst 1990	Cohort	UK	56/ modification of O'Sullivan and Mahan	23	**NR**	Recurrent GDM:1-4. Known diabetics DM:2-8, IGT:2-6, NGT:1-5	**NR**	6-12 years	BMI	**NR**
Ferraz 2007	Cohort	Brazil	70/ 75-g OGTT, (WHO)	108	**NR**	**NR**	**NR**	6.2 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Average of CRP levels were statistically high in subjects with previous GDM and abdominal

										obesity and elevated fasting glucose.
Hakkariainen 2015**	Hospital register base cohort study	Finland	489/ Fasting, 1h, 2h capillary whole blood glucose values 4.8, 10.0 and 8.7mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1h and 2h	385	**NR**	**NR**	**NR**	≤5	BMI Blood glucose Fasting plasma insulin	**NR**

			respectively after Sept 2001							
Hakkariaine n 2016**	Hospital register base cohort study	Finland	489/ Fasting, 1h, 2h capillary whole blood glucose values 4.8, 10.0 and 8.7mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1h and 2h respectively after Sept 2001	385	*Mean (SD)* GDM (1) 3637±571, GDM (2) 3671±531/ 3581±571	Primiparity (%): GDM (1) 35.9 (2) 37.9/ 54.7	Days: GDM (1) 278±10 (2) 278±10/ 279±11	≤5	Blood Pressure BMI Serum Lipids Blood glucose	**NR**

Hunger Dathe 2006	Cohort	Germany	132/medical history	50	**NR**	**NR**	**NR**	6 years	Blood Pressure BMI Blood glucose	**NR**
Lauenborg 2005	Long term follow-up	Denmark	481/Based on 3h 75g OGTT - Damm *et al.* (1993)	1,000	**NR**	**NR**	*Median (IQR)* 227 (197-249)/ 227 (197-249)	9.8	Blood Pressure BMI Fasting plasma insulin	**NR**
Meier (2005).	Case-control/experimental	Germany	15/ OGTT based on fasting glucose	**20**	*Mean (SD)* 3,615±661/ 3,165±289	**NR**	26±6 (mean±SD).	4.1±6.5	Blood pressure Blood glucose	Multivariate analysis adjusted for age and BMI
Modela 2016*	Retrospective cohort study	Poland	199/OGTT	50	**NR**	**NR**	Not reported	**7**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**

Osei 1998	Case-control	USA	15/ O'Sullivan criteria adapted by NDDG	15	Not reported	Parity similar between groups	**NR**	7	BMI Blood glucose Fasting plasma insulin	**NR**
Pimenta 2004	Prospective	Brazil	20/NDDG (1979)	20	Not reported	*Mean (SD):* 2(1)/2(2)	**NR**	5-8	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Ryan 2013	Case-control	USA	20/History confirmed by health care provider	26	**NR**	**NR**	**NR**	≤5	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Seghiri 2007	Retrospective	Italy	43/Carptenter and Coustan (1992)	22	**NR**	*Mean (SD):* 2 (1)/ 1.6 (0.8)	**NR**	7.5	BMI	**NR**

Sriharan 2002	Retrospective	Brazil	46/1999 WHO	50	**NR**	*Mean (SD):* 1.8 (2.2)/2.2 (1.8)	**NR**	6.8	Blood Pressure BMI Serum Lipids Blood glucose	Multiple logistic analysis adjusted for age, time from previous pregnancy, BMI, and family history of diabetes
Tam 2007*	Prospective cohort	Hong Kong	67/1999 WHO	136	*Mean (SD):* 3230 ± 485/3272 ± 429	Nulliparous (n=) 40/74	*Mean (SD):* 39.3 ± 2.1 /39.5 ± 1.6	8	Blood Pressure BMI Serum Lipids	Triglyceride in linear regression model adjusted for age, race, school years, metabolic syndrome

Tam 2012**	Prospective cohort	Hong Kong	94/WHO 1999	44	*Mean (SD):* 3230 (485)/ 3272(429)	**NR**	*Mean (SD):* 39.3 (2.1) /39.5 (1.6)	8	BMI Serum Lipids	**NR**
Tam 2013**	Prospective cohort	Hong Kong	94/WHO 1999	45	*Mean (SD):* 3230 (485)/ 3272(429)	**NR**	*Mean (SD):* 39.3 (2.1) /39.5 (1.6)	8	BMI Serum Lipids	Relative and absolute risk for subgroups of various glycaemic indices mid-gestation - adjusted for various factors
Tehrani 2012	Nested longitudinal case control study	Iran	29/WHO 1999	n=58 (Group 1) n=570 (Group 2)	**NR**	*Mean (SD)* 30.0 (1.7)/ Control 1 2.8 (1.5) Control 2 4.6 (2.3)	**NR**	9	Blood Pressure BMI Serum Lipids Blood glucose	Relative and absolute risk for subgroups of various glycaemic indices mid-

										gestation - adjusted for various factors
Tobias 2017	Prospective cohort analysis	USA	5292/Self-reported GDM (validated method)	84,187	**NR**	*Mean (SD)* 1.9 (1.2)/ 1.8 (1.1)	**NR**	6 to 8 ^	BMI	Adjusted analysis for baseline parameters
Tutino 2014	Nested Case Control - Abstract	Hong Kong	124/ Self-reported GDM	372	**NR**	**NR**	**NR**	8	Blood Glucose	Multivariable models for CVD risk: Adjusted for age, years since pregnancy, menopausal status, hormone use, white

										race/ethnicity, family history of MI, or stroke, history of pregnancy hypertensive disorders, BMI and parity
Verma 2002	Prospective cohort	USA	58/Carpenter and Coustan modification of NDDG	51	**NR**	P1 (n=) 42/49 P2 (n=) 64/52 >= P3 (n=) 23 (22)/16 (16)	**NR**	6, 7, 8, 9	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Wender-Ozegowska 2007	Prospective cohort	Poland	153/Hospital records	155	**NR**	**NR**	**NR**	6	Blood Pressure BMI Serum Lipids	**NR**
>10 years postpartum										

Behboudi-Gandevani 2019	Long term longitudinal follow-up	Iran	801/WHO (1998)	2594	**NR**	**NR**	**NR**	13 years	Serum Lipids	NA
Carr 2006	Cross-sectional	US	662/ Self-reported	332	**NR**	**NR**	**NR**	29.9 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	CVD and coronary heart disease specifically higher in women with prior GDM compared to no GDM. Adjusted for age, menopausal status and proband clustering.

Charwat-Resl 2017	Cross-sectional	Vienna	55/ WHO (1998)	32	**NR**	**NR**	*Mean (SD)* 16.2 ± 5.2/ 14.2 ± 4.8	16 years	Blood Pressure BMI Serum Lipids	**NR**
Gobl 2011 (1)	Prospective	Austria	120/ 75g OGTT, Fourth International Workshop conference on GDM	40	**NR**	**NR**	**NR**	10 years	Serum Lipids Blood Glucose	Fasting glucose, fasting insulin: Various models adjusted for age, age at first pregnancy, baseline percentage body fat baseline calorie intake and physical

										activity, % body fat and additional pregnancy during follow-up
Gobl 2014 (1)	Cross-sectional	Austria	108/75g OGTT, Fourth International Workshop conference on GDM	41	**NR**	**NR**	**NR**	10 years	BMI	2-hour OGTT >140mg/dL, age >35 and HDL cholesterol <50mg/dL were best predictors of metabolic syndrome up to 10 years follow-up

Gobl 2014 (1)	Cross-sectional, prospective	Austria	77/75g OGTT, Fourth International Workshop conference on GDM	41	**NR**	**NR**	**NR**	10 years	BMI Fasting plasma insulin	Moderate associations of HbA1c with measurements of plasma glucose during the OGTT.
Gunderson 2014^	Longitudinal observational study	Canada	119/ Self-reported GDM: confirmed by OGTT results from prenatal records to match definition by Diabetes Care 1997	364	**NR**	*Mean (SD):* 2.3 (0.95)/ 2.2 (1.1)	**NR**	20	Blood Pressure BMI Serum Lipids Blood glucose	Adjusted and unadjusted mean (95% CI) for cIMT by GDM history stratified by women with diabetes or metabolic syndrome. No significant

										differences seen in adjusted models.
Hakkariainen 2015** [87]	Hospital register base cohort study	Finland	489/ abnormal fasting, 1h, 2h capillary whole blood glucose values 4,8, 10.0 and 8.7mmol/l respectively (Until Sept 2001) Values changed to 11.2 and 9.9mmol/l for 1h and 2h	385	**NR**	**NR**	**NR**	≤5	BMI Blood glucose Fasting plasma insulin	**NR**

			respectively after Sept 2001							
Hakkariainen 2016** [88]	Hospital register base cohort study	Finland	489/ Fasting, 1h, 2h capillary whole blood glucose values 4.8, 10.0 and 8.7mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1h and 2h respectively after Sept 20019.9mmol/l	385	GDM (1) 3637±571, GDM (2) 3671±531/ 3581±571	Primiparity (%): GDM (1) 35.9 (2) 37.9/ 54.7	Days: GDM (1) 278±10 (2) 278±10/ 279±11	≤5	Blood Pressure BMI Serum Lipids Blood glucose	**NR**

			for 1h and 2h respectively after Sept 2001							
Heida 2015 [89]	Prospective cohort study	Dutch	1089/ Self-reported questionnaire	15,560	**NR**	No of pregnancy: 1: Not exposed: 1781 (11.5) HDP: 572 (9.3)GDM: 106 (9.7). 2: 5977 (38.4) 2226 (36.2) 360 (33.1), 3/>:7802 (50.1) 3359 (54.5) 623 (57.2)	**NR**	Mean 29 years since index pregnancy	Blood Pressure Serum Lipids	GDM associated with increased OR of having CVD, IHD, stroke or T2D. Model III adjusted for cohort, HDP, age, BMI, current smoking and alcohol consumption at study enrolment,

										total cholesterol/HDL ratio, prevalent hypertension, and T2D (for stroke, IHD and CVD outcomes only).
King 2009	Case-control	USA	20/Self-report of having GDM and OGTT	20	**NR**	GDM: 2.45 (0.9) No GDM: 2.25(0.6)	**NR**	15 years (based on child's index age)	BMI Blood Pressure Serum Lipids	Adjusted results shown for age, current use of estrogen, BMI before first child, current BMI

Lee 2007)	Retrospective	Australia	5,740/ 75g OGTT and 50g OGTT. FPG: 5.5 mmol/l and/or a 2h plasma glucose> 8.0 mmol/	783	**NR**	GDM: 2 (2–3) Control :3 (2–3),	GDM 38.4 (2.7) Control39.2 (3.4)	15 years	BMI, fasting glucose	**NR**
Linne 2002	Retrospective	Stockholm	28/ 2- hour oral glucose tolerance test (OGTT) with 75 g glucose, 2h value over >9.0mmol/L	52	**NR**	**NR**	**NR**	15 years	BMI	**NR**
Minoee 2017^	Prospective population follow-up	Iran	476/ WHO (1998)	1982	**NR**	Mean (SD): 2.7 ±	**NR**	15	Blood Pressure BMI Blood glucose	T2DM progression is 2.15-fold

						1.45/2.25 ± 1.24				higher in GDM women than controls after adjustment for age, BMI and family history of diabetes.
Minoee 2017^	Prospective population follow-up	Iran	476/ WHO (1998)	1982	**NR**	Mean (SD): 2.7 ± 1.45/2.25 ± 1.24	**NR**	15	Serum Lipids	**NR**
Pirkola 2010	Population based study	Finland	124/ 2h 75g OGTT one abnormal value - Fasting > 5.5mmol/l, 1h	5342	**NR**	**NR**	**NR**	20	BMI	GDM causes increased risk of diabetes in normal weight and overweight women, and hypertension in

			>11.0mmol/ 2h > 8mmol/l							women who are overweight pre-pregnancy. In women with normal OGTT during pregnancy, hypertension and diabetes risk didn't differ between GDM women compared to women with no risk factors for GDM
Tam 2012^	Prospective follow-up	Hong Kong	45/ WHO 1999 (Tam 2007)	94	**NR**	P1 (n=) 10/9, >=P2 (n=)84/36	**NR**	15	Total cholesterol (mmol/L)	Insulin sensitivity indices are

										independent predictors of diabetes and metabolic syndrome at 15 years postpartum even with adjustment for b-cell function or abnormal glucose tolerance status at 8 years postpartum. History of GDM at index pregnancy

										increased the odds of progression to abnormal glucose tolerance, T2DM and hypertension.
Tam 2013^^	Prospective follow-up	Hong Kong	67/WHO 1999	136	Baseline: Mean (SD): 3230 (485)/ 3272(429)	**NR**	Mean (SD): 39.3 (2.1) /39.5 (1.6)	15	BMI Serum Lipids	All glycaemic indices were predicative of abnormal glucose tolerance, diabetes mellitus and hypertension, but 2-h plasma glucose and

										glucose challenge tolerance are predictive of hypertension at 8 and 15 years postpartum. Metabolic syndrome at 15 years postpartum risk predicted by fasting plasma glucose
Verma 2002	Longitudinal follow-up study	USA	58/Carpenter and Coustan	51	**NR**	P1 (n=) 42/49 P2 (n=) 64/52	**NR**	11	Blood Pressure BMI Serum Lipids	Fasting plasma glucose risk adjusted for

			modification of NDDG			>= P3 (n=) 23 (22)/16 (16)			Blood glucose Fasting plasma insulin	maternal age, BMI at booking, AGT at 8 years, familial history of DM, gestational hypertension, preeclampsia during index pregnancy and subsequent term pregnancy (n=)
Wang 2012	Longitudinal database	USA	1142/ICD-9	18,856	**NR**	Parity > 1: GDM 53.5%/Non GDM: 36.1%	**NR**	13-50	Blood Pressure BMI	Metabolic syndrome increased in women with

										GDM with increasing age.
Winhofer 2014 (1)	Prospective follow-up	Austria	35/4th Workshop Conference of Gestational Diabetes (Based on Winzer 2004)	14	**NR**	**NR**	**NR**	10	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Xiang 2013	Observational longitudinal	USA	93/ Based on medical records	142	**NR**	Mean (SD) 3.1(1.3)/2.9 (1.2)	**NR**	>10	BMI Blood glucose Fasting plasma insulin	**NR**
No specified postpartum follow-up										
Couch 1998	Cross-sectional	Ohio	20/ O'Sullivan and NDDG criteria used	20	**NR**	**NR**	**NR**	**NR**	Serum Lipids	**NR**

Gadgil 2017	Cross-sectional	USA	13/ Self-reported	13	**NR**	GDM: 2.2 (0.6), no GDM:2.1 (0.8)	**NR**	**NR**	Blood Pressure BMI Serum Lipids	Adjustment for age and weight at 40. Women with GDM history have 3.3-fold increased risk of having diabetes
Gunderson 2010	Longitudinal observational	Canada	154/ Self-reported confirmed with OGTT	1,655	**NR**	**NR**	**NR**	**NR**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Pre-pregnancy cardiometaboli c risk factors adjusted for familial diabetes parity at conception, births during interval, time to first

										conception, smoking age at preconception examination and race
Han 2018	Retrospective cohort study	South Korea	4,970/ diagnosed based on ICD-10 codes	97,930	**NR**	**NR**	**NR**	**NR**	BMI Blood Glucose	NA
Shostrom 2017	Population base study	USA	555/Self-reported	7,572	**NR**	**NR**	**NR**	**NR**	BMI	GDM is associated with higher risk of CVD compared to women without CVD as a reference for all models (Adjusted for

										age, race/ethnicity, education, family income-poverty ratio, smoking/drinking, physical activity, total energy, BMI).
Simmons 2017	Follow-up study	New Zealand	52/ Self-reported	2582	**NR**	**NR**	**NR**	**NR**	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Thomann 2008[90]	Case control	Switzerland	18/ ADA (2004)	19	**NR**	**NR**	**NR**	**NR**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Difference shown between groups in fat distribution, estimates of

										insulin resistance, serum levels of lipids and parameters of low-grade chronic inflammation after adjusting for age and percent body fat.

Abbreviations = OGTT = oral glucose tolerance test, GCT = glucose challenge test, OGCT = oral glucose tolerance test. FPG: Fasting plasma glucose. BMI (body mass index), SBP (Systolic blood pressure), DBP (diastolic blood pressure), TC (total cholesterol), HDL (high density lipoprotein-cholesterol), LDL (low density lipoprotein-cholesterol), TG (triglycerides)

ADA: American Diabetes Association, ADIPS: Australian Diabetes in Pregnancy Society, IADPSG – International Association of Diabetes in Pregnancy Society

(+)BMI kg/m2, SBP/DBP mmHg units , all other units specified each study

Lipids collectively refers to study including total cholesterol, HDL, LDL and triglycerides.

a - abstract

*** - papers of same author are the same study**

**** - paper looked at two different time points**

(1) Studies with this subscript part of the same cohort but Winzer 2004 was used in overall meta-analysis ,Winzer <1 year postpartum, Winhofer +10 years

(2) Studies with this subscript part of the same cohort but Bozkurt 2012 used in overall meta-analysis and <1-year postpartum subgroup

Table 3.5.1-2 Findings of meta-analyses

Outcome	**Odds Ratio MD/SMD**	**95% CI**	**n= (studies)**	**n= (GDM/control)**	**n= (total)**	**Heterogeneity**
Systolic Blood Pressure (mmHg)	**MD 2.47**	**1.74, 3.40**	48	7,332/42,786	50,118	I^2 = 79% P< 0.00001
Diastolic Blood Pressure (mmHg)	**MD 1.89**	**1.32, 2.46**	48	7,025/42,470	49,495	I^2 = 83% P< 0.00001
BMI (kg/m^2)	**MD 1.54**	**1.17, 1.91**	78	26,689/ 228,619	255,308	I^2 = 97% P< 0.00001
Total cholesterol (SMD)	**SMD 0.26**	**0.15, 0.37**	48	6,817/31,744	38,561	I^2 = 89% P< 0.00001

Low density Lipoprotein (SMD)	**SMD 0.19**	**0.08, 0.30**	44	5,846/11,134	16,980	I^2 = 83% P< 0.00001
High density lipoprotein (SMD)	**SMD -0.28**	**-0.39, -0.16**	56	7,203/28,679	35,882	I^2 = 89% P< 0.00001
Triglycerides (SMD)	**SMD 0.56**	**0.42, 0.70**	45	4,110/9,065	13,175	I^2 = 88% P< 0.00001
Glucose (SMD)	**SMD 0.69**	**0.56, 0.81**	55	17,180/110,720	127,900	I^2 = 94% P< 0.00001
Insulin (SMD)	**SMD 0.41**	**0.23, 0.59**	32	2,994/5,887	8,881	I^2 = 90% P< 0.00001

Abbreviations: MD – mean difference, 95% CI – 95% Confidence Interval

Bold MD (95% CI) highlights significant result

3.5.2. Blood Pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) data were available from 60 studies, of which 48 were included in the overall meta-analysis. Quantitative summary measures showed that women with previous GDM have 2.47 mmHg (95% CI 1.74 to 3.40) higher mean SBP compared to controls (n (total)=50,118; heterogeneity: Chi^2 P<0.00001, I^2=80%) (Table 3.5.1-1) (Supplementary Figure 3.8 1)[88-130]. Of the 12 studies with data not included in the meta-analysis[126, 131-141], eight reported higher SBP in women with previous GDM compared to the control group[126, 131-134, 137, 138, 141], with five studies showing statistical significance[126, 131, 134, 138, 140] (Supplementary Table 3.8.1). Sensitivity analysis after excluding the low-quality studies showed a marginal increase in heterogeneity (Chi^2 P< 0.00001, I^2=82%). (Supplementary Table 3.8.3)

Women with previous GDM have 1.89 mmHg (95% CI 1.32 to 2.46) higher DBP compared to women without previous GDM (n=49,495, heterogeneity: Chi^2 P<0.00001, I^2=83%) (Table 3.5.1-1) (Supplementary Figure 3.8.2)[88-130]. Of the 12 studies not included in the meta-analysis[77, 126, 131-141], six reported higher DBP in women with previous GDM compared to the control group[126, 131, 132, 134, 137], with three studies showing statistical significance [131, 134, 135]. Sensitivity analysis after excluding low quality studies showed a marginal increase in heterogeneity (Chi^2 P<0.00001, I^2=85%). (Supplementary Table 3.8.4)

3.5.3. Body Mass Index

Body Mass Index (BMI) data were available from 102 studies, of which 78 were included in the overall meta-analysis. BMI was 1.54kg/m^2 higher in women with previous GDM compared to women without previous GDM (95% CI 1.17 to 1.91; n=255,308, heterogeneity: Chi^2 P<0.00001, I^2=97%)[90, 91, 93, 95-97, 99, 100, 102, 103, 105, 106,

[113, 114, 116-118, 120, 121, 123-127, 129, 130, 132, 142-178] (Table 3.5.1-1) (Supplementary Figure 3.8.3). Of the 24 studies not included in the meta-analysis[112, 126, 131, 133-135, 137-141, 174, 179-191], 12 studies reported that women with previous GDM had significantly higher BMI or were more obese than women without previous GDM[112, 126, 134, 135, 138, 140, 141, 143, 174, 180, 182-185, 188-191] (Supplementary Table 3.8.1). Sensitivity analysis after excluding low quality studies showed a decrease in heterogeneity (Chi^2 P<0.00001, I^2=95%) (Supplementary Table 3.8.5)

3.5.4. Lipids

3.5.4.1. Total Cholesterol

Total cholesterol data were available from 59 studies, 48 studies were included in the overall meta-analysis. Women with previous GDM had 0.26 SMD higher total cholesterol compared to women without previous GDM, (95% CI 0.15 to 0.37; n=38,561, heterogeneity: Chi^2 P<0.00001, I^2=89%)[89, 91, 93, 96, 97, 99-102, 106, 108, 110, 111, 113, 116, 117, 119, 121, 122, 124, 126, 127, 129, 130, 138, 143, 144, 149, 151, 152, 160, 171, 174, 175, 192-196] (Table 3.5.1-1) (Supplementary Figure 3.8.4). Of the 11 studies not included in the meta-analysis[126, 131, 133, 134, 139, 148, 174, 187, 189, 190, 197], three reported that women with previous GDM had significantly higher total cholesterol compared to the control group[126, 174, 190]. Sensitivity analysis after excluding low quality studies showed a marginal increase in heterogeneity (Chi^2 P<0.00001, I^2=90%). (Supplementary Table 3.8.6)

3.5.4.2. LDL

Low density lipoprotein (LDL) cholesterol data were available from 57 studies, of which 44 were included in the overall meta-analysis. Women with previous GDM had 0.19 SMD higher LDL compared to women without previous GDM (95% CI 0.08 to 0.30; n=16,980, heterogeneity: Chi^2 P<0.00001, I^2=83%)(Table 3.5.1-1)

(Supplementary Figure 3.8.5). [81, 91, 92, 95-97, 99-102, 105, 106, 108, 111-114, 116-120, 122, 124, 126, 128, 130, 132, 138, 142, 144, 149, 152, 160, 171, 174, 192, 194-196, 198]. Of the 13 studies not included in the meta-analysis [126, 131, 133, 136, 139, 148, 174, 187, 189, 190, 196, 197, 199], four reported that women with previous GDM had significantly higher LDL compared to the control group[126, 136, 174, 190]. Sensitivity analysis after excluding low quality studies showed an increase in heterogeneity (Chi^2 P<0.00001, I^2=85%). (Supplementary Table 3.8.7)

3.5.4.3. HDL

High density lipoprotein (HDL) cholesterol data were available from 70 studies, of which 56 were included in the overall meta-analysis. Women with previous GDM had lower HDL compared to those without previous GDM, a -0.28 SMD (95% CI -0.39 to -0.16; n=35,882, heterogeneity: Chi^2 P<0.00001, I^2=89%)[88, 89, 92, 93, 95-97, 99-103, 106, 108, 110-114, 116-123, 126, 129, 132, 138, 144, 149, 151-153, 160, 161, 173-175, 192, 194-196] (Table 3.5.1-1) (Supplementary Figure 3.8.6). Of the 14 studies not included in the meta-analysis[109, 124, 126, 131, 133, 135, 136, 139, 148, 158, 174, 187, 189, 196], five reported that women with previous GDM had significantly lower HDL than the control group[91, 126, 135, 189, 190, 196]. Sensitivity analysis after excluding low quality studies showed a marginal increase in heterogeneity (Chi^2 P<0.0001, I^2=90%). (Supplementary Table 3.8.8)

3.5.4.4. Triglycerides

Triglyceride data were available from 64 studies, of which 45 were included in the overall meta-analysis. Women with previous GDM had 0.56 SMD higher triglycerides compared to those without previous GDM (95% CI 0.42 to 0.70; n=13,175, heterogeneity: Chi^2 p<0.00001, I^2=88%)[88, 91-93, 96, 97, 99-102, 106, 110, 111, 114, 116, 117, 119-122, 129, 132, 142, 144, 146, 149, 151-153, 160, 161, 173-175, 177, 192, 194] (Table 3.5.1-1) (Supplementary Figure 3.8.7). Of the 19 studies not included in the meta-analysis [90,

[109, 126, 131, 133-136, 139, 148, 171, 174, 187, 189, 190, 195-197], seven studies reported that women with previous GDM had significantly higher triglycerides than those without previous GDM[90, 126, 135, 174, 182, 189, 190]. Sensitivity analysis after excluding low quality studies showed no difference in heterogeneity (Chi^2 P<0.00001, I^2=88%). (Supplementary Table 3.8.9)

3.5.5. Blood glucose

Blood glucose data were available from 72 studies, of which 55 were included in the overall meta-analysis. Women with previous GDM had 0.69 SMD higher blood glucose compared to those without previous GDM (95% CI 0.56 to 0.81; n=127,900, heterogeneity: Chi^2 P<0.00001, I^2=94%) [81, 88, 90, 93, 95-97, 99, 101, 102, 105-108, 110, 111, 113, 116-124, 126-128, 130, 142, 145, 146, 149, 151, 153, 154, 157, 159, 166, 169, 175, 192-195, 198, 200-203](Table 3.5.1-1) (Supplementary Figure 3.8.8). Of the 17 studies not included in the meta-analysis[109, 112, 126, 131, 133-135, 137, 152, 165, 180, 187, 189, 190, 196, 204, 205], 10 studies reported that women with previous GDM had significantly higher glucose than those without previous GDM[109, 126, 131, 135, 138, 189, 190, 196, 204, 205]. Sensitivity analysis after excluding low quality studies showed no difference in heterogeneity (Chi^2 P<0.00001, I^2=94%). (Supplementary Table 3.8.10)

3.5.6. Serum insulin

Serum insulin data were available from 44 studies, of which 32 were included in the overall meta-analysis. Women with previous GDM had 0.41 SMD higher insulin compared to those without previous GDM (95% CI 0.23 to 0.59; n=8,881, heterogeneity: Chi^2 P<0.00001, I^2=90%)[88, 92, 99, 101, 102, 106, 111, 113, 116, 120, 121, 127, 130, 144, 145, 149, 151, 159, 169, 173, 175, 192, 193, 198, 200-202]. (Table 3.5.1-1) (Supplementary Figure 3.8.9). Of the 12 studies not included in the meta-analysis[90, 97, 107, 112, 124, 126, 135, 138,

[160, 187, 189, 190], five studies reported that women with previous GDM had significantly higher glucose than those without previous GDM[97, 107, 112, 126, 135, 181]. Sensitivity analysis after excluding low quality studies showed no difference in heterogeneity (Chi^2 P<0.00001, I^2=90%). (Supplementary Table 3.8.11)

3.5.7. Subgroup analysis

We conducted subgroup analyses based on the time of postpartum follow up (<1 year postpartum, 1-5 years postpartum, 5-10 years postpartum and >10 years postpartum). The results are shown in Table 3. Systolic blood pressure, diastolic blood pressure, triglycerides and blood glucose were higher in women with previous GDM compared to those without previous GDM as early as <1 year postpartum. Triglycerides and blood glucose remained significantly elevated at 1-5 years, 5-10 years and >10 years postpartum (Table 3.5.7.1).

Table 3.5.7-1 Subgroup analysis for all cardiovascular outcomes in women with previous GDM compared to those with no previous GDM

Outcome	<1 year postpartum (95% CI)	1-5 years postpartum (95% CI)	5-10 years postpartum (95% CI)	>10 years postpartum (95% CI)
Systolic Blood Pressure (mmHg)	**3.47 (1.26-5.68)** n(total)=1,826 n=1,237 I^2= 50%, p=0.02	**2.26 (0.27, 4.25)** n(total)=19,701; n=2,567 I^2= 93%, p<0.00001	**3.96 (2.36, 5.56)** n(total)=1,965; n(exposed)=805 I^2= 17%, p=0.27	**2.58 (1.05, 4.11**) n(total)=4,941; n(exposed)=1,157 I^2= 23%, p=0.23
Diastolic Blood Pressure (mmHg)	**2.48 (0.58-4.37)** n(total)=1,749 n(exposed)= 1,137 I^2= 64%, p=0.01	**1.37 (0.20-2.54)** n(total)=19,676 n(exposed)=2,428 I^2= 89%, p<0.0001	7.17 (-1.69-16.03) n(total)=2,184 n(exposed)=916 I^2= 99%, p<0.00001	**1.23 (1.03-1.96)** n(total)=4,948 n(exposed)=1,122 I^2= 97%, p<0.00001
BMI (kg/m^2)	1.56 (-0.28-3.41) n(total)=2,534 n(exposed)=1,640 I^2= 98%, p<0.00001	**2.01 (1.24, 2.79)** n(total)=22,326; n(exposed)=,4,329 I^2= 96%, p<0.00001	**0.73 (0.22, 1.27)** n(total)=91,844 n(exposed)=6,161 I^2= 91%, p<0.00001	**1.39 (1.05, 1.73)** n(total)=13,989; n(exposed)=8,015 I^2= 0%, p=0.64

Total Cholesterol (SMD)	0.41 (-0.02,0.84) n(total)=1,722 n(exposed)=1,149 I^2= 84%, p<0.00001	**0.42 (0.21,0.64)** n(total)=3,836; n(exposed)=1,886 I^2= 86%, p<0.00001	0.04 (-0.13, 0.20) n(total)=907; n(exposed)=485 I^2= 24%, p=0.24	0.04 (-0.09, 0.17) n(total)=6,469; n(exposed)=1,555 I^2= 51%, p=0.02
LDL (SMD)	0.33 (0.06-0.60) n(total)=2,458 n(exposed)= 1,534 I^2= 84%, p<0.0001	0.25 (-0.05,0.55) n(total)=1,780 n(exposed)=1062 I^2= 87%, p<0.00001	0.05 (-0.08-0.19) n(total)=989 n(exposed)=520 I^2=0%, p=0.47	0.09 (-0.02, 0.19) n(total)=5,546 n(exposed)=1,383 I^2= 28%, p=0.10
HDL (SMD)	-0.18 (-0.23-0.59) n(total)=1,788 n(exposed)= 1,146 I^2= 87%, p=<0.00001	**-0.49 (-0.73, -0.24)** n(total)=4,506 n(exposed)=2,327 I^2= 92%, p<0.00001	-0.40 (-0.80-0.01) n(total)=2164 n(exposed)=810 I^2=93%, p=<0.00001	**-0.14 (-0.25, -0.03)** n(total)=6,805 n(exposed)=1,647 I^2= 49%, p=0.02
Triglycerides (SMD)	**0.53 (0.16-0.91)** n(total)=706 n(exposed)= 459 I^2= 76%, p<0.00001	**0.65 (0.42,0.89)** n(total)=4,334 n(exposed)=2,234 I^2= 90%, p<0.00001	**0.56 (0.04-1.08)** n(total)=1,086 n(exposed)=561 I^2=94%, p<0.00001	**0.31 (0.16, 0.46)** n(total)=3,520 n(exposed)=865 I^2= 53%, p-0.02
Glucose (SMD)	**1.12 (0.62,1.62)** n(total)=2,187	**0.67 (0.45, 0.90)** n(total)=6,233; n(exposed)=3,457 I^2= 92%, p<0.00001	**0.75 (0.20, 1.30)** n(total)=1,152	**0.58 (0.44, 0.72)** n(total)=8,807 n(exposed)=6,234 I^2= 62%, p=0.002

	n(exposed)=1,461 I^2= 93%, p<0.00001		n(exposed)=606 I^2= 94%, p<0.00001	
Insulin (SMD)	1.10 (-0.37, 2.57) n(total)=293 n(exposed)=191 I^2= 95%, p<0.00001	**0.53 (0.08-0.99)** n(total)=1762 n(exposed)=1,073 I^2= 94%, p<0.00001	**0.22 (0.06, 0.37)** n(total)=1,036 n(exposed)=542 I^2= 24%, p=0.24	**0.28 (0.07, 0.50)** n(total)=817 n(exposed)=308 I^2= 45%, p=0.10

Units as specified in above table

Abbreviations: 95% CI – 95% Confidence Interval

Bold value highlights significant result

3.6. Discussion

CVD is a global concern and contributes to the majority of deaths due to non-communicable disease (NCDs) (approximately 17.9 million deaths annually) [206]. Early detection, prevention and treatment of risk factors are critical in reducing the incidence of CVD. Pregnancy complications, such as preeclampsia and GDM are now identified as risk factors for NCDs including T2DM and CVD[78]. Women may be susceptible to long-life CVD, due to a genetic predisposition or poor lifestyle choices or a combination. Thus, pregnancy may act as a second hit for CVD in these women who already have a predisposition to metabolic syndrome, before phenotypic expression[78]. Furthermore, it is known that exposure to gestational diabetes mellitus *in utero* increases the risk of cardiovascular risk factors in offspring[207]. Therefore, we sought to determine the CVD risk factors and well as the timeline for manifestation of risk factors among women with previous GDM. Synthesizing the published evidence on conventional CVD risk factors in women with previous GDM and assessing the timeline for manifestation of risk factors, thus, provide strong evidence to plan screening strategies to identify those at risk for CVD. This review also signifies the importance of considering pregnancy complications in CVD risk stratification, thus providing an opportunity for primordial prevention. Women with previous GDM have an increase in all conventional CVD risk factors. Blood pressure (both systolic and diastolic), serum triglycerides and blood glucose are also higher in women with GDM compared to those without GDM as early as <1 year postpartum.

Our meta-analysis showed that women with previous GDM have an increase in systolic and diastolic blood pressure. It has been shown that GDM increases the risk of developing hypertension in different populations [185, 208, 209]. Daly *et al.* (2018) showed that the cumulative incidence of hypertension and ischemic heart disease was higher in women with previous GDM compared with controls, and that this difference persisted over a 25-year study period[183].

Our analysis showed that BMI was 1.57kg/m^2 higher in women with previous GDM compared to controls based on a sample size of nearly 300,000 women. While we do not know whether the women with previous GDM were obese prior to pregnancy and during pregnancy, it is likely the case for many of these women. A large scale meta-analysis showed that the unadjusted ORs of developing GDM were 2.14 (CI% 1.82 to 2.53), 3.56 (3.05-4.21) and 8.56 (5.07-16.04) for overweight, obese and severely obese women respectively, compared to normal weight pregnant women [210].Obese women have substantially higher liver fat content, and this is consistent with the impairment of fat sequestration by adipocytes in individuals developing GDM [7].

Women with previous GDM were also demonstrated to have higher total cholesterol, LDL, triglycerides and a decrease in HDL demonstrating an "at risk phenotype" compared to women without previous GDM. During the third trimester of pregnancy, women with GDM show an exaggerated elevation in serum lipids, and this may result in transient metabolic disease. [7, 211]. Studies have shown that triglycerides are significantly elevated in women with GDM compared to controls across each trimester. It has also been shown that elevated first trimester maternal triglyceride level (adjusted for BMI) is a strong predictor for future GDM [211]. Consistent with these finding, our study showed that triglycerides were elevated as early as <1 year postpartum.

We also observed a significant increase in glucose and insulin in women with previous GDM compared to controls. GDM results in a dysregulation of cytokines (particularly a reduction in adiponectin, and elevation in interleukin-6 and tumour necrosis factor-alpha) and an increase in free fatty acids which promote insulin resistance (IR) and a state of metabolic dysfunction [7]. The study by Daly *et al.* (2018) also showed that women with GDM are more likely to develop T2DM later in life over a 25-year period. In some populations, 50% of women with GDM progress to T2DM[212], and approximately one third of women with T2DM have had previous GDM[213].

This systematic review and meta-analyses are the first to observe all conventional CVD risk factors in women who experienced GDM. Our study provides robust evidence that women who experience GDM have an increase in all CVD risk factors compared to controls, based on evidence from 139 studies. Furthermore, subgroup analysis demonstrated that blood pressure, glucose and triglycerides are already elevated as early as <1 year postpartum, thereby highlighting the importance of early screening for CVD risk factors after a pregnancy complicated by GDM.

There are limitations to our findings that need acknowledgement. Firstly, GDM is a multifactorial disease, with many environmental and genetic components contributing to disease risk. Both obesity and GDM share the same causal pathway of elevated FFAs and dysregulation of cytokines leading to insulin resistance [7, 214]. Common risk factors such as advanced maternal age, familial history of T2DM or GDM in a first-degree relative (mother or sister) and Asian ethnicity contribute to a higher risk of GDM [215]. There are certain candidate genes that are associated with type II diabetes mellitus and GDM, mainly influencing insulin secretion[216]. Therefore, it is difficult to elucidate whether CVD in obese/overweight women with previous GDM is attributed to GDM alone or other pre-existing predispositions. Another limitation was the inability to adjust for important confounders such as BMI, age, and sex. Due to non-availability of data on adjusted mean values and the differences in the confounders used in studies, we were not able to use adjusted values in our meta-analyses. However, our supplementary data demonstrates various regression analyses used in studies that are adjusted for these important covariates. Secondly, substantial heterogeneity was seen for most overall outcomes, based on I^2 and Chi^2 P values. Observational studies may be subject to publication bias, although visual analysis of funnel plots showed no heterogeneity (Supplementary Figure 9A-9I). Heterogeneity was further explored through subgroup analysis, however for some subgroups heterogeneity was still evident. After sensitivity analysis of overall outcomes after

excluding low quality studies, heterogeneity was increased for most outcomes (Supplementary Table 3A, 3B, 3D, 3E, 3F). It is difficult to elucidate the reasons for heterogeneity for aggregate data. It is conventionally explained by significant differences between studies, which in our study can include definition of GDM, time of postpartum screening, methodology and study design. We can only attribute the heterogeneity seen due to genetic and environmental factors that could not be adjusted for, and recommend that more longitudinal, large scale studies are conducted to contribute to this evidence and reduce the overall heterogeneity.

Our findings signify the importance of early postpartum CVD risk screening for women who experience GDM. Metabolic syndrome is defined as a cluster of conditions including hypertension, dyslipidaemia, dysglycemia and obesity that significantly increases the risk of type II diabetes and cardiovascular disease. Our study demonstrates that women with GDM in pregnancy show clinical phenotypes that can contribute to metabolic syndrome and type II diabetes as early as within one year postpartum. Approximately 10% of women with GDM are known to develop diabetes soon after delivery. Therefore, it is necessary to implement interventions and treatment strategies as early as practical in these women in order to significantly reduce the risk of CVD later in life. A study in the UK in 2013, showed that risk factors such as SBP and total cholesterol decreased in those who attended such CVD screening, with an overall CVD risk reduction of 6.8%[217].

While the values seen in our meta-analysis for blood pressure are within a normal range, increase in blood pressure poses a continuous risk of CVD. It has been shown that a 10 mmHg increase in systolic blood pressure is associated with a 30% higher risk of ischemic heart disease[83]. We demonstrated that at <1 year postpartum, SBP in women with previous GDM was nearly 4mmHg higher than in controls. This suggests that women with previous GDM may benefit from monitoring of blood pressure as early as <1 year postpartum to reduce the risk of subsequent hypertension.

Persistence of high BMI in women with previous GDM is likely due to postpartum behaviours, and it may be beneficial to target reduction of obesity prior to gestation. A meta-analysis by Baptise-Roberts *et al.* showed that for every 1kg increase in pre-pregnancy weight, the increased odds of developing type II diabetes mellitus increased by 40%[218]. The Diabetes Prevention Program, a multi-centre randomized controlled trial, showed that intensive lifestyle changes, targeting a 7% reduction in enrolment weight, and increased physical activity in women with previous GDM, reduced the risk of diabetes incidence by 50% at 12 years postpartum [219]. Interestingly, it was shown that women with GDM lost the most amount of weight at 6 months post randomization, and increased weight again afterwards. These weight patterns correlated with a decrease in physical activity (women in the active GDM group were achieving 1.5 hours of exercise from baseline in the first year, but by the third year, they were reporting less than 30 minutes of physical activity a week, correlating with a mean weight loss of only 1.6kg). In our subgroup analysis, there was no difference in BMI between women with previous GDM and controls at <1 year postpartum, and then for the subsequent subgroups, there were significant differences in BMI[219]. Therefore, it appears that lifestyle guidance during pregnancy promotes weight loss in the first year postpartum, and compliance decreases beyond this point. Strategies to maintain a healthy weight in women with previous GDM beyond the first postpartum year, may significantly reduce their overall CVD risk.

Women with GDM experience insulin resistance (IR) and hypertriglyceridemia, which are both promoted by elevated free fatty acids (FFAs) in response to increased adiposity [7]. IR is a marker of essential hypertension, as it promotes a pro-atherogenic state through marked dyslipidaemia and elevation in inflammatory markers [220]. Atherosclerosis is also promoted by elevations in any non-HDL cholesterols. [221] The higher total cholesterol and triglycerides and the lower HDL cholesterol evident in women with previous GDM suggest an adverse serum lipid profile and as such, women with previous GDM may be at higher risk for CVD. While the values seen in

this meta-analysis are minimal, it is important to recognize that serum lipids are strong predictors of hypertension and IHD mortality, with total cholesterol/HDL ratio being the strongest predictor of IHD mortality overall [222, 223]. In our meta-analysis we observed a minimal but significant increase in non-HDL cholesterols and a decrease in HDL cholesterol, therefore suggesting that women with GDM are likely to exhibit a poor lipid profile and may benefit from regular monitoring of serum lipids.

Women with previous GDM will also benefit from regular screening of blood glucose and insulin. Towards the end of the second trimester, insulin resistance is elevated to facilitate the delivery of glucose to the fetus down a concentration gradient via placental transfer. Women who are normoglycemic during this period, have adequate β-cell function through compensatory hyperplasia of the beta cells, which causes increased insulin release upon glucose stimulation [214]. However, in women with GDM, there is a failure of β-cell compensation to protect against the increased insulin resistance and as such blood glucose is significantly elevated. This insulin resistance may not resolve after delivery and blood glucose remains elevated postpartum [214]. Therefore, monitoring and screening women for type II diabetes mellitus is very important.

3.7. Conclusion

Women with previous GDM have a higher risk for CVD as evidenced by an increase in risk factor profile compared to women with no history of GDM. Most of these risk factors are seen as early as <1 year postpartum. Therefore, women who experience GDM may benefit from CVD risk screening commencing in the early postpartum period to enable detection of modifiable risk factors.

3.8. Supplementary Data

Supplementary Table 3.8 1 Summary of studies not included in meta-analysis

Study	GDM group	Control group	Significance (p-value)
Systolic Blood Pressure (mmHg)			
Alberada 2004 (Median IQR)	120 (85-180)	110 (80-140)	**<0.05**
Bently-Lewis 2015 (Mean SD)	116±11	115±9	0.29
Hannemann 2002	118 (109–144)	113 (99–133)	NS
Hu 1998 (Median IQR)	116 (95-128)	108 (97-120)	**0.04**
Laurenborg 2005 (Median IQR)	119 (111–126)	120 (110–125)	0.206
Levka 2015 (Reported in 2016, 2017) (Median IQR)	IADSPG criteria: 110 (110-130) WHO criteria: 110 (110-130)	IADSPG criteria: 110 (110-120) WHO criteria: 110 (110-120)	NS
Retnakaran 2010 (Median [IQR]) (Similarly reported in 2011)	3 months: 111 (105-118) 12 months: 110 (103-119)	3 months: 108 (101–113) 12 months: 109 (100-115)	NR
Rukasaskul 2016 (Median [IQR])	120 (100-155)	110 (100-140)	**0.002**
Todoric 2012 (Median IQR)	106 (95–120)	118 (110–125)	NS
Ueland 2018 (Median IQR)	120 (100, 130)	110 (100, 120)	NS
Verma 2002 (Mean SD)	5 years: 121.6 ± 10.8 (88) 6 years: 121.8 ± 11.8 (87) 9 years: 122.2 ± 11.9 (57)	5 years: 119.2 ± 9.7 (79) 6 years: 117.9 ± 10.4 (79) 9 years: 117.5 ± 13.2 (50)	0.10 **0.03** 0.06
Wang 2012 (Mean SD) (adjusted for age)	131 (0.6)	128 (0.1)	**< 0.001**
Diastolic Blood Pressure (mmHg)			

Albereda 2004 (Median IQR)	78 (50-100)	70 (50-100)	**<0.05**
Bently Lewis 2015 (Mean SD)	73±8	71±7	0.09
Hanneemann 2002 (median IQR)	74 (64–92)	74 (53–92)	NS
Hu 1998 (Median IQR)	78 (55-84)	68 (56-81)	**0.02**
Laurenborg 2005 (Median IQR)	73 (66–78)	75 (70–80)	**<0.0005**
Levka 2015 (Reported in 2016, 2017) (Median IQR)	IADPSG: 70 (65-75) WHO: 70 (65-80)	IADPSG: 70 (60-75) IADPSG: 70 (65-75)	NS
Retnakaran 2010 (Median [IQR] (Similarly reported in 2011)	3 months: 66 [60–72] 12 months: 66 (60–71)	3 months: 66 (60–70) 12 Months: 64 (59–70)	
Rukasaskul 2016 (Median [IQR])	70 (50-91)	60 (60-80)	0.092
Todoric 2012 (Median IQR)	65 (60–70)	73 (65–80)	NS
Ueland 2018 (Median IQR)	70 (65, 74)	70 (65,75)	NS
Verma 2002 (Mean SD)	5 years: 72.3 ±10.6 (88) 6 years: 72.0 ± 11.1 (87) 9 years: 72.4 ± 8.8 (57)	5 years: 70.8 ± 10.4 (79) 6 years: 68.9 ± 9.3 (79) 9 years: 69.9 ± 11.2 (50)	0.36 0.07 0.20
Wang 2012 (Mean SD) (Adjusted for age)	76 (0.4)	76 (0.1)	0.2
BMI (kg/m2)			
Albereda 2004 (Median IQR)	24.8 (17.9-40.2)	24.4 (18.3-38.4)	NS
Benjamin 1993 (units unknown)	30.2 (21-44)	30.1 (23-42)	
Bently Lewis 2014	28.2±6.3	28.5±4.7	0.70
Cheung 2015 (median IQR)	32.8 (28.9–37.1)	27.8 (24.7–35.7)	**0.04**
Daly 2018 (Subgroups) (n) (%) (Normal <25kg/m^2, Overweight 25-30kg/m^2 , Obese >30kg/m^2)	Normal: 2,338 (26%) Overweight: 2,220 (24%) Obese: 3,458 (39%)	Normal: 18,514 (50%) Overweight: 7,943 (21%) Obese: 5,217 (14%)	**<0.001** for all subgroups
Hannemann 2002 (Median IQR)	25 (21–46)	25 (19–38)	NS
Hu 1998 (Median IQR)	24.6 (20.0-36.1)	22.0 (18.7-26.6)	**0.002**

Kjos 1991 (Mean SD)	6-12 weeks: 30.7 ± 5.8 3-11 months: 32 ± 7* 12-23 months: 32 ± 6*	26.8 ± 3.7	NS **<0.001** compared to 6-12 week **<0.001** compared to 6-12 week
Laurenborg 2005 (Median IQR)	27.9 (24.1–32.9)	24.6 (22.2–27.9)	**<0.0005**
Madarasz 2009 (Median IQR)	26.1 [7.7]	22.9 (4.8)	Crude: **0.001**
Perrson 2015 (%)	Underweight: 2 (1.9%) Normal weight: 48 (45.7%) Overweight: 26 (24.8%) Obesity: 29 (27.6%)	Underweight: 4 (1.3%) Normal weight: 229 (72.0%) Overweight: 62 (19.5%) Obesity: 23 (7.2%)	**<0.001**
Pirkola 2010 (Geometric Mean, 95% CI)	Normal Weight: 21.2 (20.8, 21.7) Overweight: 30.2 (29.0, 31.4)	Normal Weight: 21.2 (21.1, 21.3) Overweight: 28.8 (28.4, 29.2)	**<0.001**
Stuebe 2011 (n= unknown) (Mean (SD))	27 (7)	25 (5)	NR
Retnakaran 2010 (Median [IQR])	26.6 (23.7-31.1)	25.4 (23.0-28.9)	0.0701
Retnakaran 2010 (Median [IQR]) (Similarly reported in 2011)	3 months: 26.7 (23.5–30.7) 12 months: 26.4 (22.5–30.5)	3 months: 25.1 (22.6–28.5) 12 months: 24.2 (21.5–27.8)	NR
Ruksasakul 2016 (Median [IQR])	35.5 (17.0-35.0)	22.4 (18.3-31.7)	**0.003**
Shostrom 2017 (weighted SE)	31.7 (0.36)	29.1 (0.12)	**<0.001**
Sokup 2012 (Median IQR)	23.68 (20.96, 27.54)	22.00 (20.31, 24.33)	0.00098
Sokup 2012 (Median IQR)	24.45 (21.48–27.61)	22.00 (20.31–24.33)	**0.001**
Tam 2013	23.7 ± 3.5	24.4 ± 4.6	0.24
Todoric 2012 (8 years) (Median IQR)	27.9 (26.1–31.2)	26.6 (25–29.6)	NS
Tura 2006 (Mean (SE)	22.3 (0.4)	22.0 (0.5)	
Ueland 2018 (Median IQR)	24.8 (22.6, 27.9)*	22.6 (20.8, 24.5)	<0.05
Verma 2002 (Mean SD)	5 years: 27.2 ± 6.7 (88) 6 years: 26.3 ± 5.8 (87) 9 years: 27.5 ± 5.8 (57)	5 years: 25.0 ± 5.5 (79) 6 years: 25.4 _±5.6 (79) 9 years: 27.4 ± 8.4 (50)	0.02 0.31 0.90
Wang 2019 (Mean only)	28.97	27.27	0.21
Wang 2012 (Mean SD) adjusted for age	48.2 (1.7)	41.1 (0.4)	**< 0.001**

Cholesterol			
Serum			
Albereda 2004 (Median IQR)	5.2 (3.8-8.2)	5.1 (3.7-7.0)	
Couch 1998 (Mean SD) (adjusted values*)	221.50 (44.93)	232.46 (76.58)	NS
Hannemann 2002 (Median IQR)	4.4 (3.0–5.8)	4.8 (3.1–6.1)	NS
Hu 1998 (Median IQR)	5.1 (3.7-8.1)	5.0 (3.6-6.8)	0.6
Kjos 1991 (Mean SD)	6-12 weeks: 5.82 ± 1.27 3-11 months: 5.12 ± 0.99 12-23 months: 5.04 ± 0.75	5.10 ± 0.99	<0.001 compared to 6-12 week <0.001 compared to 6-12 week <0.001 compared to 6-12 week
Retnakaran 2011 (mmol/L)	5.31 [4.78-5.87]	4.92 [4.35-5.61]	NR
Sokup 2012 (Median IQR) (mmol/L)	5.04 (4.55–5.51)	4.56 (4.27–5.09)	0.9940 (adjusted for BMI)
Sokup 2012 (Median IQR) (mmol/L)	5.06 (4.53–5.53)	4.56 (4.27–5.09)	0.001
Steube 2011 (n= unknown) (Mean (95% CI)) (mg/dL)	Unadjusted: 164.0 (138.1-189.9 Adjusted: 165.9 (136-194.9)	Unadjusted: 176.8 (171.9-181.6) Adjusted: 175.8 (166.6-185.0)	NR
Todoric 2012 (Median IQR) (mg/dl)	203 (183–215)	204 (175–235)	NS
Verma 2002	6 years:4.90 ± 1.23(87) 9 years: 5.31 ± 0.83 (57)	6 years: 4.33 ± 0.94 9 years 4.93 ± 1.01	0.0006 0.04
LDL			
Serum			
Albereda 2004 (Median IQR)	3.4 (2.1-6.4)	3.2 (2.2-5.3)	NS
Couch 1998 (adjusted values*)	96.46 (45.59)	101.28 (49.72)	NS
Hannemann 2002 (median IQR)	2.46 (1.43–3.60)	2.94 (1.29–4.30)	NS
Kjos 1991 (Mean SD)	6-12 weeks: 3.61 ± 1.12 3-11 months: 3.12 ± 0.65* 12-23 months: 2.94 ± 0.68*	6-12 weeks: 3-11 months: 12-23 months:	P < 0.001, vs. paired 6- to 12-wk P < 0.001, vs. paired 6- to 12-wk P < 0.001, vs. paired 6- to 12-wk
Levka 2015 (Reported in 2017) (Median IQR) (mmol/L)	IADPSG: 2.66 (2.15, 3.20) WHO: 2.61 (2.10, 3.11)	IADPSG: 2.50 (2.09, 3.00) WHO: 2.52 (2.10, 3.02)	Crude=0.007, Adjusted=0.058 Crude <0.001, Adjusted 0.001
Retnakaran 2011 (Median IQR) (mmol/L)	3.85 [3.36-4.64]	3.47 [2.88-4.18]	
Sokup 2012 (Median IQR) (mmol/L)	3.10 (2.79–3.54)	2.57 (2.30–3.05)	0.4022 (adjusted for BMI)
Sokup 2012 (Median IQR) (mmol/L)	3.17 (2.77–3.62)	2.57 (2.30–3.05)	0.001

Steube 2011 (n= unknown) (Mean (95% CI)) (mg/dL)	Unadjusted: 90.9 (67.1-114.8) Adjusted: 92.8 (66.6-119)	Unadjusted: 106.2 (101.7-110) Adjusted: 102.7 (94.4-111)	NR
Tam *et al.* 2013 (8 year)	2.75 ± 0.64	2.74 ± 0.78	0.94
Todoric 2012 (Median IQR)(mg/dl)	110 (100–144)	129 (113.4–136)	NS
Verma 2002 (mean SD)	6 years: 3.15 _ 0.98 (87) 9 years:3.44 _ 0.77 (57)_	6 years: 2.76 _ 0.77 (79) 9 years 3.15 _ 0.76 (50)	0.03 0.07
HDL			
Serum			
Albereda 2004 (Median IQR)	1.4 (0.8-2.6)	1.5 (0.8-2.2)	
Couch 1998	70.65 (16.96)	69.88 (21.31)	NS
Hannemann 2002 (Median IQR)	1.27 (0.93–3.03)	1.40 (1.08–2.29)	NS
Kjos 1991 (Mean SD)	6-12 weeks: 1.22 ± 0.31 3-11 months: 1.14 ± 0.26 12-23 months: 1.20 ±0.26	1.22 ±0.26	NS NS NS
Krishnaveni 2007 (Median IQR)	NGT: 1.15 (0.1) IGT/IFG: 1.14 (0.2) DM:0.98 (0.2)	NGT: 1.14 (0.2) IGT/IFG: 1.0.9 (0.2) DM:1.11 (0.2)	0.7
Laurenborg 2005 (Median IQR)	1.4 (1.2–1.7)	**1.5 (1.3–1.8)**	**<0.0005**
Levka 2015 (Reported in 2017) (Median IQR) (mmol/L)	IADPSG: 1.40 (1.20, 1.73) WHO: 1.30 (1.08, 1.52)	IADPSG: 1.54 (1.36, 1.82) WHO: 1.54 (1.36, 1.83)	Crude= 0.123 Adjusted=0.405 Crude=0.614, Adjusted 0.909
Retnakaran 2011 (Median IQR) (mmol/L)	1.35 [1.15-1.54]	1.43 [1.24-1.65]	
Sokup 2012 (Median IQR) (mmol/L)	1.53 (1.28–1.73)	1.73 (1.56–1.82)	**0.0027** (adjusted for BMI) 0.0449 (adjusted for fasting glucose)
Sokup 2012 (Median IQR) (mmol/L)	1.53 (1.27–1.73)	1.73 (1.56–1.82)	**0.001**
Steube 2011 (n= unknown) (Mean (95% CI)) (mg/dL)	Unadjusted: 41.8 (31.3-52.3)-54.5 (52.5-56.4) Adjusted: 44.7 (33.6-55.8)	Unadjusted: 54.5 (52.5-56.4) Adjusted: 55.8 (52.2-59.3)	NR
Sung 2008 (Median IQR) (mmol/L)	pGDM-NGT1.22, 0.80–2.12 pGDM-IGT 1.17, 0.75–5.18	1.30, 1.17–2.05	NR

	pGDM-DM 1.19, 0.75–5.18		
Tam *et al.* 2013 (8 Years)	1.43 (0.29)	1.64 (0.36)	**0.001**
Todoric 2012 (Median IQR) (mg/dl)	62 (46–72)	65 (51–71)	NS
Verma 2002 (mean SD)	6 years: 1.23 ± 0.36 (87) 9 years: 1.37 ± 0.32 (57)	6 years: 1.15 ± 0.32 9 years 1.31 ± 0.32	**0.03** 0.41
Cord Blood			
Couch 1998	19.47 (8.78)	15.06 (5.87)	NS
Triglycerides			
Serum			
Albereda 2004 (Median IQR)	0.85 (0.4-4.0)	0.69 (0.33-2.17)	NS
Behboodi-Gandevani 2019 (Mean SD)	0.51 (0.55)	0.33 (0.53)	0.001
Couch 1998 (adjusted values)	236.38 (73.37)	177.96 (50.61)	NS
Hannemann 2002 (median IQR)	0.92 (0.50–1.70)	1.10 (0.40–1.75)	NS
Hu 1998 (Median IQR)	1.1 (042.5)	0.9 (044.3)	0.22
Kjos 1991 (Mean SD)	6-12 weeks: 2.12 ± 1.15 3-11 months: 1.86 ± 0.95 12-23 months: 1.81 ± 1.22§	1.32 ±0.73	**<0.03** compared to control <0.03 compared to control <0.03 compared to control
Laurenborg 2005 (Median IQR)	1.3 (0.9 –1.9)	1.0 (0.7–1.3)	**<0.0005**
Krishnaveni 2007 (Median IQR)	NGT: 0.9 (0.8, 1.4) IGT/IFG:1.3 (0.7, 1.8) DM:1.8 (1.2, 3.4)	NGT: 1.0 (0.7, 1.4) IGT/IFG: 1.1 (0.8, 1.5) DM:1.5 (0.9, 2.2)	0.8
Levka 2015 (reported in 2017)	IADPSG: 0.78 (0.66, 0.95) WHO: 0.87 (0.67, 1.17)	IADPSG:0.72 (0.58, 0.91) WHO: 0.73 (0.58, 0.91)	Crude: 0.012, Adjusted 0.109 **Crude 0.001**, Adjusted 0.004
Retnakaran 2011 (Median IQR) (mmol/L)	1.12 [0.74-1.63]	0.90 [0.66-1.26]	
Sokup 2012 (Median IQR) (mmol/L)	0.97 (0.78–12.83)	0.86 (0.67–1.05)	0.0006 (Adjusted for BMI) **<0.0001 (Adjusted for Fasting Glucose)**
Sokup 2012 (Median IQR) (mmol/L)	1.02 (0.78–1.50)	0.86 (0.67–1.05)	0**.012**

Steube 2011 (n= unknown) (Mean (95% CI)) (mg/dL[2])	Unadjusted: 133.3 (92.0-193.2) Adjusted: 136.1 (90.3-205.2)	Unadjusted: 73.6 (68.6-78.9) Adjusted: 78.3 (68.7-89.2)	NR
Tam *et al.* (2013) (8-year follow-up)	1.17 ± 1.16	0.96 ± 0.49	0.08
Tehrani *et al.* (Median IQR)	137.2 (95–173.1)	130.5 (99–167.2)	NS
Thomann 2008 (Median IQR)	0.8 (0.6–1.3)	0.8 (0.6–1.0)	**0.01**
Todoric 2012 (Median IQR)	111 (56–182)	77 (68–91)	NS
Wang 2015 (Median IOR)	1.5 (1.2–2.0)	1.3 (1.2–1.8)	0.442
Verma 2002 (mean SD)	6 years: 1.60 ± 1.46 (87) 9 years: 1.11 ± 0.81 (57)	6 years: 1.04 ± 0.85 (79) 9 years 0.89 ± 0.50 (50)	**0.01** 0.11
Insulin			
Serum			
Carr *et al.* 2006 (Median IQR)	102 (15–1656.7)	83.5 (7.6–566.4)	**0.005** Adjusted:0.001
Hunger Dathe 2006	7.5 (3.0-70)	6.0(1.5-21.9)	**<0.03**
Lauenborg 2005 (Median IQR)	53.8 (34.9 –78.3)	31.0 (23.0–48.0)	**<0.0005**
Madarasz 2009 (Median IQR) (uIU/mL)	229 (111)	111 (97)	Crude: **0.0001,** adjusted 0.001
Pimenta (Median IQR semi-range)	66 (30)	48 (24)	0.27
Ruksasakul (2016) (Median IQR) (uIU/mL)	5.4 (2.0-46.6)	4.4 (2.0-28.8)	0.495
Sokup 2012 (Median IQR) (pmol/L)	54.87 (41.67–80,56)	63.20 (54.87–71.53)	0.1755(adjusted for BMI)
Sokup 2012 (Median IQR) (pmol/L)	48.00 (36.00–69.60)	54.60 (47.40–61.80)	0.260
Steube 2011 (n= unknown) (Mean (95% CI)) (u/mL[2])	Unadjusted: 15.3 (8.8-26.7) Adjusted: 12.1 (7.1 -20.8)	Unadjusted: 7.5 (6.8-8.4) Adjusted: 6.8 (5.8-8.1)	NR
Sung 2008 (Median IQR) (pmol/L)	pGDM-NGT:0.99 (0.41–3.49) pGDM-IGT:1.15, (0.42–6.69) pGDM-DM: 1.27, (0.61–2.16)	0.80, (0.50–1.68)	NR
Thomann 2009 (Median IQR)	51.7 (33.4–61.5)	45.4 (34.6–60.5)	0.1
Verma 2002 (Mean SD) (n=)	Postprandial 4 years: 288.91 ±148.62 (n=106) Postprandial 5 years: 219.46 ± 205.57	Postprandial 4 years:236.82 ± 93.06 (101) Postprandial 5 years:164.60 ± 92.37	0.004 0.05 0.71

	(88) Postprandial 6 years: 122.93 ± 110.43 (87) Fasting 9 years: 4.51 ±2.13 (57)	(79) Postprandial 6 years:116.68 ± 86.81 (79) Fasting 9 years:3.63 ± 0.37 (50)	**0.005**
Glucose			
Serum			
Akinci 2011 (n=, % IFG)	57 (29.3%)	2 (2.8%)	**0.001** Adjusted for prepregnancy BMI and history of T2D :0.02
Albereda 2004 (% IFG)	6.5%	0%	**0.048**
Gadgil 2017 (%)	Normal 37.5 Prediabetes (IFG) 27.5 Diabetes 35.0	Normal 49.7 Prediabetes 30.8 Diabetes 19.5	
Hannemann 2002 (Median IQR)	4.5 (4.0–5.0)	4.4 (3.9–5.0)	NS
Hu 1998 (Median IQR)	4.5 (3.8-5.7)	4.2 (1.8-6.4)	0.46
Krishnaveni 2007 (Median IQR)	NGT:5.3 (5.2, 5.8) IGT/IFG:6.0 (5.8, 6.1) DM:10.6 (7.2, 14.3)	NGT:5.2 (4.9, 5.6) IGT/IFG:6.1 (5.8, 6.4) DM:7.5 (6.0, 9.5) 0.02	**0.02**
Laurenborg 2005 (% (n= case/control)	11.0% (53/481)	4.3% (39/910)	**<0.0005**
Madarasz 2009 (% impaired FG)	5.9%	0	
Retnakaran 2010 (Median [IQR] mmol/L)	4.7 (4.4-5.0)	4.4 (4.2-4.7)	
Retnakaran 2010 (Median [IQR]mmol/L)	3 months: 4.7 (4.3–5.0) 12 months: 4.8 (4.5–5.2)	3 months: 4.4 (4.1–4.6) 12 months: 4.5 (4.4–4.7)	NR
Rukasaskul 2016 (Median [IQR] mg/dL)	90.5 (69-306)	73.6 (65-107)	**<0.001**
Seghieri (C-Peptide/FPG) (Mean (SD)	0.08 ± 0.04	0.12 ± 0.04	0.009
Sokup 2012 (Median IQR) (mmol/L)	4.50 (4.61–5.33)	4.72 (4.50–4.78)	**0.0001** (adjusted for BMI)

Sokup 2012 (Median IQR) (mmol/L)	4.83 (4.61–5.27)	4.72 (4.50–4.78)	**0.015**
Steube 2011 (n= unknown) (Mean (95% CI)) (mg/dL)	Unadjusted: 82.8 (70.8-94.8) Adjusted: 89.0 (75.8-102.3)	Unadjusted: 72.6 (70.3-74.8) Adjusted: 76.5 (72.3-80.6)	NR
Tam *et al.* 2013 (8 year and 15 year) (n= (%))	8 year: NGT: 40 (59.7) IFG and/or IGT: 21 (31.3) DM: 6 (9.0) 15 year: NGT: 22 (48.9) IFG and/or IGT: 12 (26.6 DM: 11 (24.4)	8 year: NGT: 112 (82.3) IFG and/or IGT:21 (15.4) DM:3 (2.2) 15 years: NGT: 75 (79.8) IFG and/or IGT:14 (14.9) DM:5 (5.3)	**0.001** **0.001**
Tutino (sample size unknown) (Mean (SD)	8.6±2.9 mmol/L vs	7.9±2.6 mmol/L	, p = 0.014
Verma 2002 (Mean SD)	Postprandial 4 years: 5.85 ± 2.08 (n=106) Postprandial 5 years: 5.20 ± 1.27 (88) Postprandial 6 years: 4.96 ± 1.84 (87) Fasting 9 years: 4.51 ± 2.13 (57)	Postprandial 4 years: 4.95 ± 0.72 (101) Postprandial 5 years:4.36 ± 0.73 (79) Postprandial 6 years: 4.39 ± 0.70 (79) Fasting 9 years: 3.63 ± 0.37 (50)	0.0001 0.0001 0.02 0.005

Supplementary Table 3.8 2 Quality assessment of included studies using Newcastle Ottowa-Scale

Quality assessment	Selection				Comparability	Exposure			Total Score
	1	2	3	4	1	1	2	3	
Ajala 2011	c	a	c	a	NA	d	a	c	3
Ajala 2015	a	a	b	a	age-matched	d	a	c	4
Akini 2008	a	b	b	a	30 age-matched	d	a	c	4
Akini 2010	a	a	b	a	age-matched, had a pregnancy at the same period	d	a	c	5
Akini 2011 (A)	a	a	b	a	age-matched, had a pregnancy at the same period	d	a	c	5
Akini 2011 (B)	a	a	b	a	age-matched, had a pregnancy at the same period	d	a	c	5
Akini 2013	a	a	b	a	age and BMI	d	a	b	5
Albareda 2003	a	a	b	a	NA	d	a	b	4
Albareda 2004	a	a	b	a	NA	b	a	c	4
Anastasiou 1998	a	b	b	a	NA	d	a	c	3
Anastasiou 2015	a	a	NA	NA	NA	d	NA	NA	2
Banerjee 2012	a	a	b	a	NA	d	a	c	4
Behboodi 2019	a	a	a	a	*	e	a	c	6
Benjamin 1993	a	a	b	a	delivered during the same time period	d	a	c	5
Bently Lewis 2015	a	a	b	a	matched 1:1 to women with NGT (n=96) by age, BMI, gravidity and parity	d	b	c	4
Bently Lewis 2016	a	a	b	a	NA	d	a	c	4
Bian 2000	a	a	b	a	NA	d	a	b	4
Bo 2006	a	a	b	a	NA	d	a	b	4

Bowes 1996	a	b	b	a	NA	d	a	c	3
Bozcurt 2010	a	a	b	a	NA	d	a	c	4
Bozcurt 2012	a	a	b	a	NA	d	a	c	4
Caliskan 2014	b	a	b	a	age- and sex-matched controls	d	a	c	4
Carpenter 1988	a	a	b	a	NA	d	a	c	4
Carr 2006	a	a	b	a	NA	c	a	c	4
Chan 1992	a	b	b	a	individually matched for race age and body mass index were Included	d	a	c	4
Charwat-Resl 2017	a	a	b	a	NA	d	a	b	3
Cheung 2015	b	b	b	a	NA	d	a	c	2
Cocilovo 1989	a	b	b	a	NA	d	a	c	3
Couch 1998	a	b	b	a	NA	e	a	c	3
Crowe 2012	a	b	b	a	not adjusted	d	a	c	3
Da 2016	a	b	b	a	NA	d	a	c	3
Daly 2018	a	a	b	a	age and timing of pregnancy (up to 3 months	d	a	c	5
Davenport 2012	a	a	b	a	NA	d	a	c	4
Davis, 1999	a	b	b	a	NA	d	a	c	3
Dinglas 2017	a	a	b	a	NA	d	a	b	4
Donhorst 1990	a	a	b	a	NA	d	a	b	4
Egeland 2010	a	a	b	a	age and geographic	d	a	b	5
Eroglu 2006	a	a	b	a	age- and gravidity matched patients with	d	a	c	5

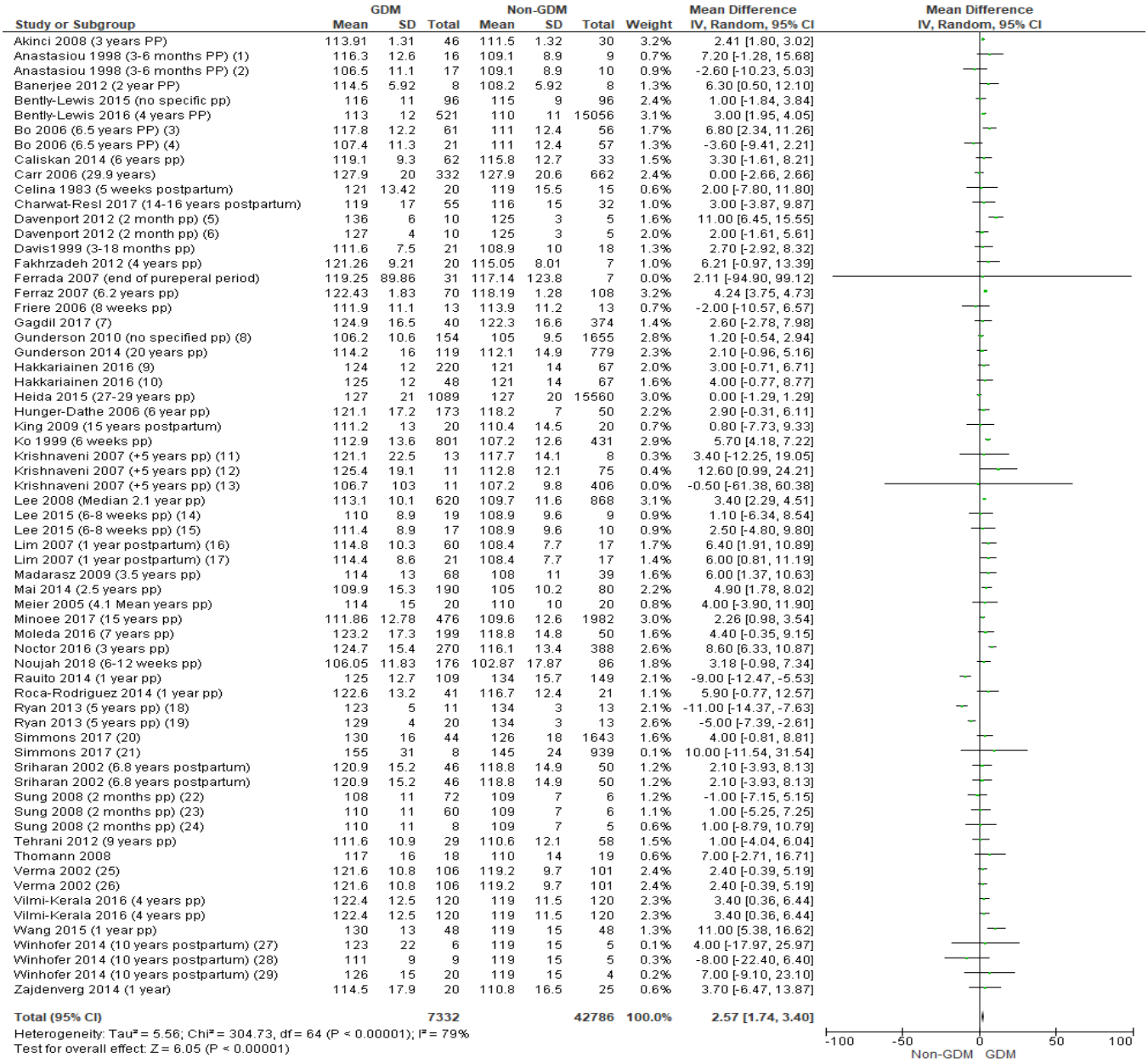
Fakhrzadeh 2012	a	a	b	a	body mass index (BMI), age and follow-up period from the index pregnancy	d	a	c	5
Ferrada 2007	a	a	b	a	NA	e	a	c	4
Ferraz 2007	a	a	b	a	NA	d	a	c	4
Friere 2006	a	b	b	a	NA	d	a	c	3
Gadgil 2017	a	a	a	a	NA	d	a	c	5
Gobl 2011	a	a	c	a	NA	e	b	c	3
Gobl 2013	a	a	c	a	NA	d	b	c	3
Gobl 2014 (A)	a	a	c	a	NA	d	b	c	3
Göbl 2014 (B)	a	a	c	a	NA	d	b	c	3
Goueslard 2016	b	b	b	a	NA	d	a	c	1
Gunderson 2010	b	a	a	b		a	a	c	3
Gunderson 2014	b	a	a	b		a	a	b	4
Han 2018	b	a	a	b		b	b	a	4
Hakkariainen 2015	a	a	a	a		a	a	a	7
Hakkariainen 2016	a	a	a	a		a	a	a	7
Heida 2015	a	a	a	a	NA	d	a	b	4
Homko 2001	a	b	b	a	age- and weight-matched nondiabetic pregnant women	d	a	c	4
Hu 1998	a	b	b	a	age	d	a	c	4
Hunger Dathe 2006	a	b	b	a	NA	c/d	a	c	3
Kessous 2013	b	a	b	a	NA	d	a	c	3

King 2009	a	b	b	a	age, body mass index, and time since GDM-affected pregnancy	c	a	c	4
Kjos 1991	a	a	a	a		a	a	c	6
Ko 1999	a	a	b	a	age-matched	d	a	c	5
Kousta 2003	a	a	b	a	ethnicity, parity and time since delivery	d	a	c	5
Krishnaveni 2007	a	a	b	a	NA	d	a	c	4
Lauenborg 2005	a	a	a	b	**	a	b	b	5
Lee, A. J., *et al.* (2007)	a	a	b	a	NA	d	a	c	4
Lee, H., *et al.* (2008)	a	a	b	a	age-matched	d	a	c	5
Lee, Y. P., *et al.* (2015)	a	a	b	a	age and weight	d	a	c	5
Levka 2015	a	a	a	b		a	a	c	5
Levka 2016	a	a	a	b		a	a	c	5
Levka 2017	a	a	a	b		a	a	b	5
Lim 2007	a	a	b	a	age- and BMI-matched women	d	a	b	5
Linn 2002	a	a	b	a	NA	d	a	c	4
Ma, Y., *et al.* (2018).	a	b	b	a	NA	d	a	c	3
Madarasz 2009	a	a	b	a	**	a	a	b	5
Magenheim, R., *et al.* (2010).	a	b	b	a	NA	d	a	c	3
Maghbooli, Z., *et al.* (2010).	a	b	b	a	NA	d	a	c	3
Mai 2014	a	a	a	a		a	a	c	5

McKenzie- Sampson 2018	b	a	b	a	NA	d	a	c	3
McLachlan 2005	a	b	b	a	19 age- and BMI-matched	d	a	c	4
Meier, J. J., *et al.* (2005).	a	b	b	a	NA	d	a	c	3
Minoee 2017	a	a	a	a	*	e	a	c	5
Minoee 2017	a	a	a	a		e	a	c	5
Modela 2016	a	b	a	a	**	e	a	a	6
Morbiducci 2009	c	a	a	a		e	a	a	5
Noctor 2015	a	a	a	a		a	a	c	5
Noctor 2016	a	a	a	a		a	a	c	5
Noujah 2017	a	a	a	b		a	a	c	5
Noujah 2018	a	a	a	b		a	a	c	5
Osei 1998	a	a	a	a	**	a	a	a	8
Ozuguz 2011	a	a	a	a		a	a	c	5
Pacini 2012	c	c	e	a		e	a	a	3
Perrson 2015	b	a	a	a		a	b	c	4
Pimenta 2004	a	a	a	a	**	a	a	c	7
Pirkola 2010	a	a	a	a	**	a	a	c	7
Prikoszovich 2011	a	a	a	a	**	a	a	a	8
Rauito 2014	a	a	a	a		d	b	a	5
Rawal 2018	b	a	a	a		a	a	c	5
Retnakaran 2009	a	a	a	a		a	a	a	7
Retnakaran 2010	a	a	a	a		a	a	a	7
Retnakaran 2010	a	a	a	a		a	a	a	7
Retnakaran 2011	a	a	a	a		a	a	a	7
Rivas 2010	a	a	a	a		a	a	a	7

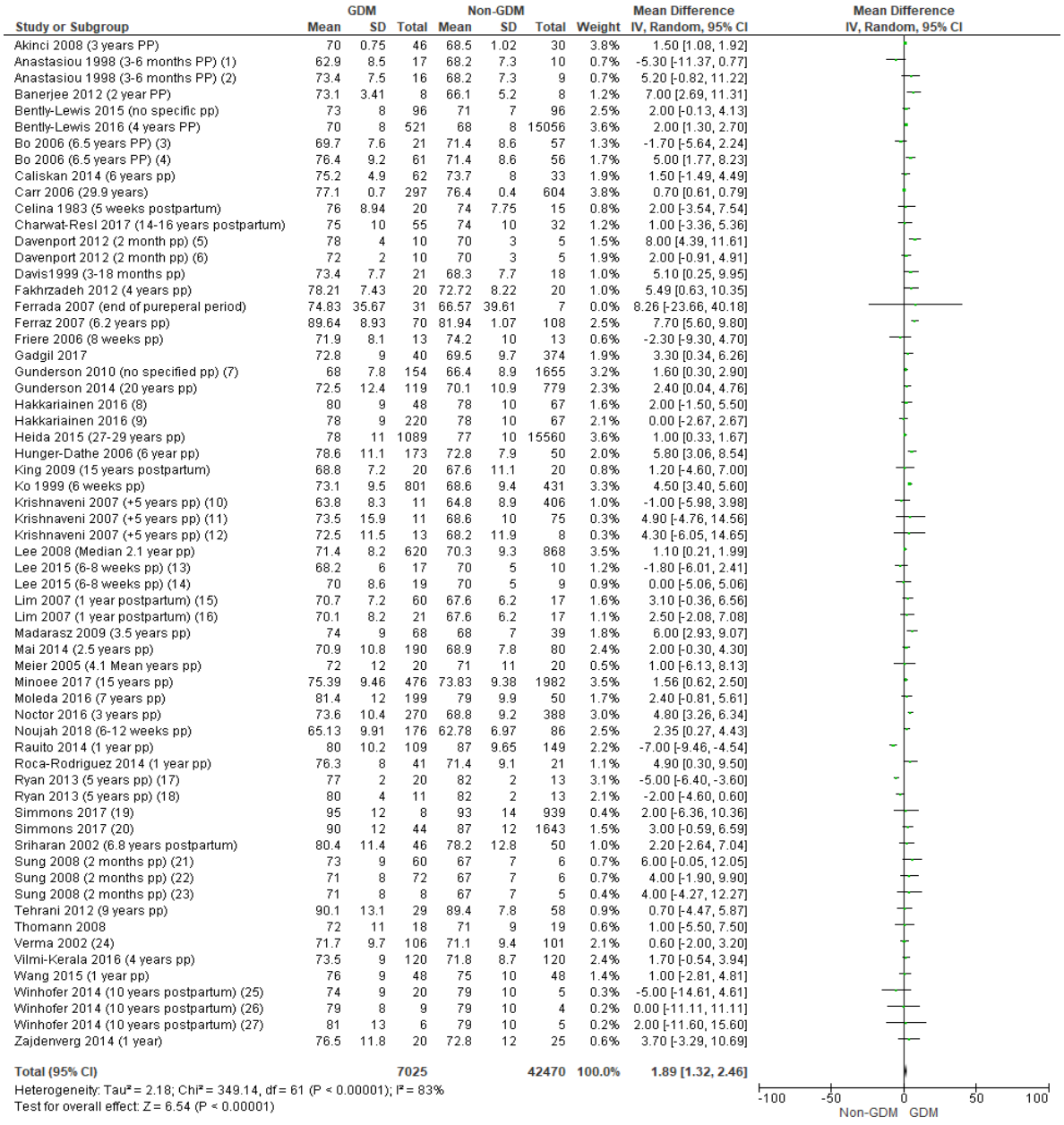
Roca-Rodrigeuz 2012	a	a	a	a	**	a	a	a	8
Roca-Rodrigeuz 2014	a	a	a	a	**	a	a	a	8
Ruksasakul 2016	a	a	a	a	**	a	a	a	8
Ryan 1995	c	a	c	a		e	a	a	4
Ryan 2013	a	a	a	a		d	a	a	5
Sartore 2011	a	a	a	a		a	a	a	7
Seck 2019	a	a	a	a		a	a	a	7
Seghiri 2007	a	a	a	a		a	a	c	6
Shen 2018	a	a	a	a		a	a	c	6
Shen 2019	a	a	a	a		a	a	c	6
Shostrom 2017	b	b	a	a		e	a	c	3
Simmons 2017	b	a	a	a		d	a	a	5
Sokup 2012	a	a	a	a	**	a	a	a	8
Sokup 2012	a	a	a	a	**	a	a	a	8
Sriharan 2002	a	a	a	a		a	a	a	6
Steube 2011	a	a	a	a		a	a	c	6
Sung 2008	a	a	a	a	**	a	a	c	7
Tam 2007	a	a	a	a	**	a	a	a	7
Tam 2012	a	a	a	a	**	a	a	a	8
Tam 2013	a	a	a	a	**	a	a	a	8
Tehrani 2012	a	a	a	a	**	a	a	c	7
Ueland 2018	a	a	a	b	*	a	a	a	6
Thomann 2008	a	a	a	a	**	a	a	a	8
Tobias 2007	b	a	a	b		d	a	c	3
Todoric 2012	a	a	a	a	**	a	a	c	7
Tura 2006	a	a	a	a	**	a	a	c	7
Verma 2002	a	a	a	a	*	a	a	c	7

Vigneault 2015	b	a	a	a		d	a	c	4
Vilmi-Kerala 2016	a	a	a	a	**	a	a	a	8
Vitoratos 2001	a	b	a	a		a	a	a	6
Wang 2012	a	b	b	a		a	a	a	5
Wang 2015	a	a	a	a	**	a	a	a	8
Wang 2019	c	a	b	a		a	a	d	4
Wender-Ozegowska 2007	b	a	a	a		d	a	c	4
Winhofer 2013	a	a	a	a	**	a	a	a	8
Winhofer 2014	a	a	a	a	**	a	a	a	8
Winofer 2014	a	a	a	a	**	a	a	a	8
Winzer 2004	a	a	a	a	**	a	a	a	8



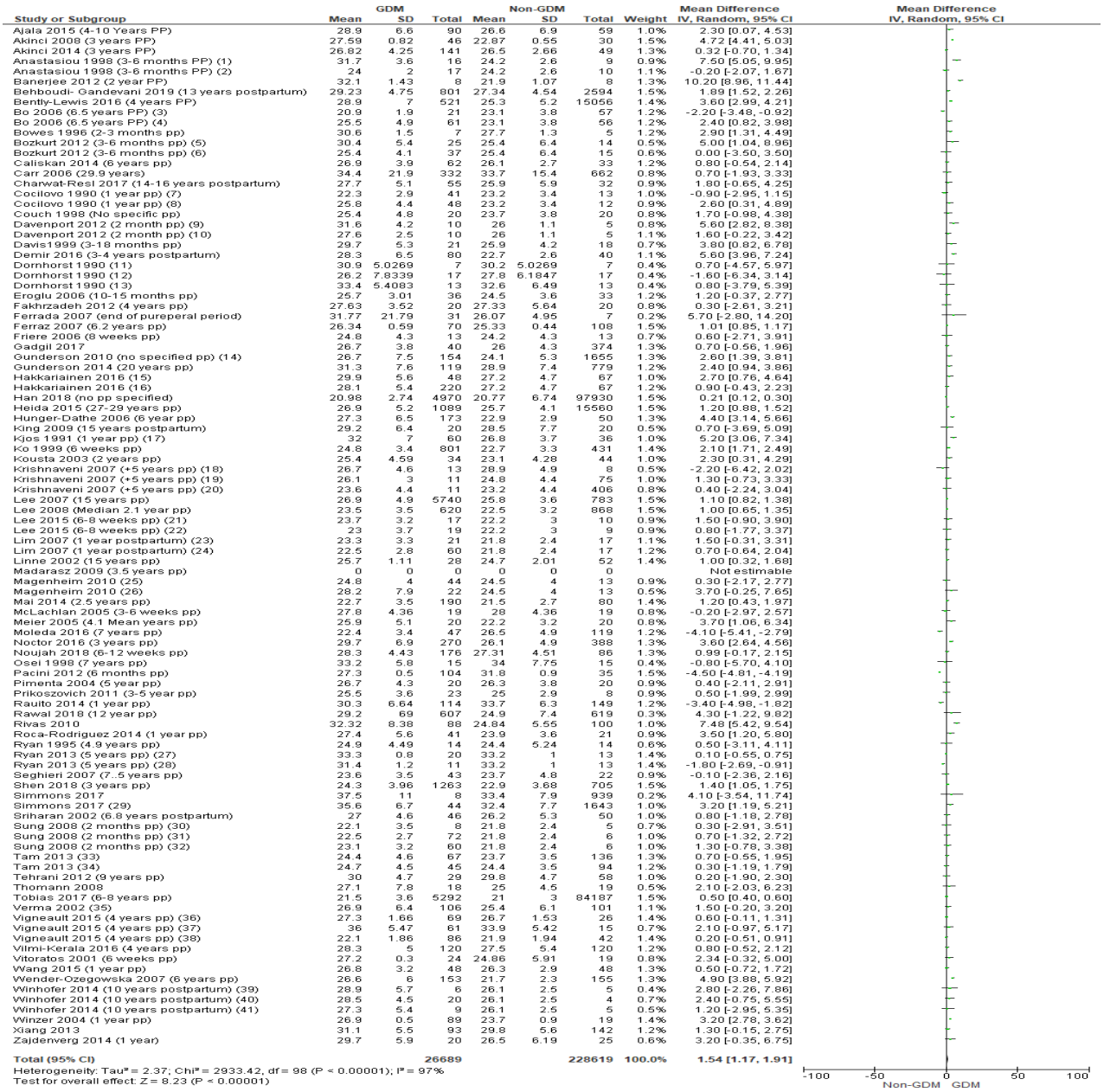
Footnotes
(1) Obese GDM
(2) Nonobese GDM
(3) pGDM-BMI > 25, any MS components
(4) pGDM-BMI < 25, no MS components
(5) pGDM-Hyperglycemic
(6) pGDM-Normoglycemic
(7) no specific postpartum follow-up
(8) Follow-up at 0, 7 10 and 15 years pp
(9) <5 years pp -GDM with 1 abnormal OGTT
(10) <5 years pp -GDM with 2 abnormal OGTT
(11) DM
(12) IGT/IFG
(13) GDM-NGT
(14) GDM-NGT
(15) GDM-IGT
(16) GDM-NGT
(17) GDM-IGT
(18) Premenopasual GDM
(19) Postmenopausal GDM
(20) < 50 years
(21) > 50 years
(22) Previous GDM with Normal Glucose Tolerance
(23) Previous GDM with Impaired Glucose Tolerance
(24) Previous GDM with DM
(25) 4 years postpartum
(26) 4 years postpartum
(27) pGDM-IGR
(28) pGDM-NGT
(29) pGDM-T2DM

Supplementary Figure 3.8 1 Meta-analysis of systolic blood pressure (mmHg) in women with previous gestational diabetes mellitus compared to women without a history of GDM



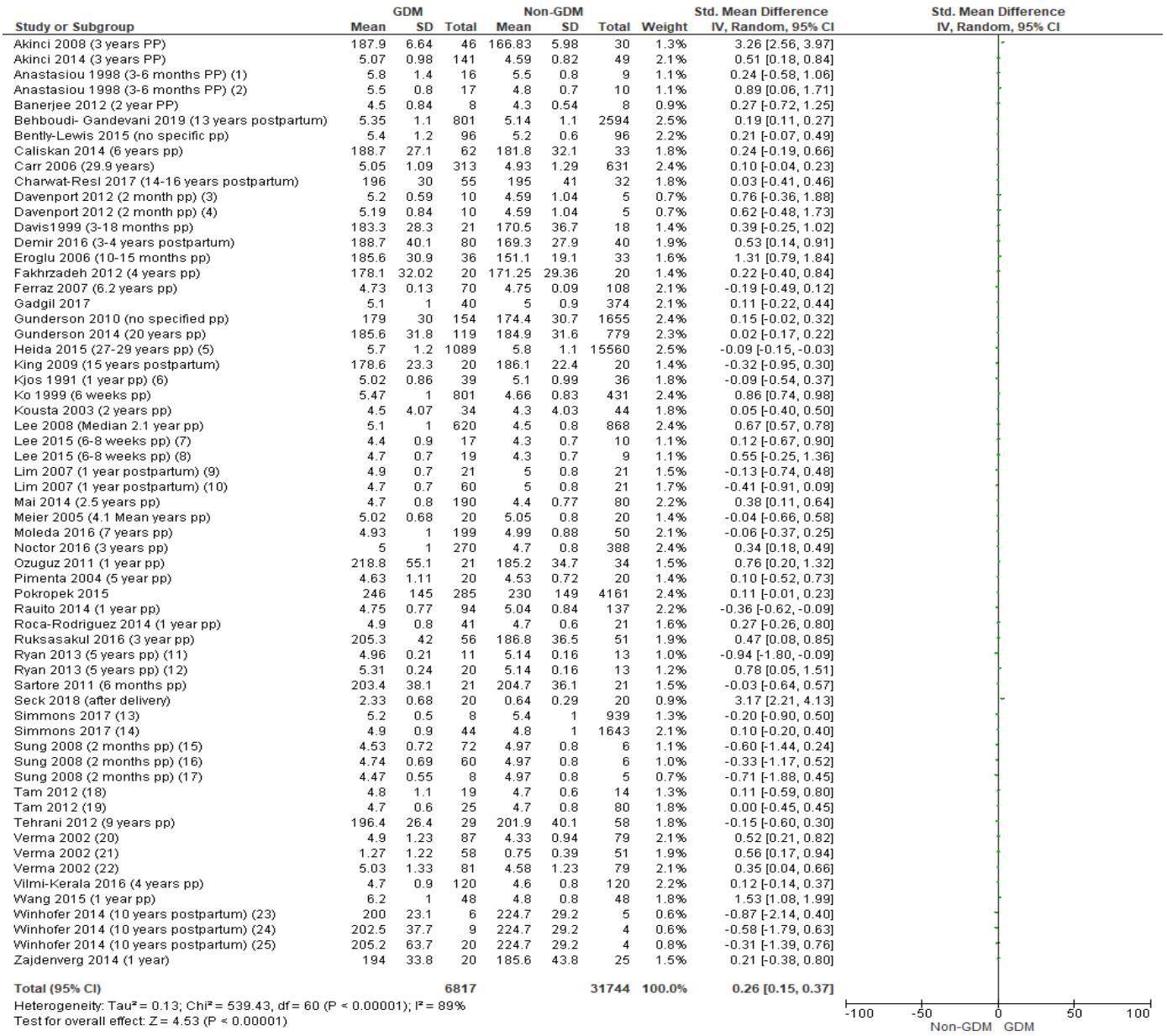
Footnotes
(1) Nonobese GDM
(2) Obese GDM
(3) pGDM- BMI < 25, no MS components
(4) pGDM- BMI > 25, any MS components
(5) pGDM-hyperglycemic
(6) pGDM-Normoglycemic
(7) Follow-up at 0, 7 10 and 15 years pp
(8) <5 year pp -GDM with 2 Abnormal OGTT
(9) <5 year postpartum-GDM with 1 abnormal OGTT
(10) NGT
(11) IGT/IFG
(12) DM
(13) GDM-IGT
(14) GDM-NGT
(15) GDM-NGT
(16) GDM-IGT
(17) Postmenopausal GDM
(18) Premenopausal GDM
(19) > 50 years old
(20) < 50 years old
(21) Previous GDM with Impaired Glucose Tolerance
(22) Previous GDM with Normal Glucose Tolerance
(23) Previous GDM with DM
(24) 4 years postpartum
(25) pGDM-T2DM
(26) pGDM-NGT
(27) pGDM-IGR

Supplementary Figure 3.8 2 Meta-analysis of diastolic blood pressure (mmHg) in women with previous gestational diabetes mellitus compared to women without a history of GDM.



Footnotes
(1) Obese GDM
(2) Nonobese GDM
(3) pGDM-BMI <25, no MS components
(4) pGDM-BMI> 25, any MS components
(5) pGDM-IR
(6) pGDM-IS
(7) BG exceeded 2nd SD for glucose values of O'Sullivan
(8) OGTT exceeded 3rd SD for O'Sullivan Values
(9) pGDM-hyperglycemic
(10) pGDM-normoglycemic
(11) pGDM-diabetic
(12) pGDM-NGT
(13) pGDM-IGT
(14) Follow-up at 0, 7 10 and 15 years pp
(15) < 5 year pp -GDM with 2 abnormal OGTT
(16) < 5 year pp -GDM with 1 abnormal OGTT
(17) 3-11 months postpartum
(18) GDM-DM
(19) GDM-IGT/IFG
(20) GDM-NGT
(21) GDM-IGT
(22) GDM-NGT
(23) GDM IGT
(24) GDM-NGT
(25) pGDM-NGT
(26) pGDM-AGT
(27) Postmenopausal GDM
(28) Premenopausal GDM
(29) <50 years
(30) Previous GDM with DM
(31) Previous GDM with Normal Glucose Tolerance
(32) Previous GDM with Impaired Glucose Tolerance
(33) 8 years follow-up
(34) 15 years follow-up
(35) 4 years postpartum
(36) Overweight
(37) Obese
(38) Normal Weight
(39) pGDM-IGR
(40) pGDM-T2DM
(41) pGDM-NGT

Supplementary Figure 3.8 3 Meta-analysis of body mass index (kg/m2) in women with previous gestational diabetes mellitus compared to women without a history of GDM.

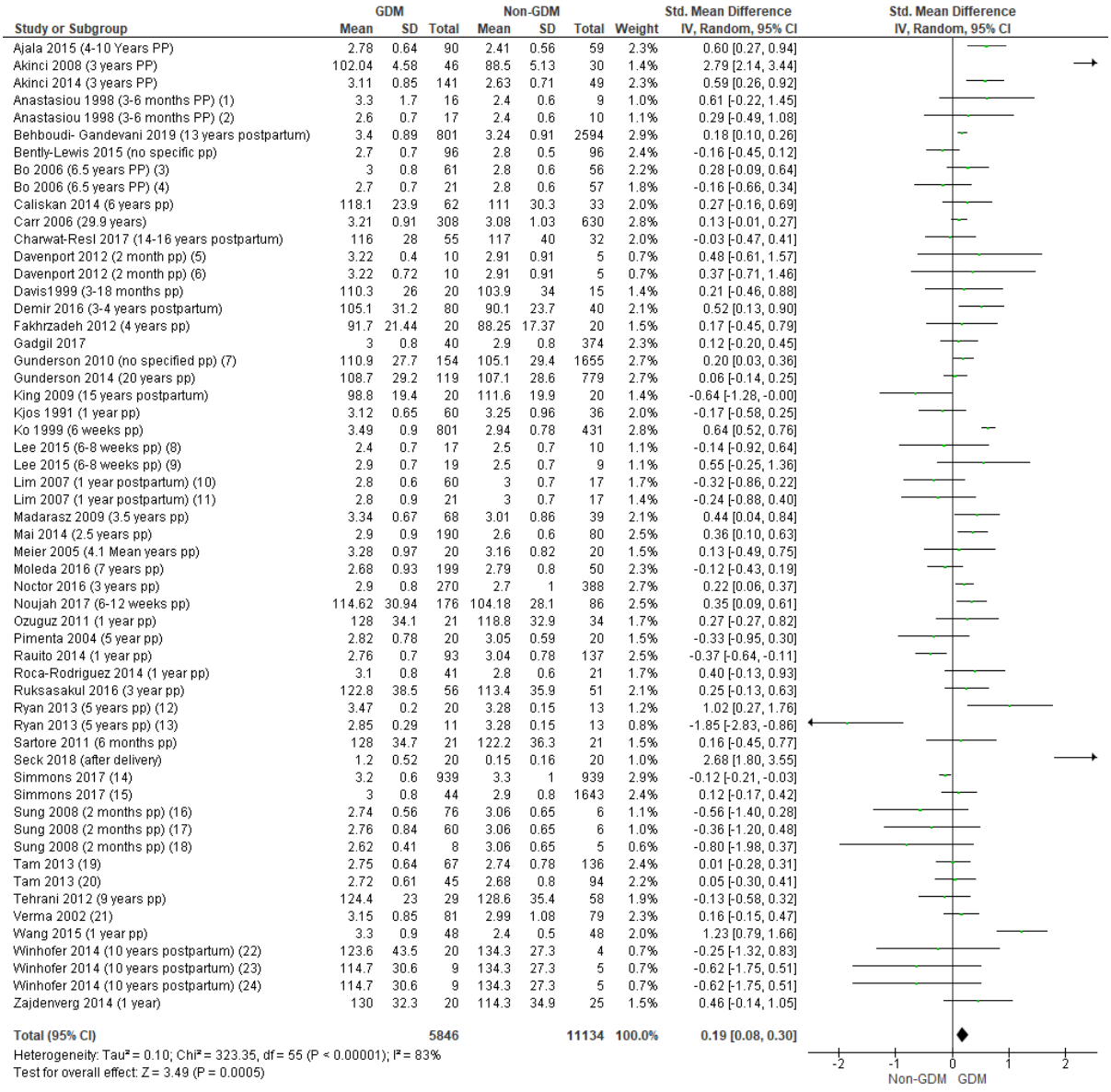


Study or Subgroup	GDM Mean	GDM SD	GDM Total	Non-GDM Mean	Non-GDM SD	Non-GDM Total	Weight	Std. Mean Difference IV, Random, 95% CI
Akinci 2008 (3 years PP)	187.9	6.64	46	166.83	5.98	30	1.3%	3.26 [2.56, 3.97]
Akinci 2014 (3 years PP)	5.07	0.98	141	4.59	0.82	49	2.1%	0.51 [0.18, 0.84]
Anastasiou 1998 (3-6 months PP) (1)	5.8	1.4	16	5.5	0.8	9	1.1%	0.24 [-0.58, 1.06]
Anastasiou 1998 (3-6 months PP) (2)	5.5	0.8	17	4.8	0.7	10	1.1%	0.89 [0.06, 1.71]
Banerjee 2012 (2 year PP)	4.5	0.84	8	4.3	0.54	8	0.9%	0.27 [-0.72, 1.25]
Behboudi- Gandevani 2019 (13 years postpartum)	5.35	1.1	801	5.14	1.1	2594	2.5%	0.19 [0.11, 0.27]
Bently-Lewis 2015 (no specific pp)	5.4	1.2	96	5.2	0.6	96	2.2%	0.21 [-0.07, 0.49]
Caliskan 2014 (6 years pp)	188.7	27.1	62	181.8	32.1	33	1.8%	0.24 [-0.19, 0.66]
Carr 2006 (29.9 years)	5.05	1.09	313	4.93	1.29	631	2.4%	0.10 [-0.04, 0.23]
Charwat-Resl 2017 (14-16 years postpartum)	196	30	55	195	41	32	1.8%	0.03 [-0.41, 0.46]
Davenport 2012 (2 month pp) (3)	5.2	0.59	10	4.59	1.04	5	0.7%	0.76 [-0.36, 1.88]
Davenport 2012 (2 month pp) (4)	5.19	0.84	10	4.59	1.04	5	0.7%	0.62 [-0.48, 1.73]
Davis1999 (3-18 months pp)	183.3	28.3	21	170.5	36.7	18	1.4%	0.39 [-0.25, 1.02]
Demir 2016 (3-4 years postpartum)	188.7	40.1	80	169.3	27.9	40	1.9%	0.53 [0.14, 0.91]
Eroglu 2006 (10-15 months pp)	185.6	30.9	36	151.1	19.1	33	1.6%	1.31 [0.79, 1.84]
Fakhrzadeh 2012 (4 years pp)	178.1	32.02	20	171.25	29.36	20	1.4%	0.22 [-0.40, 0.84]
Ferraz 2007 (6.2 years pp)	4.73	0.13	70	4.75	0.09	108	2.1%	-0.19 [-0.49, 0.12]
Gadgil 2017	5.1	1	40	5	0.9	374	2.1%	0.11 [-0.22, 0.44]
Gunderson 2010 (no specified pp)	179	30	154	174.4	30.7	1655	2.4%	0.15 [-0.02, 0.32]
Gunderson 2014 (20 years pp)	185.6	31.8	119	184.9	31.6	779	2.3%	0.02 [-0.17, 0.22]
Heida 2015 (27-29 years pp) (5)	5.7	1.2	1089	5.8	1.1	15560	2.5%	-0.09 [-0.15, -0.03]
King 2009 (15 years postpartum)	178.6	23.3	20	186.1	22.4	20	1.4%	-0.32 [-0.95, 0.30]
Kjos 1991 (1 year pp) (6)	5.02	0.86	39	5.1	0.99	36	1.8%	-0.09 [-0.54, 0.37]
Ko 1999 (6 weeks pp)	5.47	1	801	4.66	0.83	431	2.4%	0.86 [0.74, 0.98]
Kousta 2003 (2 years pp)	4.5	4.07	34	4.3	4.03	44	1.8%	0.05 [-0.40, 0.50]
Lee 2008 (Median 2.1 year pp)	5.1	1	620	4.5	0.8	868	2.4%	0.67 [0.57, 0.78]
Lee 2015 (6-8 weeks pp) (7)	4.4	0.9	17	4.3	0.7	10	1.1%	0.12 [-0.67, 0.90]
Lee 2015 (6-8 weeks pp) (8)	4.7	0.7	19	4.3	0.7	9	1.1%	0.55 [-0.25, 1.36]
Lim 2007 (1 year postpartum) (9)	4.9	0.7	21	5	0.8	21	1.5%	-0.13 [-0.74, 0.48]
Lim 2007 (1 year postpartum) (10)	4.7	0.7	60	5	0.8	21	1.7%	-0.41 [-0.91, 0.09]
Mai 2014 (2.5 years pp)	4.7	0.8	190	4.4	0.77	80	2.2%	0.38 [0.11, 0.64]
Meier 2005 (4.1 Mean years pp)	5.02	0.68	20	5.05	0.8	20	1.4%	-0.04 [-0.66, 0.58]
Moleda 2016 (7 years pp)	4.93	1	199	4.99	0.88	50	2.1%	-0.06 [-0.37, 0.25]
Noctor 2016 (3 years pp)	5	1	270	4.7	0.8	388	2.4%	0.34 [0.18, 0.49]
Ozuguz 2011 (1 year pp)	218.8	55.1	21	185.2	34.7	34	1.5%	0.76 [0.20, 1.32]
Pimenta 2004 (5 year pp)	4.63	1.11	20	4.53	0.72	20	1.4%	0.10 [-0.52, 0.73]
Pokropek 2015	246	145	285	230	149	4161	2.4%	0.11 [-0.01, 0.23]
Rauito 2014 (1 year pp)	4.75	0.77	94	5.04	0.84	137	2.2%	-0.36 [-0.62, -0.09]
Roca-Rodriguez 2014 (1 year pp)	4.9	0.8	41	4.7	0.6	21	1.6%	0.27 [-0.26, 0.80]
Ruksasakul 2016 (3 year pp)	205.3	42	56	186.8	36.5	51	1.9%	0.47 [0.08, 0.85]
Ryan 2013 (5 years pp) (11)	4.96	0.21	11	5.14	0.16	13	1.0%	-0.94 [-1.80, -0.09]
Ryan 2013 (5 years pp) (12)	5.31	0.24	20	5.14	0.16	13	1.2%	0.78 [0.05, 1.51]
Sartore 2011 (6 months pp)	203.4	38.1	21	204.7	36.1	21	1.5%	-0.03 [-0.64, 0.57]
Seck 2018 (after delivery)	2.33	0.68	20	0.64	0.29	20	0.9%	3.17 [2.21, 4.13]
Simmons 2017 (13)	5.2	0.5	8	5.4	1	939	1.3%	-0.20 [-0.90, 0.50]
Simmons 2017 (14)	4.9	0.9	44	4.8	1	1643	2.1%	0.10 [-0.20, 0.40]
Sung 2008 (2 months pp) (15)	4.53	0.72	72	4.97	0.8	6	1.1%	-0.60 [-1.44, 0.24]
Sung 2008 (2 months pp) (16)	4.74	0.69	60	4.97	0.8	6	1.0%	-0.33 [-1.17, 0.52]
Sung 2008 (2 months pp) (17)	4.47	0.55	8	4.97	0.8	5	0.7%	-0.71 [-1.88, 0.45]
Tam 2012 (18)	4.8	1.1	19	4.7	0.6	14	1.3%	0.11 [-0.59, 0.80]
Tam 2012 (19)	4.7	0.6	25	4.7	0.8	80	1.8%	0.00 [-0.45, 0.45]
Tehrani 2012 (9 years pp)	196.4	26.4	29	201.9	40.1	58	1.8%	-0.15 [-0.60, 0.30]
Verma 2002 (20)	4.9	1.23	87	4.33	0.94	79	2.1%	0.52 [0.21, 0.82]
Verma 2002 (21)	1.27	1.22	58	0.75	0.39	51	1.9%	0.56 [0.17, 0.94]
Verma 2002 (22)	5.03	1.33	81	4.58	1.23	79	2.1%	0.35 [0.04, 0.66]
Vilmi-Kerala 2016 (4 years pp)	4.7	0.9	120	4.6	0.8	120	2.2%	0.12 [-0.14, 0.37]
Wang 2015 (1 year pp)	6.2	1	48	4.8	0.8	48	1.8%	1.53 [1.08, 1.99]
Winhofer 2014 (10 years postpartum) (23)	200	23.1	6	224.7	29.2	5	0.6%	-0.87 [-2.14, 0.40]
Winhofer 2014 (10 years postpartum) (24)	202.5	37.7	9	224.7	29.2	4	0.6%	-0.58 [-1.79, 0.63]
Winhofer 2014 (10 years postpartum) (25)	205.2	63.7	20	224.7	29.2	4	0.8%	-0.31 [-1.39, 0.76]
Zajdenverg 2014 (1 year)	194	33.8	20	185.6	43.8	25	1.5%	0.21 [-0.38, 0.80]
Total (95% CI)			**6817**			**31744**	**100.0%**	**0.26 [0.15, 0.37]**

Heterogeneity: Tau² = 0.13; Chi² = 539.43, df = 60 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.53 (P < 0.00001)

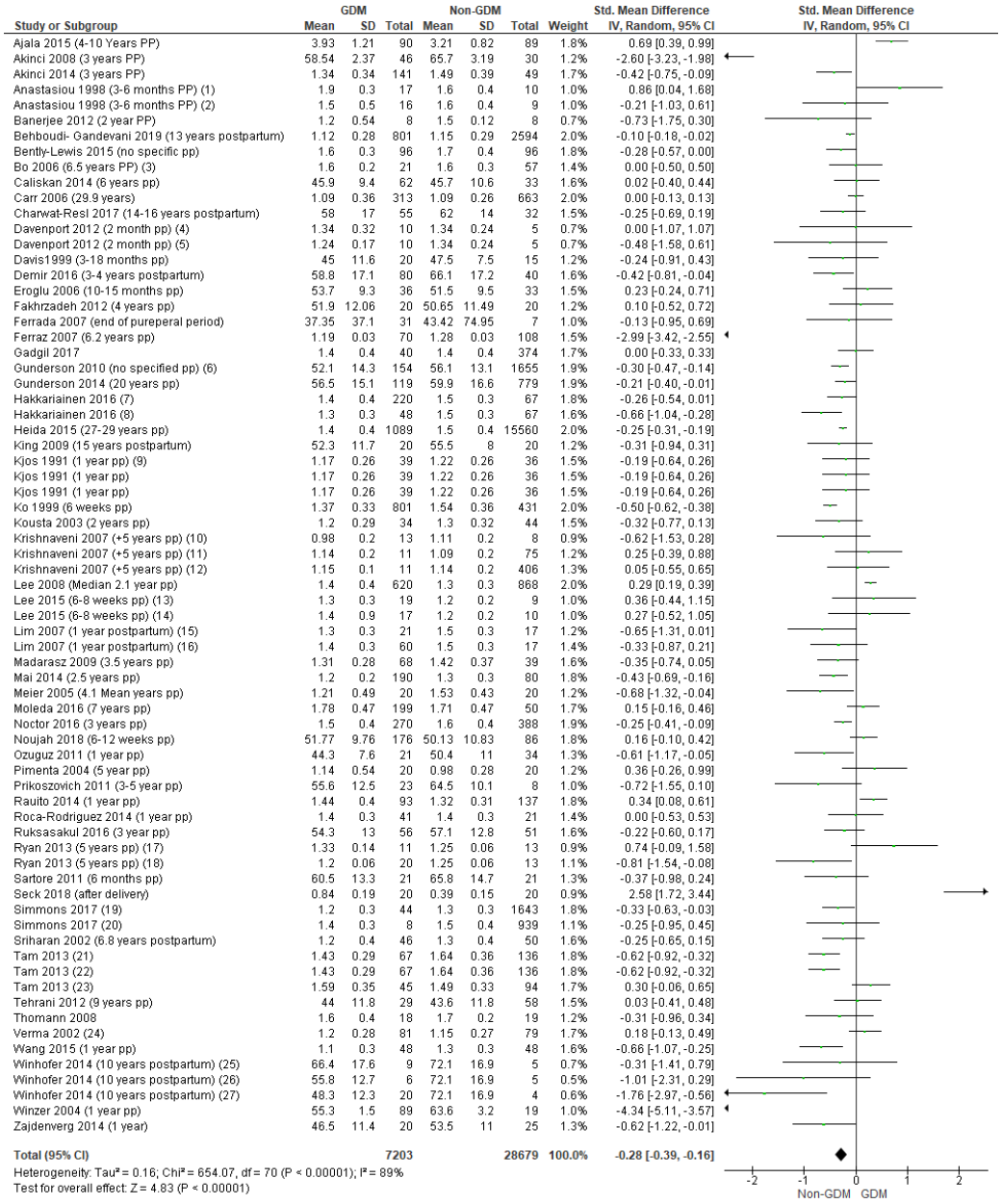
Footnotes
(1) Obese GDM
(2) Nonobese GDM
(3) pGDM-normoglycemic
(4) pGDM-hyperglycemic
(5) Follow-up at 0, 7 10 and 15 years pp
(6) 24-35 month
(7) GDM-IGT
(8) GDM-NGT
(9) GDM IGT
(10) GDM NGT
(11) Premenopausal GDM
(12) Postmenopausal GDM
(13) > 50 years
(14) < 50 years
(15) Previous GDM with Normal Glucose Tolerance
(16) Previous GDM with Impaired Glucose Tolerance
(17) Previous GDM with DM
(18) AGT
(19) NGT
(20) 6 years postpartum
(21) 11 years postpartum
(22) 7 years postpartum
(23) pGDM-IGR
(24) pGDM-NGT
(25) pGDM-DM

Supplementary Figure 3.8 4 Meta-analysis of total cholesterol in women with previous gestational diabetes mellitus compared to women without a history of GDM



Footnotes
(1) Obese GDM
(2) Nonobese GDM
(3) pGDM-BMI > 25, any MS components
(4) pGDM-BMI < 25, no MS components
(5) pGDM-normoglycemic
(6) pGDM-hyperglycemic
(7) Follow-up at 0, 7 10 and 15 years pp
(8) GDM-IGT
(9) GDM-NGT
(10) GDM NGT
(11) GDM IGT
(12) Postmenopausal GDM
(13) Premenopausal GDM
(14) > 50 years
(15) < 50 years
(16) Previous GDM with Normal Glucose Tolerance
(17) Previous GDM with Impaired Glucose Tolerance
(18) Previous GDM with DM
(19) 8 years postpartum
(20) 15 years follow-up
(21) 7 years postpartum
(22) pGDM-T2DM
(23) pGDM-NGT
(24) pGDM-NGT

Supplementary Figure 3.8 5 Meta-analysis of low-density lipoprotein in women with previous gestational diabetes mellitus compared to women without a history of GDM

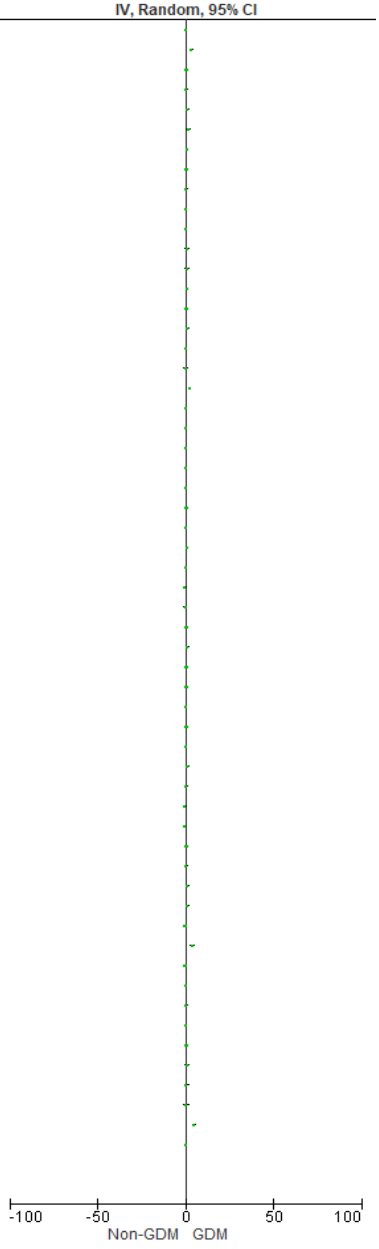


Footnotes
(1) Nonobese GDM
(2) Obese GDM
(3) pGDM-BMI < 25, no MS components
(4) pGDM-normoglycemic
(5) pGDM-hyperglycemic
(6) Follow-up at 0, 7 10 and 15 years pp
(7) <5 year pp -GDM with 1 Abnormal OGTT
(8) <5 year pp pp -GDM with 2 Abnormal OGTT
(9) 24-35 months
(10) pGDM-DM
(11) pGDM-IGT/IFG
(12) pGDM-NGT
(13) GDM-NGT
(14) GDM-IGT
(15) GDM IGT
(16) GDM NGT
(17) Premenopausal GDM
(18) Premenopausal GDM
(19) <50 years
(20) >50 years
(21) 8 years postpartum
(22) 8 years postpartum
(23) 15 years postpartum
(24) 7 years postpartum
(25) pGDM-NGT
(26) pGDM-IGR
(27) pGDM-T2DM

Supplementary Figure 3.8 6 Meta-analysis of high-density lipoprotein in women with previous gestational diabetes mellitus compared to women without a history of GDM

Study or Subgroup	GDM Mean	GDM SD	GDM Total	Non-GDM Mean	Non-GDM SD	Non-GDM Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ajala 2015 (4-10 Years PP)	1.14	0.56	90	0.95	0.59	59	2.1%	0.33 [-0.00, 0.66]
Akinci 2008 (3 years PP)	138.48	20.46	46	82.93	6.38	30	1.5%	3.34 [2.63, 4.06]
Akinci 2014 (3 years PP)	1.35	0.75	141	1.01	0.65	49	2.1%	0.47 [0.14, 0.80]
Anastasiou 1998 (3-6 months PP) (1)	0.96	0.35	17	0.84	0.47	10	1.4%	0.29 [-0.49, 1.08]
Anastasiou 1998 (3-6 months PP) (2)	1.62	0.94	16	0.84	0.47	9	1.3%	0.93 [0.07, 1.80]
Banerjee 2012 (2 year PP)	1.1	0.24	8	0.7	0.3	8	1.0%	1.39 [0.27, 2.52]
Bently-Lewis 2015 (no specific pp)	2.2	1.5	96	1.3	0.7	96	2.2%	0.77 [0.47, 1.06]
Bozkurt 2012 (3-6 months pp) (3)	119.5	51.1	25	89.7	44.8	14	1.6%	0.60 [-0.07, 1.26]
Bozkurt 2012 (3-6 months pp) (4)	106.4	68.4	37	89.7	44.8	15	1.7%	0.26 [-0.34, 0.86]
Caliskan 2014 (6 years pp)	130.7	44.5	62	125.4	58.4	33	2.0%	0.11 [-0.32, 0.53]
Carr 2006 (29.9 years)	1.732	1.75	313	1.669	1.75	633	2.4%	0.04 [-0.10, 0.17]
Davenport 2012 (2 month pp) (5)	1.58	0.96	10	0.73	0.35	5	0.9%	0.97 [-0.17, 2.12]
Davenport 2012 (2 month pp) (6)	1.51	1.07	10	0.73	0.35	5	1.0%	0.81 [-0.32, 1.93]
Davis1999 (3-18 months pp)	141.6	79.7	21	94.7	31.5	17	1.6%	0.73 [0.07, 1.39]
Demir 2016 (3-4 years postpartum)	128.2	113.7	80	79.9	29.5	40	2.1%	0.51 [0.12, 0.89]
Eroglu 2006 (10-15 months pp)	89.8	31	36	61.3	16	33	1.8%	1.13 [0.62, 1.64]
Fakhrzadeh 2012 (4 years pp)	109.3	58.46	20	105.95	41.32	20	1.7%	0.06 [-0.56, 0.68]
Ferrada 2007 (end of pureperal period)	159.7	2,590.39	31	98.05	1,260.89	7	1.3%	0.02 [-0.80, 0.85]
Ferraz 2007 (6.2 years pp)	1.48	0.14	70	1.25	0.07	108	2.1%	2.22 [1.84, 2.60]
Gadgil 2017	1.4	0.6	40	1.3	0.6	374	2.1%	0.17 [-0.16, 0.49]
Gunderson 2010 (no specified pp) (7)	79	36.6	154	65.6	32.1	1655	2.3%	0.41 [0.25, 0.58]
Gunderson 2014 (20 years pp)	100.3	48.3	119	89.5	51	779	2.3%	0.21 [0.02, 0.41]
Hakkariainen 2016 (8)	1.2	0.6	48	1	0.6	67	2.1%	0.33 [-0.04, 0.70]
Hakkariainen 2016 (9)	1.1	0.5	220	1	0.6	67	2.2%	0.19 [-0.08, 0.46]
King 2009 (15 years postpartum)	138.5	88.4	20	94.9	38.4	20	1.6%	0.63 [-0.01, 1.26]
Kjos 1991 (1 year pp) (10)	1.41	0.8	39	1.32	0.73	36	1.9%	0.12 [-0.34, 0.57]
Kousta 2003 (2 years pp)	1	0.43	34	0.7	0.33	44	1.9%	0.79 [0.32, 1.25]
Lee 2008 (Median 2.1 year pp)	3.2	2	620	2.7	1.6	868	2.4%	0.28 [0.18, 0.38]
Lee 2015 (6-8 weeks pp) (11)	1.3	1.2	19	1.7	0.9	9	1.4%	-0.35 [-1.15, 0.45]
Lee 2015 (6-8 weeks pp) (12)	1.6	1.6	17	1.7	0.9	10	1.4%	-0.07 [-0.85, 0.71]
Lim 2007 (1 year postpartum) (13)	1.2	0.6	60	0.9	0.4	17	1.8%	0.53 [-0.02, 1.07]
Lim 2007 (1 year postpartum) (14)	1.7	1.1	21	0.9	0.4	17	1.6%	0.91 [0.23, 1.58]
Mai 2014 (2.5 years pp)	1.3	0.9	190	0.9	0.5	80	2.2%	0.50 [0.23, 0.76]
Meier 2005 (4.1 Mean years pp)	1.29	0.56	20	0.95	0.57	20	1.6%	0.59 [-0.04, 1.22]
Moleda 2016 (7 years pp)	1.11	0.69	199	1.06	0.97	50	2.2%	0.07 [-0.24, 0.38]
Noctor 2016 (3 years pp)	1.3	0.9	270	0.9	0.5	388	2.4%	0.58 [0.42, 0.74]
Noujah 2018 (6-12 weeks pp)	115.64	73.74	176	93.09	53.84	86	2.2%	0.33 [0.07, 0.59]
Ozuguz 2011 (1 year pp)	171.1	113.9	21	83.7	43	34	1.7%	1.11 [0.52, 1.69]
Pimenta 2004 (5 year pp)	1.14	0.54	20	0.99	0.34	20	1.7%	0.33 [-0.30, 0.95]
Prikoszovich 2011 (3-5 year pp)	85.2	38.6	23	97	37.5	8	1.4%	-0.30 [-1.11, 0.51]
Rauito 2014 (1 year pp)	1.24	0.61	93	1.49	0.66	137	2.2%	-0.39 [-0.65, -0.12]
Roca-Rodriguez 2014 (1 year pp)	1.2	0.5	41	0.9	0.4	21	1.8%	0.63 [0.09, 1.17]
Ruksasakul 2016 (3 year pp)	136.38	144	56	89.52	54.4	51	2.1%	0.42 [0.04, 0.80]
Ryan 2013 (5 years pp) (15)	1.69	0.47	11	1.3	0.11	13	1.3%	1.15 [0.27, 2.03]
Ryan 2013 (5 years pp) (16)	1.41	0.13	20	1.3	0.11	13	1.5%	0.88 [0.14, 1.61]
Sartore 2011 (6 months pp)	75.8	24.6	21	79.2	31.9	21	1.7%	-0.12 [-0.72, 0.49]
Seck 2018 (after delivery)	1.47	0.31	20	0.51	0.19	20	1.0%	3.66 [2.61, 4.71]
Simmons 2017 (17)	1.3	0.5	8	1.5	0.9	939	1.5%	-0.22 [-0.92, 0.47]
Simmons 2017 (18)	1.3	0.7	44	1.3	0.7	1643	2.2%	0.00 [-0.30, 0.30]
Tam 2013	1.33	0.8	45	1.06	0.57	94	2.1%	0.41 [0.05, 0.77]
Tam 2013 (19)	1.17	1.16	67	0.96	0.49	136	2.2%	0.27 [-0.02, 0.56]
Verma 2002 (20)	1.94	2.4	81	1.03	0.5	79	2.2%	0.52 [0.20, 0.83]
Winhofer 2014 (10 years postpartum) (21)	232.6	220.9	20	91.7	20.3	5	1.1%	0.68 [-0.32, 1.68]
Winhofer 2014 (10 years postpartum) (22)	107.1	40.9	9	91.7	20.3	5	1.0%	0.41 [-0.70, 1.51]
Winhofer 2014 (10 years postpartum) (23)	104.7	28.7	6	91.7	20.3	4	0.8%	0.45 [-0.84, 1.74]
Winzer 2004 (1 year pp)	104.9	7	89	71.8	7.3	19	1.4%	4.66 [3.86, 5.46]
Zajdenverg 2014 (1 year)	87	38.1	20	88.1	63.1	25	1.7%	-0.02 [-0.61, 0.57]
Total (95% CI)			**4110**			**9065**	**100.0%**	**0.56 [0.42, 0.70]**

Heterogeneity: Tau² = 0.22; Chi² = 448.57, df = 56 (P < 0.00001); I² = 88%
Test for overall effect: Z = 7.69 (P < 0.00001)



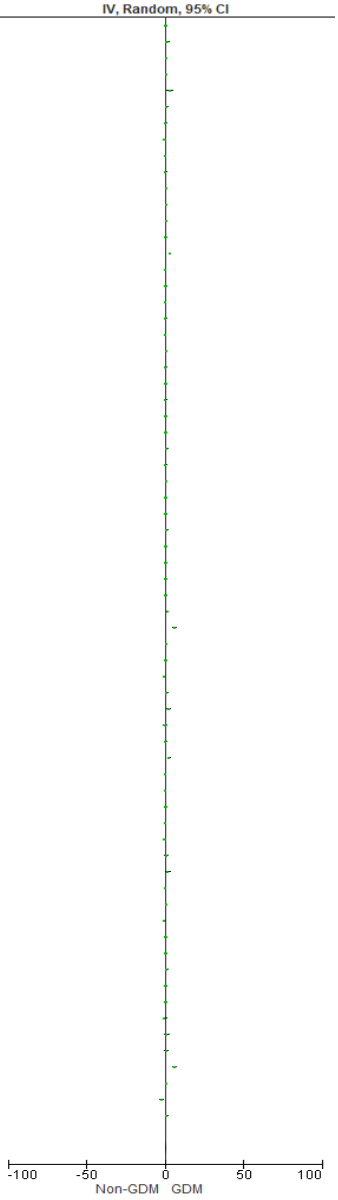
Footnotes
(1) Nonobese GDM
(2) Obese GDM
(3) pGDM-IR
(4) pGDM-IS
(5) pGDM-hyperglycemic
(6) pGDM-normoglycemic
(7) Follow-up at 0, 7 10 and 15 years pp
(8) <5 year pp - GDM with 2 Abnormal OGTT
(9) <5 year pp - GDM with 1 Abnormal OGTT
(10) 24-35 months
(11) GDM-NGT
(12) GDM-IGT
(13) GDM NGT
(14) GDM IGT
(15) Premenopausal GDM
(16) Postmenopausal GDM
(17) >50 years
(18) <50 years
(19) 8 years postpartum
(20) 7 years postpartum
(21) pGDM-T2DM
(22) pGDM-NGT
(23) pGDM-IGR

Figure

Supplementary Figure 3.8 7 Meta-analysis of triglycerides in women with previous gestational diabetes mellitus compared to women without a history of GDM

Study or Subgroup	GDM Mean	GDM SD	GDM Total	Non-GDM Mean	Non-GDM SD	Non-GDM Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ajala 2015 (4-10 Years PP)	4.99	0.6	90	4.64	0.45	59	1.8%	0.64 [0.30, 0.97]
Banerjee 2012 (2 year PP)	5.5	0.78	8	4.7	0.12	8	0.8%	1.36 [0.24, 2.47]
Bo 2006 (6.5 years PP) (1)	5.1	0.5	21	4.8	0.4	57	1.5%	0.69 [0.18, 1.21]
Bo 2006 (6.5 years PP) (2)	5.3	0.6	61	4.8	0.4	56	1.7%	0.97 [0.58, 1.35]
Bowes 1996 (2-3 months pp)	5.7	0.2	7	5	0.2	5	0.3%	3.23 [1.28, 5.18]
Bozkurt 2012 (3-6 months pp) (3)	95.8	16.2	25	83.8	8.3	14	1.3%	0.84 [0.16, 1.53]
Bozkurt 2012 (3-6 months pp) (4)	88.4	12.7	37	83.8	8.3	15	1.4%	0.39 [-0.22, 0.99]
Caliskan 2014 (6 years pp)	92.3	6.9	62	92.9	4.5	33	1.7%	-0.10 [-0.52, 0.33]
Carr 2006 (29.9 years)	9.39	4.37	302	8.04	3.86	620	2.0%	0.33 [0.20, 0.47]
Charwat-Resl 2017 (14-16 years postpartum)	104	55.3	55	84.6	6.5	32	1.6%	0.43 [-0.01, 0.88]
Davis1999 (3-18 months pp)	5.3	0.4	21	5	0.5	18	1.3%	0.65 [0.01, 1.30]
Demir 2016 (3-4 years postpartum)	89.3	11.5	80	78.1	9.2	40	1.7%	1.03 [0.63, 1.43]
Eroglu 2006 (10-15 months pp)	93.4	12.8	36	83.5	9.2	33	1.5%	0.87 [0.38, 1.37]
Fakhrzadeh 2012 (4 years pp)	92.25	9.35	20	87.6	7.82	20	1.3%	0.53 [-0.10, 1.16]
Ferraz 2007 (6.2 years pp)	5.55	0.21	70	5.14	0.06	108	1.6%	2.93 [2.50, 3.36]
Gunderson 2010 (no specified pp) (5)	83.9	10.9	154	81.6	8	1655	2.0%	0.28 [0.11, 0.44]
Gunderson 2014 (20 years pp)	104.2	29.3	119	92.4	18.8	779	1.9%	0.58 [0.38, 0.77]
Hakkariainen 2016 (6)	5.5	0.5	220	5.4	0.4	67	1.9%	0.21 [-0.07, 0.48]
Hakkariainen 2016 (7)	5.8	1.4	48	5.4	0.4	67	1.7%	0.42 [0.04, 0.79]
Han 2018 (no pp specified)	85.99	20.97	4970	85.09	17.44	97930	2.0%	0.05 [0.02, 0.08]
Hunger-Dathe 2006 (6 year pp)	4.8	0.6	132	4.4	0.3	50	1.8%	0.74 [0.41, 1.08]
King 2009 (15 years postpartum)	92.6	14	20	89.1	10.7	20	1.4%	0.28 [-0.35, 0.90]
Ko 1999 (6 weeks pp)	5.48	1.6	801	4.84	0.77	431	2.0%	0.47 [0.35, 0.59]
Kousta 2003 (2 years pp)	5.3	0.43	34	5.1	0.49	44	1.6%	0.43 [-0.03, 0.88]
Lee 2007 (15 years pp)	5.2	1.1	5470	4.5	0.6	783	2.0%	0.67 [0.59, 0.74]
Lee 2008 (Median 2.1 year pp)	5.8	1.8	620	5.2	0.7	868	2.0%	0.47 [0.36, 0.57]
Lee 2015 (6-8 weeks pp) (8)	5.2	0.5	17	4.6	0.5	10	1.1%	1.16 [0.31, 2.01]
Lee 2015 (6-8 weeks pp) (9)	4.8	0.4	19	4.6	0.5	9	1.1%	0.45 [-0.35, 1.25]
Lim 2007 (1 year postpartum) (10)	5.4	0.7	21	5	0.4	17	1.3%	0.67 [0.01, 1.33]
Lim 2007 (1 year postpartum) (11)	5.3	0.6	60	5	0.4	17	1.5%	0.53 [-0.02, 1.07]
Mai 2014 (2.5 years pp)	5.2	1.2	190	4.7	0.5	80	1.9%	0.48 [0.21, 0.74]
McLachlan 2005 (3-6 weeks pp)	5.11	0.741	19	4.54	0.4795	19	1.3%	0.89 [0.22, 1.56]
Moleda 2016 (7 years pp)	5.3	0.7	199	4.9	0.6	50	1.8%	0.59 [0.27, 0.90]
Noctor 2016 (3 years pp)	5.07	0.95	270	4.65	0.41	388	2.0%	0.61 [0.45, 0.77]
Noujah 2018 (6-12 weeks pp)	91.81	18.25	186	82.19	9.68	86	1.9%	0.60 [0.34, 0.86]
Osei 1998 (7 years pp)	96.4	30.9839	15	83.7	7.36	15	1.2%	0.55 [-0.18, 1.28]
Ozuguz 2011 (1 year pp)	104.1	20.2	21	81.2	10.3	34	1.4%	1.52 [0.90, 2.14]
Pacini 2012 (6 months pp)	5.08	0.08	104	4.62	0.06	35	1.1%	6.06 [5.24, 6.87]
Pimenta 2004 (5 year pp)	5.1	0.4	20	4.8	0.3	20	1.3%	0.83 [0.18, 1.48]
Pokropek 2015	126	65	135	106	33	2005	2.0%	0.56 [0.38, 0.73]
Rauito 2014 (1 year pp)	5.41	0.47	86	5.7	0.64	109	1.8%	-0.51 [-0.79, -0.22]
Roca-Rodriguez 2014 (1 year pp)	5.4	0.6	41	4.9	0.2	21	1.5%	0.98 [0.43, 1.54]
Ryan 2013 (5 years pp) (12)	5.9	0.2	20	5.5	0.1	13	1.0%	2.32 [1.40, 3.23]
Ryan 2013 (5 years pp) (13)	5.5	0.2	11	5.5	0.1	13	1.1%	0.00 [-0.80, 0.80]
Sartore 2011 (6 months pp)	88.2	9.1	21	83.9	20.5	21	1.4%	0.27 [-0.34, 0.87]
Seck 2018 (after delivery)	1.26	0.24	20	0.7	0.23	20	1.1%	2.34 [1.51, 3.16]
Shen 2018 (3 years pp)	5.43	0.99	1263	5.23	0.52	705	2.0%	0.23 [0.14, 0.33]
Simmons 2017 (14)	5.4	0.9	8	5.4	0.8	939	1.3%	0.00 [-0.70, 0.70]
Simmons 2017 (15)	5.5	1	44	5.1	0.8	1643	1.8%	0.50 [0.20, 0.80]
Sriharan 2002 (6.8 years postpartum)	5.7	0.9	46	5.5	1.1	50	1.7%	0.20 [-0.20, 0.60]
Sung 2008 (2 months pp) (16)	4.9	0.4	72	5	0.4	6	1.1%	-0.25 [-1.08, 0.59]
Sung 2008 (2 months pp) (17)	5.5	0.6	60	5	0.4	6	1.1%	0.84 [-0.01, 1.69]
Sung 2008 (2 months pp) (18)	6.7	1.1	8	5	0.4	5	0.6%	1.74 [0.36, 3.11]
Tehrani 2012 (9 years pp)	90.1	13.1	29	89.4	7.8	58	1.6%	0.07 [-0.38, 0.52]
Thomann 2008	5.1	0.6	18	4.7	0.4	19	1.3%	0.77 [0.10, 1.44]
Tura 2006 (4-6 months pp)	40.1	17.6	24	48.7	18.7	23	1.4%	-0.47 [-1.05, 0.11]
Verma 2002 (19)	4.51	2.13	57	3.63	0.37	50	1.7%	0.55 [0.17, 0.94]
Vigneault 2015 (4 years pp) (20)	5.58	0.63	86	5.18	0.65	42	1.7%	0.62 [0.25, 1.00]
Vigneault 2015 (4 years pp) (21)	6.05	0.7	61	5.38	0.66	15	1.4%	0.96 [0.37, 1.54]
Vigneault 2015 (4 years pp) (22)	5.63	0.58	69	5.32	0.61	26	1.6%	0.52 [0.07, 0.98]
Vilmi-Kerala 2016 (4 years pp)	5.6	0.6	120	5.3	0.3	120	1.9%	0.63 [0.37, 0.89]
Winhofer 2014 (10 years postpartum) (23)	86.9	10	20	89.3	7.5	4	0.8%	-0.24 [-1.32, 0.84]
Winhofer 2014 (10 years postpartum) (24)	136.5	56.2	6	89.3	7.5	5	0.6%	1.02 [-0.28, 2.32]
Winhofer 2014 (10 years postpartum) (25)	102	18.2	9	89.3	7.5	5	0.8%	0.77 [-0.38, 1.91]
Winzer 2004 (1 year pp)	90.7	1.3	89	82.8	1.2	19	0.9%	6.11 [5.14, 7.08]
Xiang 2013	5.31	0.59	93	4.93	0.5	142	1.9%	0.70 [0.44, 0.97]
Xiong 2013 (1.9 years pp)	6.85	1.97	20	11.37	1.91	19	1.1%	-2.28 [-3.11, -1.46]
Zajdenverg 2014 (1 year)	83.2	13	20	71.6	9.4	25	1.3%	1.02 [0.40, 1.65]
Total (95% CI)			**17180**			**110720**	**100.0%**	**0.69 [0.56, 0.81]**

Heterogeneity: Tau² = 0.20; Chi² = 1153.40, df = 67 (P < 0.00001); I² = 94%
Test for overall effect: Z = 10.74 (P < 0.00001)

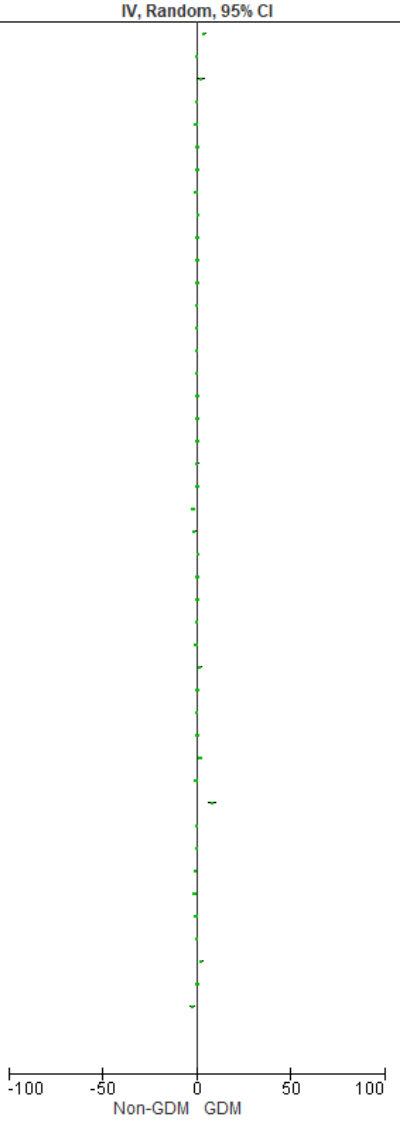


Footnotes
(1) pGDM- BMI < 25 no MS components
(2) pGDM- BMI > 25 some MS components
(3) pGDM-IR
(4) pGDM-IS
(5) Follow-up at 0, 7 10 and 15 years pp
(6) <5 years pp -GDM with 1 Abnormal OGTT
(7) <5 years pp -GDM with 2 Abnormal OGTT
(8) GDM-IGT
(9) GDM-NGT
(10) GDM IGT
(11) GDM NGT
(12) Postmenopausal GDM
(13) Premenopausal GDM
(14) >50 years
(15) <50 years
(16) Previous GDM with Normal Glucose Tolerance
(17) Previous GDM with Impaired Glucose Tolerance
(18) Previous GDM with DM
(19) 9 years postpartum
(20) Normal Weight
(21) Obese
(22) Overweight
(23) pGDM-T2DM
(24) pGDM-IGR
(25) pGDM-NGT

Supplementary Figure 3.8 8 Meta-analysis of blood glucose in women with previous gestational diabetes mellitus compared to women without a history of GDM

Study or Subgroup	GDM Mean	GDM SD	GDM Total	Non-GDM Mean	Non-GDM SD	Non-GDM Total	Weight	Std. Mean Difference IV, Random, 95% CI
Akinci 2008 (3 years PP)	16.28	2.83	46	7.25	0.78	30	1.8%	3.95 [3.16, 4.75]
Akinci 2014 (3 years PP)	7.44	5.51	141	6.06	3.26	49	2.6%	0.27 [-0.05, 0.60]
Bowes 1996 (2-3 months pp)	19.4	5.3	7	8.7	1.5	5	0.9%	2.34 [0.72, 3.96]
Caliskan 2014 (6 years pp)	11.6	6.1	62	10.3	4.1	33	2.5%	0.23 [-0.19, 0.66]
Charwat-Resl 2017 (14-16 years postpartum)	36.4	42	55	46.5	38.8	32	2.4%	-0.24 [-0.68, 0.19]
Davis1999 (3-18 months pp)	114	99	21	77	24	18	2.1%	0.49 [-0.15, 1.13]
Demir 2016 (3-4 years postpartum)	13.7	11.9	80	7	3.9	40	2.5%	0.67 [0.28, 1.06]
Eroglu 2006 (10-15 months pp)	7.5	3.1	36	8.6	5.7	33	2.4%	-0.24 [-0.71, 0.23]
Fakhrzadeh 2012 (4 years pp)	10.19	5.04	20	6.44	4.52	20	2.1%	0.77 [0.12, 1.41]
Ferraz 2007 (6.2 years pp)	51.95	4.02	70	49.98	4.43	108	2.6%	0.46 [0.15, 0.76]
Gunderson 2010 (no specified pp) (1)	14	10.1	154	10.8	6.9	1655	2.8%	0.44 [0.28, 0.61]
Hakkariainen 2015 (2)	12.2	7.4	48	9.3	4.6	134	2.6%	0.53 [0.19, 0.86]
Hakkariainen 2015 (3)	9.8	5.6	26	8.6	5.3	132	2.5%	0.22 [-0.20, 0.64]
Hakkariainen 2015 (4)	11.7	9.4	220	9.3	4.6	134	2.7%	0.30 [0.09, 0.52]
Hakkariainen 2015 (5)	10.1	5.9	92	9.4	8.1	119	2.7%	0.10 [-0.18, 0.37]
Hakkariainen 2015 (6)	11.7	9.4	220	9.3	4.6	134	2.7%	0.30 [0.09, 0.52]
Hakkariainen 2015 (7)	12.2	7.4	48	9.3	4.6	134	2.6%	0.53 [0.19, 0.86]
Hakkariainen 2015 (8)	12.9	5.8	47	9.4	8.1	119	2.6%	0.46 [0.12, 0.80]
Hakkariainen 2015 (9)	11.4	6.3	56	8.6	5.3	132	2.6%	0.50 [0.18, 0.81]
King 2009 (15 years postpartum)	13.1	5.4	20	11.4	5.2	20	2.1%	0.31 [-0.31, 0.94]
Kousta 2003 (2 years pp)	63	70.2	34	30	34.5	44	2.4%	0.62 [0.16, 1.07]
Lee 2015 (6-8 weeks pp) (10)	19.1	10.8	19	60.3	38.9	9	1.6%	-1.71 [-2.64, -0.78]
Lee 2015 (6-8 weeks pp) (11)	22	22.7	17	60.3	38.9	10	1.7%	-1.26 [-2.12, -0.39]
Lim 2007 (1 year postpartum) (12)	91.5	61	21	56.2	11.4	17	2.1%	0.75 [0.09, 1.41]
Lim 2007 (1 year postpartum) (13)	77.2	35.5	60	56.2	11.4	17	2.3%	0.65 [0.10, 1.20]
Mai 2014 (2.5 years pp)	9.2	5.2	190	7	3.5	80	2.7%	0.46 [0.20, 0.72]
Moleda 2016 (7 years pp)	13.7	8.7	199	13.7	8.5	50	2.6%	0.00 [-0.31, 0.31]
Osei 1998 (7 years pp)	12.45	13.8	15	13.75	4.23	15	2.0%	-0.12 [-0.84, 0.59]
Ozuguz 2011 (1 year pp)	13.5	3.1	21	7.3	3.4	34	2.1%	1.86 [1.21, 2.51]
Pacini 2012 (6 months pp)	60	4	104	57	5	35	2.5%	0.70 [0.31, 1.09]
Pokropek 2015	16	13	134	14	12	1972	2.8%	0.17 [-0.01, 0.34]
Roca-Rodriguez 2014 (1 year pp)	96.1	58.1	41	60.3	30.8	21	2.3%	0.70 [0.16, 1.24]
Ryan 2013 (5 years pp) (14)	90	11	20	71	5	13	1.7%	2.02 [1.15, 2.90]
Ryan 2013 (5 years pp) (15)	70	15	11	71	5	13	1.8%	-0.09 [-0.89, 0.71]
Seck 2018 (after delivery)	17.02	0.24	20	3.59	2.25	20	0.6%	8.23 [6.23, 10.22]
Tura 2006 (4-6 months pp)	4.54	0.24	24	4.55	0.29	23	2.2%	-0.04 [-0.61, 0.53]
Verma 2002 (16)	89.59	61.12	57	78.48	47.92	50	2.5%	0.20 [-0.18, 0.58]
Vigneault 2015 (4 years pp) (17)	77.93	32.2	69	95.23	32.2	26	2.4%	-0.53 [-0.99, -0.08]
Vigneault 2015 (4 years pp) (18)	59.49	29.7	86	84.66	29.9	42	2.5%	-0.84 [-1.22, -0.46]
Vigneault 2015 (4 years pp) (19)	123.44	56.3	61	128.07	55.4	15	2.2%	-0.08 [-0.65, 0.48]
Vilmi-Kerala 2016 (4 years pp)	5.2	3.6	120	4.6	3.6	120	2.7%	0.17 [-0.09, 0.42]
Winzer 2004 (1 year pp)	61.2	4.2	89	50.4	3.6	19	2.1%	2.61 [2.00, 3.22]
Xiang 2013	75	55.6	93	48.6	56.3	142	2.7%	0.47 [0.20, 0.73]
Xiong 2013 (1.9 years pp)	6.85	1.97	20	11.37	1.91	19	1.8%	-2.28 [-3.11, -1.46]
Total (95% CI)			**2994**			**5887**	**100.0%**	**0.41 [0.23, 0.59]**

Heterogeneity: Tau² = 0.30; Chi² = 410.28, df = 43 (P < 0.00001); I² = 90%
Test for overall effect: Z = 4.46 (P < 0.00001)



Footnotes
(1) Follow-up at 0, 7 10 and 15 years pp
(2) <5 year pp -GDM with 2 Abnormal OGTT
(3) 10 year pp -GDM with 1 Abnormal OGTT
(4) <5 year pp -GDM with 1 Abnormal OGTT
(5) 5-10 year pp -GDM with 1 Abnormal OGTT
(6) <5 year pp -GDM with 1 Abnormal OGTT
(7) <5 year pp -GDM with 2 Abnormal OGTT
(8) 5-10 year pp -GDM with 1 Abnormal OGTT
(9) 10 year pp -GDM with 2 Abnormal OGTT
(10) GDM-NGT
(11) GDM-IGT
(12) GDM IGT
(13) GDM NGT
(14) Postmenopausal GDM
(15) Premenopausal GDM
(16) 9 years postpartum
(17) Overweight
(18) Normal Weight
(19) Obese

Supplementary Figure 3.8 9 Meta-analysis of insulin in women with previous gestational diabetes mellitus compared to women without a history of GDM

Supplementary Table 3.8 3 Sensitivity analysis for SBP (mmHg)

Analysis	Studies	Participants	MD	95% CI	Chi² P=	I² (%)
All Studies	46	49,963	2.47	1.61, 3.32	P< 0.00001	80%
After Sensitivity analysis	39	47,687	2.53	1.61, 3.44	P< 0.00001	82%

Supplementary Table 3.8 4 Sensitivity analysis for DBP (mmHg)

Analysis	Studies	Participants	MD	95% CI	Chi² P=	I² (%)
All Studies	46	49,580	1.87	1.30, 2.44	P< 0.00001	83%
After Sensitivity analysis	39	47,064	1.83	1.22, 2.44	P< 0.00001	85%

Supplementary Table 3.8 5 Sensitivity analysis for BMI (kg/m2)

Analysis	Studies	Participants	MD	95% CI	Chi² P=	I² (%)
All Studies	78	255,308	1.54	1.17, 1.91	P< 0.00001	97%
After Sensitivity analysis	65	163,156	1.52	1.14, 1.90	P< 0.00001	95%

Supplementary Table 3.8 6 Sensitivity analysis for total cholesterol

Analysis	Studies	Participants	SMD	95% CI	Chi² P=	I² (%)
All Studies	48	38,561	0.26	0.15, 0.37	P< 0.00001	89%
After Sensitivity analysis	43	36,534	0.26	0.14, 0.39	P< 0.00001	90%

Supplementary Table 3.8 7 Sensitivity analysis for low-density lipoprotein

Analysis	Studies	Participants	SMD	95% CI	Chi² P=	I² (%)
All Studies	44	16,980	0.19	0.08, 0.30	P< 0.00001	83%
After Sensitivity analysis	39	14,957	0.19	0.07, 0.31	P< 0.00001	85%

Supplementary Table 3.8 8 Sensitivity analysis for high-density lipoprotein

Analysis	Studies	Participants	SMD	95% CI	Chi² P=	I² (%)
All Studies	56	35,882	-0.28	-0.39, -0.16	P< 0.00001	89%
After Sensitivity analysis	51	33,859	-0.28	-0.405,-0.17	P< 0.00001	90%

Supplementary Table 3.8 9 Sensitivity analysis for triglycerides

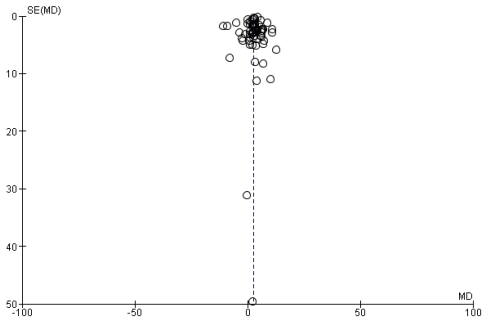
Analysis	Studies	Participants	SMD	95% CI	Chi² P=	I² (%)
All Studies	46	13,175	0.56	0.42, 0.70	P< 0.00001	88%
After Sensitivity analysis	43	13,045	0.56	0.41, 0.70	P< 0.00001	88%

Supplementary Table 3.8 10 Sensitivity analysis for glucose

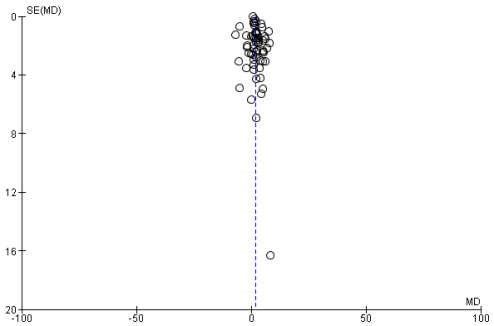
Analysis	Studies	Participants	SMD	95% CI	Chi² P=	I² (%)
All Studies	55	127,900	0.69	0.56, 0.82	P< 0.00001	94%
After Sensitivity analysis	49	125,632	0.62	0.50, 0.75	P< 0.00001	94%

Supplementary Table 3.8 11 Sensitivity analysis for insulin

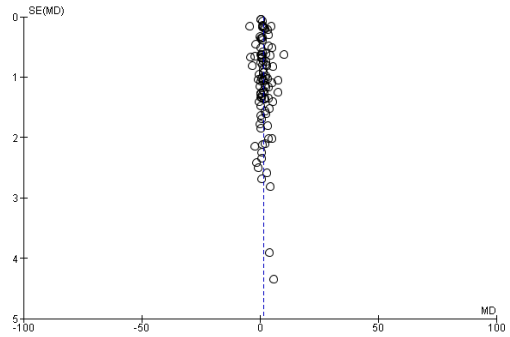
Analysis	Studies	Participants	SMD	95% CI	Chi² P=	I² (%)
All Studies	32	8,881	0.41	0.23, 0.59	P< 0.00001	90%
After Sensitivity analysis	27	6,795	0.41	0.20, 0.61	P< 0.00001	90%


SE(MD)
MD

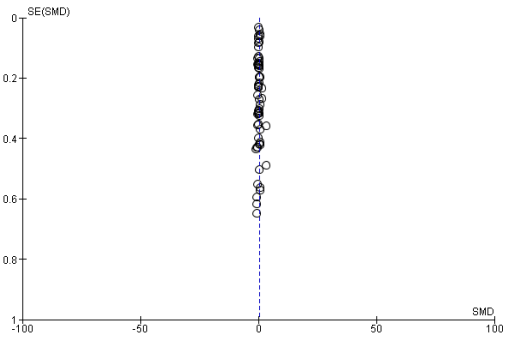
(A)


SE(MD)
MD

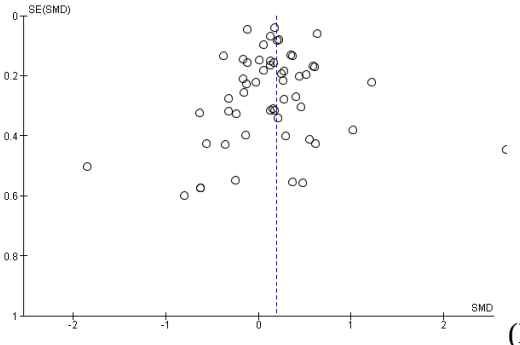
(B)


SE(MD)
MD

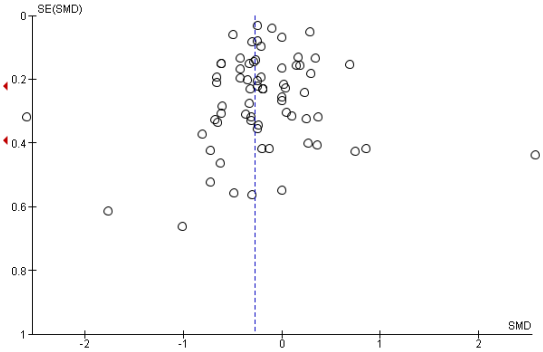
(C)


SE(SMD)
SMD

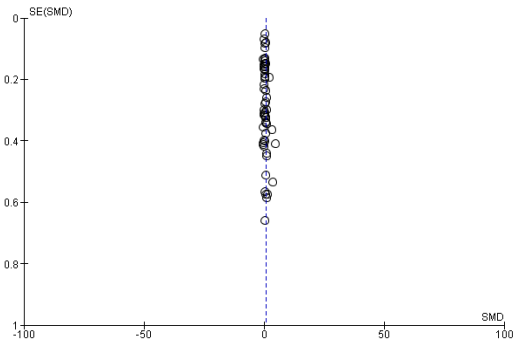
(D)


SE(SMD)
SMD

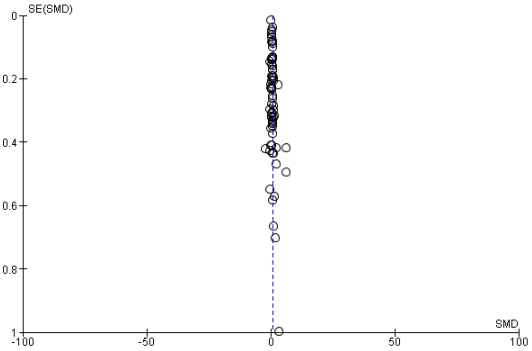
(E)


SE(SMD)
SMD

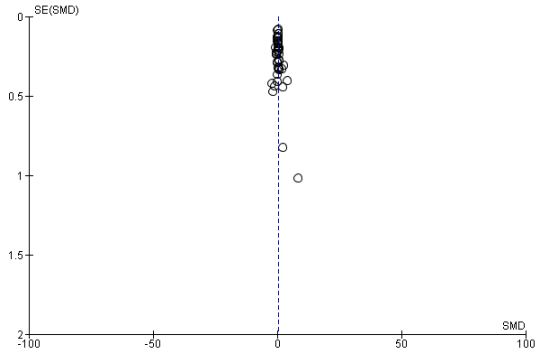
(F)


SE(SMD)
SMD

(G)


SE(SMD)
SMD

(H)



Supplementary Figure 3.8 10 Funnel plots for meta-analyses of cardiovascular risk factors in women with previous gestational diabetes mellitus compared to women without a history of GDM(A) systolic blood pressure; (B) diastolic blood pressure; (C) body mass index; (D) total cholesterol; (E) low density lipoprotein; (F) high density lipoprotein; (G) triglycerides; (H) blood glucose; (I) blood insulin

(I)

Chapter 4

4. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: a systematic review and meta-analysis

Maleesa M Pathirana , Zohra Lassi , Claire T Roberts, Prabha H Andraweera

4.1. Statement of Authorship

Title of Paper	Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: A systematic review and meta-analysis
Publication Status	Published – 2020
Publication Details	**Pathirana MM,** Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis. J Dev Orig Health Dis. 2020 Dec;11(6):599-616. doi: 10.1017/S2040174419000850. Epub 2020 Jan 6. PMID: 31902382.

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Acquiring data, knowledge, analysis, drafting
Overall Percentage (%)	70%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature	**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Zohra S Lassi	
Contribution to the Paper	Conceptualisation, acquiring data, analysis, drafting	
Signature		**Date 14 Feb 2022**

Name of Co-Author	Claire Roberts	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Name of Co-Author	Prabha Andraweera	
Contribution to the Paper	Conception, acquiring data, knowledge, drafting	
Signature		**Date 28/02/2022**

4.2. Abstract

Gestational diabetes mellitus is a pregnancy complication that affects 1 in 7 pregnancies. Emerging evidence demonstrates that children born of pregnancies complicated by GDM may be at increased risk of cardiovascular disease (CVD) in adulthood. Therefore, the aim of this study was to determine cardiovascular factors in offspring exposed to GDM *in utero*. PubMed, CINAHL, SCOPUS, and EMBASE databases were searched. Information was extracted on established CVD risk factors including blood pressure, lipids, blood glucose, fasting insulin, body mass index (BMI) and endothelial/microvascular function. The review protocol is registered in PROSPERO (CRD42018094983).Prospective and retrospective studies comparing offspring exposed to GDM compared to controls (non-GDM pregnancies) were considered. We included studies which defined GDM based on the IADPSG definition, or prior definitions. The PRISMA guidelines were followed in conducting this systematic review. Methodological quality was assessed using the Newcastle – Ottawa Quality Assessment Scale. Study selection, data extraction and quality assessment were done by two independent reviewers. The data were pooled using a random-effects model. Of 59 eligible studies, 24 were included in the meta-analysis. Offspring exposed to GDM had higher systolic blood pressure (mean difference (MD): 1.75 mmHg, 95% CI 0.57-2.94; eight studies, 7,264 participants), BMI z-score (MD: 0.11 (95% CI 0.02- 0.20; 9 studies, 8,759 participants) and glucose (standard MD (SMD) 0.43, 95%CI 0.08-0.77; 11 studies, 6,423 participants) than control participants. In conclusion, offspring exposed to GDM have elevated systolic blood pressure, BMI and glucose. Those exposed to GDM *in utero* may benefit from early childhood blood pressure measurements

4.3. Introduction

The incidence of cardiovascular disease (CVD) has shown a rapid increase over the last decade. In 2012, there were an estimated 17.6 million deaths from CVD, accounting for 31.43% of global mortality [224]. Emerging evidence demonstrates an association between gestational diabetes mellitus (GDM) and CVD with risk factors for CVD being more prevalent among women who experienced gestational diabetes (GDM) compared to those who did not[34, 224]

Prevalence of GDM varies between populations, but it is estimated to affect 1 in 7 pregnancies[79]. The definition of GDM has changed over recent years, as it has become apparent that mild glucose intolerance in pregnancy which was not formerly considered as GDM increases the risk of developing type 2 diabetes mellitus (T2DM) and CVD in later life[225]. A recent meta-analysis showed a 7.5-fold increase in the risk of T2DM among women who experience GDM[34].

Emerging evidence also suggests that children born after pregnancies complicated by GDM may also be at increased risk of CVD in adult life. Tam *et al.* (2017) showed that for every 1-SD (standard deviation) increase in maternal glycaemic level, there was an increase in the adjusted Odds Ratio for impaired glucose tolerance in the offspring[226]. A meta-analysis conducted by Aceti *et al.* and colleagues demonstrated that systolic blood pressure was higher in offspring of women who experienced GDM than controls[52].

At present there is no systematic review comparing the main conventional CVD risk factors between offspring exposed to GDM *in utero* compared to controls. Both vascular and metabolic CVD risk factors constitute metabolic syndrome which is a well-established risk factor for CVD[227] . Therefore, synthesising evidence on all CVD risk factors will provide important information that can guide preventive strategies to reduce the global burden of CVD.

The primary objective of this study was to conduct a comprehensive systematic review and meta-analyses of all relevant studies published until October 2018 to assess conventional CVD risk factors including systolic and diastolic blood pressure, body mass index, lipids, blood glucose and insulin levels. As a secondary objective, we aimed to assess all relevant studies that assessed microvascular function.

4.4. Methods

4.4.1. Search strategy

All studies describing the association between GDM and offspring cardiovascular disease risks were identified by searching the following electronic databases: PubMed CINAHL, SCOPUS and EMBASE with an end of search date of April 18, 2018. Subsequently we updated the literature search to include all relevant articles published until October 17, 2018. The review protocol is registered in PROSPERO (CRD42018094983). No amendments have been made to the current protocol.

The review was undertaken with reference to the PRISMA guidelines[228]. The search strategy is as follows**:** ("gestational diabetes*" OR "pregnancy induced diabetes" OR "diabetic pregnancy") AND (offspring OR newborn OR baby OR babies OR children OR infant OR neonat* OR adolescen* OR adult) AND ("blood pressure" OR diabetes OR cardiovascular OR metabolic OR hypertension OR BMI or "body mass index" OR obesity OR overweight OR lipids OR lipid OR cholesterol OR triglyceride* OR glucose OR insulin OR vascular). We included case-control studies, cohort studies and clinical trials. Conference abstracts were also screened. Previous systematic reviews and meta-analyses on relevant topics were identified, and references from eligible reviews were checked for additional studies. All identified studies were assessed for relevance by two independent authors (MP, PA). Data were independently extracted by two authors (MP, PA). Discrepancies were resolved by discussion.

4.4.2. Inclusion criteria

The population of interest and exposure were offspring at any follow up visit born to women who experienced GDM during pregnancy. We selected studies that assessed conventional CVD risk factors in offspring exposed to GDM *in utero* compared to

offspring not exposed to GDM *in utero*. The CVD risk factor outcomes were blood pressure, BMI, serum and cord blood lipids, and serum and cord blood insulin and glucose.

We included studies that defined GDM based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG). However, as diagnostic criteria have recently changed, we included studies that used prior diagnostic criteria of GDM including the 1999 World Health Organization definition, and other regional definitions. The definitions of GDM of included studies are detailed in Table 1. Studies that did not have the above definition/s of GDM, those that did not define study groups and those that compared GDM and another risk group collectively were excluded. Studies that compared offspring exposed to GDM with offspring exposed to impaired glucose tolerance *in utero* were included, in the review but were not included in the meta-analysis. The data from these studies are presented in Table 2.

Data were extracted independently and in duplicate for outcomes systolic blood pressure, diastolic blood pressure, body mass index (BMI), serum and cord lipid levels (total cholesterol, low density lipoprotein (LDL) high density lipoprotein (HDL), non-HDL and triglycerides), blood glucose, fasting insulin and measures of vascular/endothelial function. When the same cohort was reported in multiple publications at different ages, the study reporting on the older age group was included in the meta-analysis. We considered both studies published in English, and studies that could be translated to English. We contacted authors via email for missing information or data clarification if necessary, and if authors did not respond then any relevant data from their respective studies were included in Supplementary Table S1.

4.4.3. Statistical analysis

The following data were collected from each included study: definition of GDM, age of offspring at follow-up, number of cases/exposed to GDM *in utero* and controls/not-exposed to GDM *in utero*, birthweight and gestational age at birth of cases and controls. For each outcome measure, mean and standard deviation (SD) were used in meta-analyses. When mean and SD were not reported, Standard Error of Mean (SEM) and 95% CI was converted to SD via statistical software[229]. For studies reporting using Median and IQR, the results are detailed in Supplementary Table S1. The Standard Mean Difference (SMD) or Mean Difference (MD) and the 95% CI were calculated using a random-effects model. SMD was used when the outcome was measured in different units across trials and MD when units were consistent.

The meta-analysis was performed using Cochrane Collaborations RevMan software (Review Manager Version 5.1.1) based on an inverse variance method. As per protocol, the random-effects model was selected to account for the variation in different criteria used to diagnose GDM among the studies. However, to ensure that the results were not influenced by the choice of model, each analysis was repeated using a fixed-effects model. No difference in results was seen between the two models (results not shown). Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the Chi^2 P value was less than 0.1. To assess publication bias, funnel plots were used. The methodological quality and risk of bias was assessed using Newcastle - Ottawa Quality Assessment Scale (Supplementary Table S2) [230]. Sensitivity analyses were performed to evaluate heterogeneity for outcomes when omitting low quality

studies. Two authors (MP, PA) independently assessed the quality of each study included in the review. The discrepancies were resolved through discussions.

4.5. Results

4.5.1. Search Results

A total of 4,359 articles were identified from the literature search. One hundred and twelve articles were eligible for full text review. Of these, 59 were included in the review and 25 were included in the meta-analyses. The reasons for excluding 53 studies are detailed in Figure 4.5.1.1. We contacted nine authors for additional data, with responses from four authors (44.4% response), however the authors of these four studies did not have data that could be used in the meta-analyses and hence are included in Supplementary Table 4.8.1.

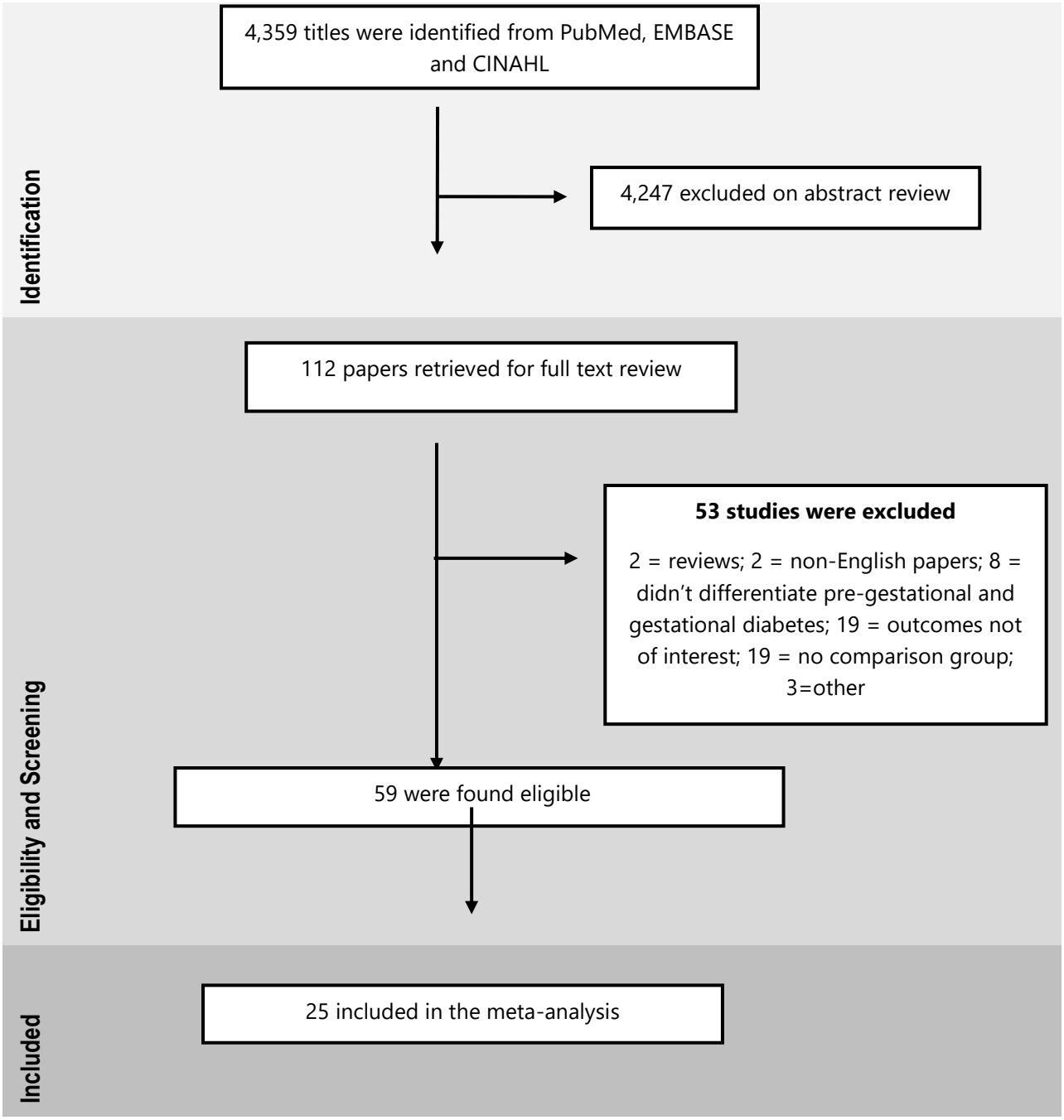


Figure 4.5.1.1 PRISMA Flow diagram of study selection

Table 4.5.1-1 Characteristics of the included studies

Author	Year	Study design	Country	Definition of GDM	Exposed/Non-exposed (n=)	Birthweight cases/Control(g)	Gestational age cases/control (weeks)	Follow up (years)	Outcome measure considered
Kaseva	2018	Multi-cohort study	Finland	(Both cohorts): OGTT at 26-28 weeks: Indications for screening: glycosuria, prior GDM, suspected fetal macrosomia, previous macrosomic infant (birth weight 44500 g), maternal pre-pregnancy BMI ⩾25 kg m− 2, and maternal age ⩾40 years. Overnight fasting by using a 75-g oral glucose load. Cutoff limits for GDM were used for venous blood glucose: 45.5 mmol l − 1 at fasting, 411.0 mmol l − 1 and 48.0 mmol l − 1, 1 and 2 h after the glucose load, respectively. A diagnosis of GDM was made with one abnormal value in the OGTT.	191/547	ESTER cohort: 3651 (601)/ 3519 (466) ALYS cohort: 3881 (648)/ 3555 (462)	ESTER cohort: 39.0 (1.8)/ 39.8 (1.5) ALYS cohort: 39.0 (1.5)/ 40.0 (1.3)	23-25 years after delivery	BMI (kg/m^2)

Kearny	2018	Cohort study	USA	Based on hospital records from two major hospitals with a neonatal care unit in the metropolitan area of Quebec City (Hospital Saint-François d'Assise, Centre Hospitalier de l'Université Laval – CHUL) or according to administrative data from the provincial health plan registry (Régie de l'assurance maladie du Québec)	56/ 30	3346 ± 442/ 3267 ± 558	38.8 ± 1.4/ 39.5 ± 1.2	Between 3-12 years after delivery	BMI (kg/m^2) BMI-z score
Le Moullec	2018	Cohort study	France	Confirmed based on hospital, medical records with following criteria: Positive screening for GDM based on a OGTT (1-hr post load 50-g plasma glucose, 11.1 mmol/l), had a diagnosis of GDM based on a 100-g OGTT (OGTT with at least two pathologic values defined as: fasting, _ 5.3 mmol/l; 1-hr, 10.0 mmol/l; 2-hr, 8.6 mmol/l; 3-hr, 7.8 mmol/l), and/or had received insulin treatment during pregnancy. A small number of participants (< 0.5%; n = 6) with no available data	600/600	3183 ± 563/ 3047 ± 500	Not reported	Average 6 years after delivery	BMI centile

				were also classified into the GDM group if they combined high fasting (or postprandial) glycaemic values with intense medical monitoring during pregnancy.					
Mietten	2018	Cohort study	Finland	An oral 75 g 2-hr glucose tolerance test (OGTT)was performed for all subjects at weeks 22-29 of pregnancy, with the exception of 3 subjects with OGTT performed at weeks 31- 33. OGTT was considered diagnostic for GDM if any of the measures were pathological. The following diagnostic thresholds were used: fasting plasma glucose >5.3 mmol/L, 1 h plasma glucose (10.0 mmol/L) or 2 h plasma glucose (8.6 mmol/L)	15/13	3500 ± 120/ 3540 ± 130	39.8 ± 0.33/ 40.54.7 ± 0.32	After birth	Cord blood total cholesterol, Lipids (mmol/L)
Wang	2018	Popula-tion based	China	Based on American diabetes association	1,500/ 23, 471	Not reported	39.1 ± 1.1/ 39.3 ± 1.1	6 years	BMI z-score

		cohort study							
Hammou-nd	2017	Cohort study	The Netherlands	75-gram oral glucose tolerance test or elevated fasting glucose (exact cut offs not shown)	24/ T1D: 27 T2D: 22	3,582±576/ T1D: 3,506±556, T2D: 3,701±509	39±2.0/ T1D: 37±1.3, T2D: 38±1.7	5 years after delivery	Overweight/obese
Li	2017	Prospective cohort study	USA	Self-reported questionnaire	756/14,253	No mean reported	Not reported	11 years after delivery	BMI
Tam	2017	Longitudinal cohort study	Hong Kong	All women underwent a standard 75-g oral glucose tolerance test (OGTT) between 24 and 32 weeks of gestation, GDM diagnosed based on **HAPO criteria**	132/ 794	Not reported	Not reported	7 years after delivery	BMI (kg/m^2) BMI Percentile SBP (mmHg) DBP (mmHg) Glucose (mmol/L) Lipids (mmol/L).

Bozkurt Ω	2016	Descriptive Study	Austria	4th International Workshop Conference on GDM criteria	32/ DM (26) Control: (18)	63.0 ± 24.0/ DM: 71.3 ± 29.3) Control:66.6 ± 22.1)+	not reported	Average 6 years after birth	BMI-SDS, Insulin (μU/ml)
Hakanen	2016	Longitudinal study	Finland	Diagnosed by hospital records	520/ T1D: 67, Ctrl:6316	3600 (600)/ Control 3500 (500) T1D 3700 (700)	39.4 (2.5)/ Control: 39.7 (2.4) T1D: 38.5 (2.0)	Average 1-12 after delivery	BMI Peak (kg/m^2)
Lopez Morales	2016	Cross Sectional	Spain	Diagnosed in medical records	38/ Women with normal gestation (still pregnant) =38	not reported	not reported	Infant (after birth)	Cord blood glucose (mg/dl) Cord blood insulin (U/ml) Cord blood lipids (mg/dl)

Zhao	2016	Cross Sectional	Multicentre(Australia, Brazil, Canada, China Colombia-a, Finland, India, Kenya, Portugal, South Africa, UK, USA).	Varied between international centres but included WHO, ADA, modified ADA and modified WHO definitions – women would self-report GDM and the research team confirmed the diagnostic criteria at the time of diagnosis	206/4.354	3,415 (623)/ 3,274 (576)	38.3 (2.1)/ 38.6 (2.2)	9-11 years after delivery	BMI
Chang	2015	Retrospective	China	**American Diabetes Association:** Women with abnormal 50g OGTT (>7.8mmol/L) underwent further	356/ 500	3700 ±120 / 3200 ± 800	Not reported	6 years after birth	BMI (kg/m2) SBP (mmHg)

		cohort study		fasting 3h 75g OGTT. GDM diagnosed with criteria: (BG > 5.3mmol/L at baseline, > 10mmol/L at 1h, >8.6mmol/L at 2h, 7.8mmol/L at 3h.					
Krishnaveni	2015	Cohort study	India	**Carpenter and Coustan**: two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min) (reported in 2005 study)	26/ CTRL: 165 Offspring of diabetic fathers: 22	not reported	not reported	13.5 years after delivery	BMI (kg/m2) SBP and DBP (mmHg) Glucose (mmol/L) Insulin (pmol/L) Lipids (mmol/L)
Page ^	2015	Cohort study	USA	Based on protocol Page 2012	10/ 9	not reported	not reported	Average 9-10 years after delivery	BMI (kg/m^2) BMI percentile

Rutowska ^	2015	Prospective Cohort	Poland	Not specified	261/ 153	3330 ± 53/ 3420 ± 54	not reported	Approx. 3 years after delivery	BMI percentile
Wilk	2015	cohort study	Poland	Hospital records	50/ 46	not reported	not reported	7-15 years after delivery	BMI SDS BMI percentile Glucose (mg/dL), Insulin (mg/dL)
Zhao	2015	cohort study	China	Women with risk factors for GDM underwent 85-g OGTT at <12 weeks gestation, OGTT repeated at 24-28 weeks if normal results. All women with low risk for GDM did normal 24-32 weeks gestation. 1999 WHO diagnostic criteria for GDM since January 1 2003. GDM diagnosis based on IGT (fasting blood	LGA: 149/284 AGA: 771/1401 SGA: 148/180	GDM (followed) 3256 ± 405, GDM (not followed) 3172 ± 509/ Control followed: 3261 ± 391, Control not followed: 3254 ± 417	GDM (followed) 38.9 ± 0.9 (not followed) 38.4 ± 1.5/ Control followed:39.5 ± 1.0, Control not	5-10 years after delivery	BMI percentile

				glucose <7.0 mmol/l and 2-h postprandial blood glucose ⩾7.8–11.0 mmol/l) or DM (fasting blood glucose ⩾7.0 mmol/l or 2-h postprandial blood glucose ⩾11.1 mmol/l) positive results			followed:39.1 ± 0.7		
Holder	2014	Cohort study	USA	Self-reported	45/ 210	3,242.54±959.59/3,297.93±603.99	not reported	Average 15 years after delivery	BMI (kg/m^2) BMI-Z Score Plasma glucose (mmol/L)
Koing	2014	Retrospective case-control	Germany	Three women were diagnosed with **Hesse Diabetes Society diagnosis:** Fasting: ≥ 90 mg/dl, 1 h postprandial: ≥ 160 mg/dl, 2 h postprandial ≥ 140 mg/dl in venous plasma. Some women were diagnosed who exceeded only one of these 3 threshold values in a venous blood specimen. Other women referred to by clinicians, based on DDG and AGA values: GDM was diagnosed if at least 2	130/77	3 406.62 ± 463.69/3 456.09 ± 463.25	not reported	6 months after delivery	BMI (kg/m2) BMI percentile

				measured values exceeded the limits of **Carpenter and Coustan** after ingestion of 75 g glucose, only one exceeded value was declared as impaired glucose tolerance. GDM can also be diagnosed if only one of the predetermined cut-offs is exceeded, whereas these values – based on the results of the **HAPO-Study** – differ slightly from the former criteria: Fasting: ≥ 92 mg/dl, 1 h postprandial: ≥ 180 mg/ dl, 2 h postprandial ≥ 153 mg/dl.					
Page	2014	Cohort study	USA	Based on protocol Page 2012	37/ 25	3186 ± 113/ 3454 ± 79	not reported	5-16 years old (average 7-9 years after delivery)	BMI (kg/m^2) BMI-z score BMI percentile

Davis	2013	Longitudinal Cohort	USA	Self-reported	47/163	3900 (800)/3700 (600)	not reported	Average 10-11 years after birth	BMI (kg/m2) BMI percentile BMI z-score Glucose (mg/dl) Insulin (µU/ml)
Eslamain	2013	Cohort study	Iran	**World Health Organization**, diagnosed as either: Fasting plasma glucose 5.1–6.9 mmol/L or: 1-hour plasma glucose 10.0 mmol/L. Following a 75 g oral glucose load 2-hour plasma glucose 8.5–11.0 mmol/L following a 75 g oral glucose load	112/ 159	3336.07±630/3259.75 ±490	37.72±1.7/39.1.3 3	Infant (after birth)	BMI (kg/m2) Cord blood glucose (mg/dL) Cord blood insulin (µU/ml) Cord blood

									Lipids (mg/dL)
Farfel^	2013	Cohort study	Israel	159 males, 113 females/ Diagnosed by hospital records	Female (113) Male (159)/ PDGM, Male (34) Female (23) Control, Male (198) Control (147)	Male 3423±537 Female 3230±510/ PGDM Male 3451±535, Female 3210±364. CTRL Male 3344±372, Female 3228±324	Not reported	17 years after delivery	BMI >85th percentile
Nehring	2013	Retrospective	Germany	GDM cases found from medical records	195/ 7,160	3479 (3417–3540)/ 3413 (3403–3424)	3413 (3403–3424)/ 39.4 (39.3–39.4)	Average 5.8 years	BMI (kg/m^2)

		cohort study						after delivery	
Nielsen	2013	Population based cohort study	Denmark	**Rigshospitalet University Hospital modification of the White classification**: Oral glucose challenge test (OGTT) in gestational weeks 24–26 if they met one of the following criteria: (1) previous birth of a baby with birthweight >4500 g; (2) maternal overweight >130%; (3) family history of diabetes; (4) glycosuria or (5) previous obstetrical complications or late miscarriage. (Diagnostic values not specified)	34/ PreGDM (185), control (737)	3803 (780) / PreGDM: 3327 (648), control: 3482 (551)	38.9 (1.9)/ PREGDM: 36.5 (1.8) control: 38.8 (2.0)	18-20 years after delivery	BMI (kg/m^2)
Page^	2013	Cohort study	USA	Based on protocol Page 2012	10/ 19	not reported	not reported	Average 9 years after delivery	BMI-z score SBP(mmHg) Glucose (mg/dL) Insulin (uLu/ml)

Pham	2013	Retrospective cohort study	USA	Normal screening at 24-28 weeks (unless considered at risk, tested in first trimester). 50g- 1-hour glucose challenge test of greater/equal to 140 mg/dL, then given a 100-g 3-hour glucose tolerance test if 1-h challenge was positive. Needed 1/4 of the possible measurements to be diagnosed. Diagnosis followed **National Diabetes Data Group** prior to April 2007, then changed to **Carpenter and Coustan** criteria after April 2007.	459/ 2,185	3,406 ±496 /3,404 ±442	39.3 ±1.0/ 39.6 ±0.9	2-4 years after delivery	BMI percentile
Retnakar-an Ω	2013	Sub study of prospective observational study	Canada	Those with and without an abnormal 50g glucose challenge screening test undergo 3-h 100g OGTT for ascertainment of antepartum glucose intolerance status (i.e. either GDM or non-GDM) based on **National Diabetes Data Group (NDDG)**, measurements at 20 minutes- 1h, 2h and 3h.	36/ 68	3411 [3110-3635]/ 3415 [3144-3628]	not reported	1 year after delivery	BMI z-score Fasting glucose (mmol/L) Lipids (mmol/L)

Baptise-Roberts	2012	Prospective Cohort	USA	All women provided fasting blood specimen if it was 120 mg/dL or higher, or if it rose to over 175 mg/dL at the end of 1 h and did not return to normal in the 2- and 3-h specimens. GDM diagnosed based on these criteria: (1) she was newly diagnosed with diabetes during pregnancy; (2) she initiated insulin during pregnancy; (3) she displayed an abnormal glucose tolerance test result; or (4) she had a blood glucose level of 200 mg/dL or more at any time during pregnancy.	484/ 27,874	3302 ± 584/3190 ± 484	not reported	7 years after birth	BMI (kg/m^2) BMI z-score BMI Percentile
Borogon-o	2012	Prospective Cohort	Canada	**National Diabetes Data Group** criteria	36/68	3,411 [3,110–3,635]/ 3,415 [3,144–3,628]	not included	1 year after birth	Fasting glucose (mmol/L) Fasting insulin (pmol/L)

Chandler Laney	2012	Cohort study	USA	Self-reported, confirmed with hospital records	Normal weight: (11), Overweigh-t (13)/ Normal weight (19) Overweigh-t (8)	not reported	not reported	Average 7-8 years after birth	BMI percentile Glucose (mg/dL)[2], Insulin (mg/dL)[2]
Page ^	2012	Cohort study	USA	Not reported in abstract (Based on protocol): Fasting glucose <126 mg/dl (7 mM) from families of a proband with GDM diagnosed within the previous 5 years)	35/ 14	not reported	not reported	Average 8 years after delivery	BMI (kg/m^2) BMI z-score
Patel	2012	prospecti ve populatio n-based	England	GDM was defined as any record of a diagnosis of gestational diabetes at any time during the pregnancy in women without existing diabetes at the start of pregnancy. (At time of study recruitment: all	27/Control: (4384), existing diabetes	1.45 (1.28)/ Control: 0.038 (0.97), existing diabetes: 0.28 (1.32), glycosuria: 0.18 (1.04)	38.6 (1.48)/ Control: 39.4 (1.85), existing diabetes: 37.5	15 years after delivery	BMI z-score SBP and DBP(mmHg) Glucose

		cohort study		pregnant women to have urine tested for glycosuria and proteinuria at every antenatal clinic visit. Glycosuria was defined as a record of at least ++ (equal to 13.9 mmol/l or 250 mg/100 ml) on at least two occasions at any time during the pregnancy.) GDM was tested further to these results, diagnosed in the medical records as GDM with no history of existing diabetes.	(23), glycosuria (154)		(1.86), glycosuria: 39.7 (1.63)		(mmol/L) Insulin (IU/L) Lipids (mmol/L)
Jahan	2011	Cohort study	Bangladesh	Diagnosed with fasting blood glucose, and 2 h after 75 g oral glucose tolerance test (OGTT). Women who had repeatedly elevated fasting (>7.0 mmo1/L) or postprandial (9 mmol/L) blood glucose values.	30/ DM (n=45) control (n=30)	3000 (2100-4500)/ DM: 3100 (1700-4800), NDM: 2700 (2000-3800)	not reported	Infant (after birth)	Insulin (mmol/L)
Tsadok	2011	Population based cohort	Israel	Reported on hospital records	293/ 59,499	3411 ± 616/ 3301 ± 483	not reported	17 years after delivery	BMI (kg/m^2) SBP and DBP

Boersch-mann 2010	2010	Prospecti ve cohort	Germany	**German Diabetes Association -** an oral glucose tolerance test (OGTT) with a 75-g glucose load. Women were considered to have GDM if two of three capillary blood glucose values exceeded the following limits: _5 mmol/l (fasting) before an oral glucose tolerance test,_10.0 mmol/l after 60 min, and 8.6 mmol/l after 120 min.	77/148	Not reported	Not reported	11	BMI percentile
Krishnav-eni	2010	Cohort study	India	**Carpenter and Coustan:** two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min)	Female (23) Male (12)/ Control: Female (191) male (190), Offspring of diabetic fathers	not reported	not reported	9.5 years after delivery	BMI (kg/m^2) BMI percentile SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l)

					Male: (20), Female (19)				Lipids (mmol/l)
Lawlor	2010	Longitudinal Cohort	England	GDM was defined as any record of a diagnosis of gestational diabetes at any time during the pregnancy in women without existing diabetes at the start of pregnancy. (At time of study recruitment: all pregnant women to have urine tested for glycosuria and proteinuria at every antenatal clinic visit. Glycosuria was defined as a record of at least ++ (equal to 13.9 mmol/l or 250 mg/100 ml) on at least two occasions at any time during the pregnancy.) GDM was tested further to these results, diagnosed in the medical records as GDM with no history of existing diabetes.	53/ Control: (10,126) Existing diabetes (40) Glycosuria (372)	3,711 (655)/ Control: 3,416 (536), existing diabetes: 3,248 (787), glycosuria: 3,511 (534)	38.2 (1.9)/ Control: 39.5 (1.9) Existing diabetes: 37.5 (2.6), Glycosuria: 39.5 (1.8)	Average 9-11 years after delivery	BMI z-score
Pirokla	2010	Longitudinal cohort study	Finland	GDM risk factors; 40 years, BMI 25 kg/m2, prior GDM, previous delivery of a macrosomia infant (birth weight 4,500 g), glycosuria, and suspected fetal	Normal weight (n=49),	Overweight: 3700 (3490–3920) Normal 3670 (3530–	Overweight: 38.5 (37.8–39.1), Normal 39.0	16 years after delivery	BMI (kg/m^2)

				macrosomia in the current pregnancy. Glucose tolerance testing, performed after an overnight fast, conducted by administering a 2-h, 75-g oral glucose tolerance test (OGTT): 5.5, 11.0, and 8.0 mmol/l at fasting and at 1 h and 2 h after the glucose load, respectively. Diagnosis of GDM was set after one abnormal value in the OGTT, according to prevailing national guidelines	Overweight (n=35)/ Control total (??) Normal weight: (503), Overweight (n=154)	3820)/ Overweight=3780 (3680–3880), Normal weight: 3690 (3640-3740), Total: 3480(3460-3500).	(38.6–39.5)/ Overweight 39.4 (39.1–39.6), Normal weight 39.5 (39.4–39.7) Total 39.5(39.4-39.5)		
Tam	2010	Longitudinal cohort	Hong Kong	GDM defined based on **WHO criteria**: Gestational impaired glucose tolerance (IGT) (i.e., fasting PG level of 7.0 mmol/L and 2-hour PG level of 7.8–11.1 mmol/L, and GDM (i.e., fasting PG level of 7.0 mmol/L and/or 2-hour PG level of 11.1 mmol/L). WHO criteria states that "pregnant women who meet WHO criteria for diabetes mellitus of IGT are classified as having GDM."	42/87	3,248 (351)/3,273 (454)	Based on Tam *et al.* 2008 with larger (n=): 39.6±0.2/ 39.5±0.2	15 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Glucose (mmol/L), Lipids (mmol/L)

Catalano	2009	Prospecti ve Cohort	USA	**National Diabetes Data Group** (NDDG)	25/38	3,373 ± 532/3,376 ± 496	38.7 ± 1.3/ 39.4 ± 1.2	Average 8.8 years after birth	BMI(kg/m2) BMI z-score SBP and DBP (mmHg) Glucose (mmol/L) Insulin (pmol/L) HOMA-IR Lipids (mmol/L)
Vaarasm -aki	2009	Prospecti ve cohort study	England	Risk factors: glycosuria, prior gestational diabetes, suspected foetal macrosomia (birth weight 4500 g) in the current pregnancy, previous delivery of a macrosomic infant, body mass index (BMI) 25 kg/m2 and age more than 40 yr. A history of prior gestational diabetes or glycosuria in the current pregnancy	96/ 3,909	3,727 (577)/ 3,517 (471)	38.8 (1.7)/ 39.5 (1.5)	16 years after delivery	BMI SBP and DBP (mmHg), Glucose (mmol/L) Insulin

				warrants an earlier OGTT. Diagnosed with 2-h, 75-g oral glucose tolerance test (OGTT) usually at 26–28 week of gestation: one or more abnormal OGTT values (cut-off values for venous blood samples are 4.8 mmol/L at 0 min, 10.0 mmol/L at 60 min and 8.7 mmol/L at 120 min).					(milliunits/L) Lipids (mmol/L),
Wright	2009	Cohort study	USA	Screening at 26-28 weeks with non-fasting 50-g 1h oral glucose challenge. If test result was abnormal (i.e. blood glucose value of >140 mg/dl) then women were referred for fasting 3-h 100 OGTT. Two or more abnormal results were a diagnosis for GDM: a blood glucose>95 mg/dl at baseline, >180 mg/dl at 1 h, >155 mg/dl at 2 h, or >140 mg/dl at 3 h.	51/ Control n=1035, IGT n=152	3510 (52)/ control= 3510/52, IGT 3600 (52)	not reported	3 years after delivery	BMI (kg/m2) BMI percentile BMI z-score SBP (mmHg)
Buzinaro	2008	Cohort study	Brazil	Based on OGTT Values (cut-offs not specified)	23/ Control (17) Hyperglycaemia (23)	not reported	not reported	average 12- 16 years after birth	BMI (kg/m2), SBP and DBP (mmHg) Glucose

									(mg/dL) Lipids (mg/dL)
Clausen	2008	Retrospective cohort study	Denmark	OGTT - GDM was based on risk indicators: family history of diabetes, overweight (20%) prepregnancy, prior GDM, delivery of macrosomic baby, glycosuria. Women with these risk indicators and two capillary blood glucose measurements > 4.1 mmol/L were offered a 3h 50g OGTT. OGTT was abnormal if more than two of seven values during the test exceeded mean 3 SDs for a reference group of normal weight non-pregnant women without family history of diabetes (Until Sep 1982 venous plasma used for OGTT, after then capillary whole blood)	168/128	3410 (530)/ 3474 (481)	273 (247–284)// 280 (253–298)	18-27 years after delivery	Glucose (mmol/L)
Pirokla	2008	Cohort Study	Finland	Risk factors for diagnosis: glycosuria, prior gestational diabetes, suspected foetal macrosomia (birth weight .4500 g) in the current pregnancy,	22/ T1D: 16, control: 25	3.708 (3.538–3.886)/ T1D: 3.818 (3.482–	39.2 (38.7–39.7)/ T1D: 37.5 (36.8–	Mean 4.9 years after delivery	SBP and DBP (mmHg) Cord blood

				previous delivery of a macrosomic infant, body mass index (BMI) 25 kg/m^2 and age more than 40 yr. A history of prior gestational diabetes or glycosuria in the current pregnancy warrants an earlier OGTT. Diagnosed with 2-h, 75-g oral glucose tolerance test (OGTT) usually at 26–28 week of gestation: one or more abnormal OGTT values (cut-off values for venous blood samples are 4.8 mmol/L at 0 min, 10.0 mmol/L at 60 min and 8.7 mmol/L at 120 min).		4.185), Control: 3.666 (3.452–3.893)	38.2), 39.3 (38.8–39.8)		insulin (pmol/L)
Tam	2008	Longitudinal cohort study	Hong Kong	DM defined based on **WHO criteria**: Gestational impaired glucose tolerance (IGT) (i.e., fasting PG level of 7.0 mmol/L and 2-hour PG level of 7.8–11.1 mmol/L, and GDM (i.e., fasting PG level of 7.0 mmol/L and/or 2-hour PG level of 11.1 mmol/L). WHO criteria states that "pregnant women who meet	63/ 101	3292±52/ 3245±45	39.6±0.2/ 39.5±0.2	Average 7-8 years after delivery	BMI (kg/m^2) BMI percentile SBP (mmHg) and DBP (mmHg) Glucose

				WHO criteria for diabetes mellitus of IGT are classified as having GDM."					(mmol/L) Insulin (pmol/L) Lipids (mmol/L)
Lee	2007	Cohort study	South Korea	**National Diabetes Data Group:** 50 g glucose challenge test was performed; if the 1 h plasma glucose value was 130 mg/dL (7.2 mmol/L), a 3 h oral glucose tolerance test (OGTT) was performed during 28–32 weeks of gestation.	202 / 96	3344.6 ± 585.0/ 3286.6 ± 612.4	38.6 ± 1.5/ 38.7 ± 2.2	Average 4 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Lipids (mmol/L) Glucose (mmol/L) Insulin (mg/mL).
Boney	2005	Longitudinal Cohort	USA	**National Diabetes Data Group** criteria described by **Carpenter and Coustan**	**LGA:** 42/43 **AGA:** 52/42	**LGA:** 4107 (386)/ 4132 (285)	not reported	11 years after birth	BMI percentile BP >90th

						AGA: 3316 (310)/ 3370 (282)			percentile (BP Is either SBP or DBP) (mmHg) Glucose (mmol/L) Lipids (mmol/L)
Jaber	2005	Cohort study	Saudi Arabia	Venous fasting glucose concentration of >5.5 mol/L or of >8.0 mmol/L 2 hours after a 75g oral glucose load or both.	26/ Control (n=32), FDM (n=21)	3640 ± 690/ CTRL: 3.30 ± 0.59 FDM: 3.18 ± 0.86	37.38 ± 0.64/ CTRL:37.28 ± 0.73, FDM: 37.48 ± 0.60	Approximately 2 weeks after delivery	BMI (kg/m^2) Glucose range(mmol/L) Insulin range (pmoL/L)
Krishnav-eni	2005	Cohort study	India	**Carpenter and Coustan:** two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min)	41/ Control: 588 Offspring of	3344 ± 421/ CTRL: 2973 ± 408, ODF: 2869 ± 305	39.1 ±1.2/CTRL 39.0 ± 1.8, ODF:39.1 ± 1.2	1 and 5 years after delivery	Fasting plasma glucose

					diabetic fathers: 41				(pmol/l)
Gillman	2003	Prospective Cohort	USA	Self-reported questionnaire	Female (246), Male (219)/ Female (n=7735), Male (n=6681),	Female: 3.55 (0.56) Male 3.68 (0.61)/ Female 3.44 (0.48) Male 3.58 (0.51)	Not reported	Average 9-14 years after delivery	BMI Percentile
Vohr	1999	Prospective observational study	USA	24-28 weeks screening, GDM diagnosis made on initial 1h 50-g glucose screen >130 mg/dl, followed by two abnormal values in a 100-g oral glucose tolerance test. **Criteria of O'Sullivan *et al.* modified by Carpenter and Coustan (recent 1999):** fasting plasma glucose >95 mg/dl and 1-h >180 mg/dl, 2-h >155 mg/dl, and 3-h ^140 mg/dl.	**LGA:** 47/46 **AGA:** 59/55	**LGA:** 4100 ± 3800/ 4200 ± 2900 **AGA:** 3300 ± 300/ 3400 ± 3000	**LGA:** 39.4 ± 1/ 40.0± 1, **AGA:** 39.4 ± 1/ 39.7 ± 1	4-7 years after delivery	BMI (kg/m^2)

Silverma-n †	1998	long term prospecti ve cohort	USA	Unclear - from hospital records (From Silverman *et al.* 1995)	Unclear	not reported	not reported	14-17 years after delivery	BMI (kg/m^2)
Whitaker	1998	Cohort study	USA	24-32 weeks screening, 1-h 50-g oral glucose load - glucose screening values >7.77mmol/L (140mg/dL) called back for 3-h 100-g OGTT. GDM diagnosed based on calculations **Carpenter and Coustan (recent 1998)**	63/ Control=25 7, Normal OGTT=159, No OGTT=45	not reported	Not reported	5-10 years after delivery	BMI z-score BMI percentile
Plagema-nn	1997	Retrospe ctive study	Germany	Diagnosed 26-28 weeks gestation by Furmann: a 50-g OGTT using the following criteria (two or more abnormal values): fasting venous blood glucose over 5.55 mmol/l, 1-h value over 8.88 mmol/l, 2-h value over 7.22 mmol/l	57/ 156	3500.8 ±50.8 (117)/ 3443.5 ± 45.5 (200)	not reported	Average 1-9 years delivery	Plasma insulin (mIU/ml)
Plagema-nn	1997	Cohort study	Germany	Diagnosed 26-28 weeks gestation by Furmann: a 50-g OGTT using the following criteria (two or more abnormal values): fasting venous blood glucose over	69/ 129	3460.1 ± 50.7/ 3411.2 ± 56.8	not reported	Average 1-9 years	Glucose (mmol/l),

				5.55 mmol/l, 1-h value over 8.88 mmol/l, 2-h value over 7.22 mmol/l				after delivery	Insulin (pmol/l)
Vohr	1995	Prospective cohort study	USA	Screening 24-28 weeks, GDM diagnosis made on initial 1h 50-g glucose screen >130 mg/dl, followed by two abnormal values in a 100-g oral glucose tolerance test. **Criteria of O'Sullivan *et al.* modified by Carpenter and Coustan:** fasting plasma glucose >95mg/dl and 1-h >180 mg/dl, 2-h >155 mg/dl, and 3-h ^140 mg/dl.	**LGA:** 57/74 **AGA:** 62/69	**LGA:** 4,064 ± 305/:4,095 ± 267 **AGA:** 3,301 ± 280/ 3,282 ± 238	**LGA:** 39 ± 1/40 ± 1 **AGA:** 39 ± 1/ 39 ± 1	20 hours after delivery	BMI (kg/m^2)
Teng 2017		Longitudinal cohort	India	**IADPSG criteria:** 75 g Oral Glucose Tolerance Test (OGTT) and if serum glucose level was over 1mmol/l at 0 h, or 10.0 mmol/l at 1 h, or 8.5 mmol/l at 2 h, GDM was diagnosed	123/ 80	not reported	not reported	14 years after delivery	Glucose (mmol/L) Lipids(mmol/L)

^ - abstract only

+ - birthweight centiles used rather than birthweight

† - (n=) not known for GDM or non-GDM group

The assessment of methodological quality identified 25 studies of high quality (scored 7-8), 25 studies of moderate quality (scored 4-6), and 9 studies of low quality (scored 1-3) (Supplementary Table 4.8.2). No publication bias was evident for relevant outcomes. Studies were found for all relevant outcomes, except microvascular function and therefore we could not report on this outcome in the review.

4.5.2. Systolic Blood Pressure:

Systolic blood pressure (SBP) data were available from 15 studies, of which eight were included in the meta-analysis. The age of follow-up of offspring ranged from three years to 16 years of age. Based on quantitative summary measures, the meta-analysis demonstrated that offspring exposed to GDM *in utero* have 1.75mmHg (95% CI 0.57-2.94) higher SBP compared to controls (*n*(total)=7,309, *n*(exposed to GDM)=584; p=0.33, I^2 = 13%) (Figure 4.5.2-1)[231-238] . Sensitivity analyses was not performed as no low-quality studies were included in the analysis. Of the seven studies not included in the meta-analysis [226, 239-244] four reported a significant increase in SBP among offspring exposed to GDM compared to controls. (Supplementary Table 4.8.1). [226, 239, 242, 243]

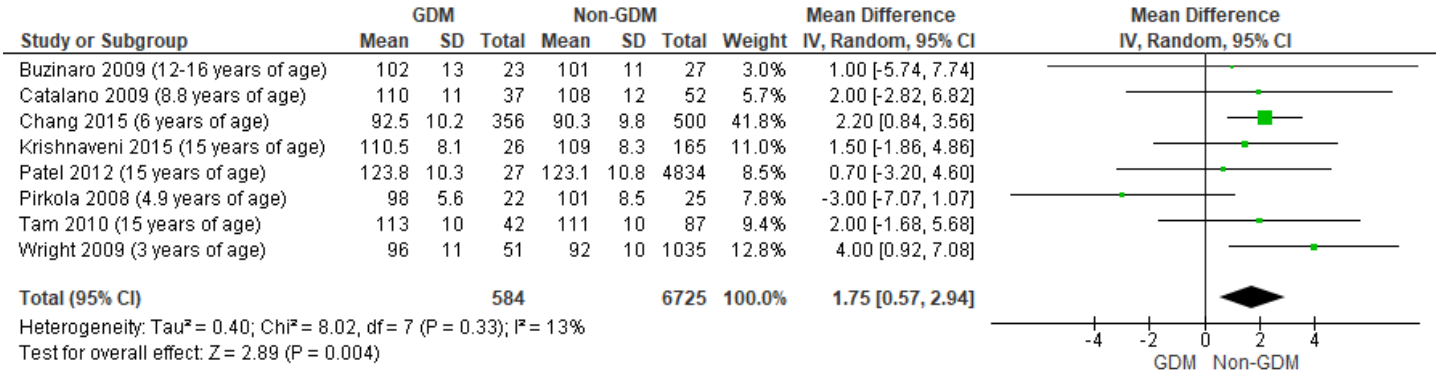


Figure 4.5.2.1 Mean difference in systolic blood pressure (mmHg) in those exposed to GDM *in utero* and controls

4.5.3. Diastolic Blood Pressure

Diastolic blood pressure (DBP) data were available from 13 studies of which six were included in the meta-analysis. The age at follow-up ranged between eight to 16 years of age. The meta-analysis demonstrated no difference in DBP among GDM-exposed offspring and controls (MD: -0.24 (95% CI -2.33-1.85; (*n*(total)= 5,367, *n*(exposed to GDM)=177; p=0.08, I^2 = 50%[231, 232, 234-236]; (Figure 4.5.3.1). Sensitivity analyses was not performed as no low-quality studies were included in the analysis. Seven studies were not included in the meta-analysis[226, 238-244], of which two reported a significantly higher DBP in GDM offspring compared to controls (Supplementary Table 4.8.1)[242, 243].

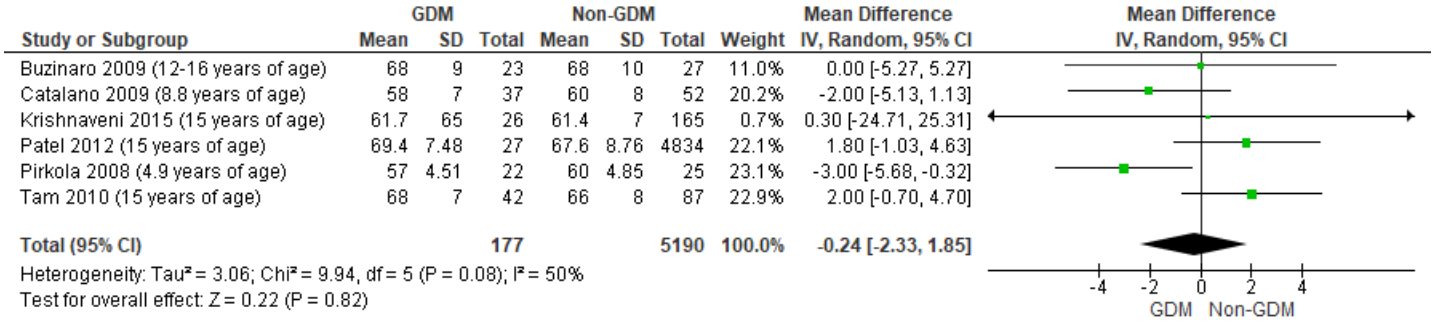


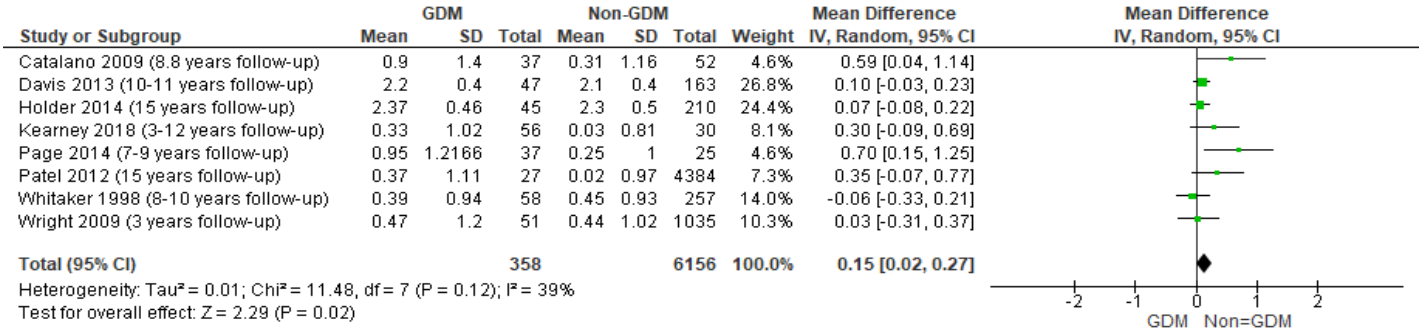
Figure 4.5.3.1 Mean difference in diastolic blood pressure (mm Hg) in those exposed to GDM *in utero* and controls

4.5.4. BMI

BMI data (i.e. BMI-z score, BMI (kg/m^2), and/or BMI-percentile, BMI peak, BMI SD) were available from 48 studies. BMI z-score and BMI (kg/m^2) are reported in the meta-analysis and other BMI data are reported in the non-meta-analysis (Supplementary Table 4.8.1)

BMI z-score data were reported in 14 studies, of which nine were included in the meta-analysis. The age at follow-up ranged from three years to 15 years of age. Offspring exposed to GDM *in utero* showed an increase in BMI z-score compared to controls (MD 0.11 95% CI 0.02-0.20; *n*(total)= 31,485, *n*(exposed to GDM)=1,858; p=0.14, I^2 = 34%)[232, 235, 237, 245-249] (Figure 4.5.4.1). Five studies were not included in the meta-analysis[241, 250-253], with two reporting significantly higher BMI z-scores in GDM-exposed offspring compared to controls[250, 252] (Supplementary Table 4.8.1).

Figure 4.5.4.1 Mean difference in BMI z-score in those exposed to GDM *in utero* and controls.



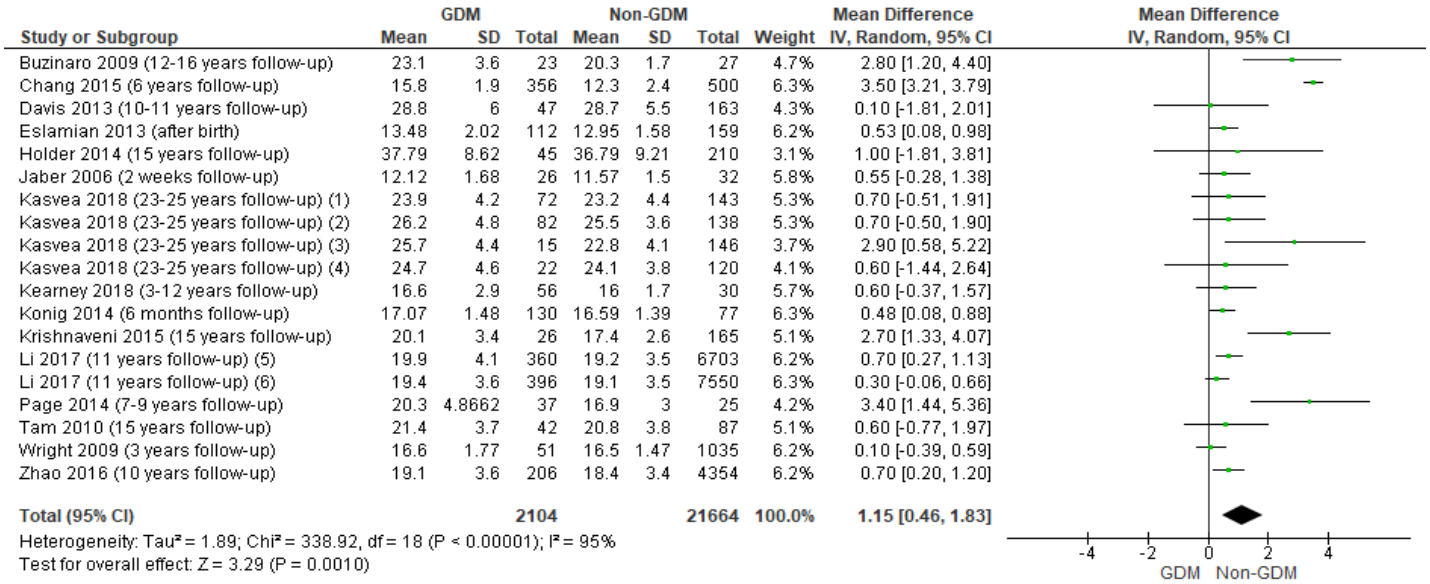
Sensitivity analysis showed no difference in heterogeneity when removing low quality studies (Table 4.5.4.1).

Table 4.5.4-1 Sensitivity analysis for BMI Z-Score

Analysis	Studies	N=	SMD	95% CI	Chi² P=	I² (%)
Normal	9	31,485	0.11	0.02,0.20	0.15	34
Sensitivity	8	31,275	0.13	0.01,0.25	0.10	42

BMI (kg/m^2) data were available from 31 studies. Sixteen studies were included in the meta-analysis, with the age at follow up ranging broadly from <48 hours after birth to 25 years of age. Quantitative summary measures obtained through meta-analysis showed a 1.06 kg/m^2 increase in BMI among those exposed to GDM *in utero* compared

to controls (95% CI 0.40- 1.73; *n*(total)= 23,864, *n*(exposed to GDM)=2,154; p<0.00001, I^2 = 95%; Figure 4.5.2)[231-234, 236, 237, 245-248, 254-258]. Sensitivity analysis showed no difference in heterogeneity when removing low quality studies (Table 4.3). Fifteen studies were not included in the meta-analysis[226, 239, 240, 242, 244, 250, 252, 257, 259-265], of which seven studies showed significantly higher BMI among offspring exposed to GDM compared to controls [239, 243, 250, 252, 257, 259, 263] (Supplementary Table 4.8.1).Krishnaveni *et al.* (2010) reported a significant association between females exposed to GDM *in utero* compared to female controls (p<0.001)[239]. One study which showed statistical significance did not report on the sample size for either GDM or control groups[263].



Footnotes
(1) ESTER cohort (female)
(2) ESTER Cohort Male
(3) AYLS Cohort (female)
(4) AYLS Cohort (male)
(5) Male
(6) Female

Figure 4.5.4.2 Mean difference in BMI (kg/m2) in those exposed to GDM *in utero* and controls

Table 4.5.4-2 Sensitivity analysis for BMI (kg/m2)

Analysis	Studies	N=	SMD	95% CI	Chi² P=	I² (%)
Normal	16	23,768	1.15	0.46,1.83	<0.00001	95
Sensitivity	15	23,654	1.10	0.42, 1.78	<0.00001	95

BMI percentiles were reported in 21 studies, of these, five reported a higher BMI within obese/overweight BMI percentiles among those exposed to GDM *in utero* compared to controls (i.e ≥85th centile) [226, 250, 266-268] (Supplementary Table 4.8.1.).

4.5.5. Lipids

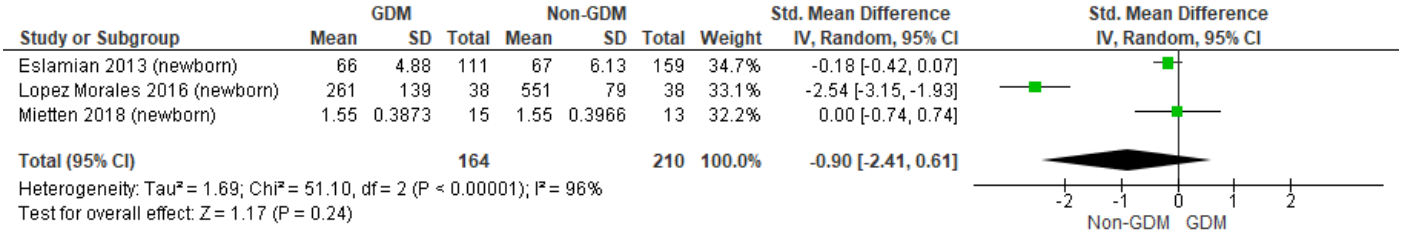
Studies on cord blood and serum lipids (i.e. total cholesterol, LDL, HDL and triglycerides) were included.

4.5.5.1. Total cholesterol

Total cholesterol data were available from 12 studies (nine serum cholesterol, three cord blood cholesterol). Five studies on total serum cholesterol were included in the meta-analysis. The age of follow-up ranged from 8 to 16 years. There was no significant difference in total serum cholesterol between GDM and control groups. (SMD -0.01 95% CI -0.28-0.25; *n*(total)= 662 *n*(exposed to GDM)=251; p=0.07, I^2 = 54%; Figure 4.5A) [231, 232, 234, 236, 269].The four studies that were not included in the meta-analysis showed no difference in total cholesterol between those exposed to GDM and controls (Supplementary Table 4.8.1).[226, 240, 242, 244]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

Three studies on cord blood total cholesterol were included in the meta-analysis. Quantitative summary measures did not show a significant difference in total cord blood cholesterol between GDM and control groups. (SMD -0.90 95% CI -2.41-0.61, *n*(total)= 374, *n*(exposed to GDM)=164; p<0.00001, I^2 = 96%; Figure 4.5.5.1.1B)[254, 270]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

(A)



(B)

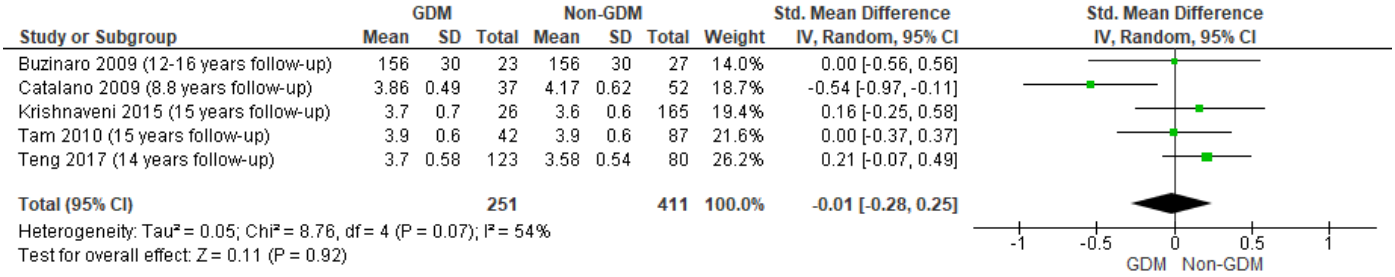


Figure 4.5.5.1.1 (A) Standard mean difference in serum blood total cholesterol in those exposed to GDM *in utero* and controls (B) Standard mean difference in cord blood total cholesterol in those exposed to GDM *in utero* and controls

4.5.5.2. LDL

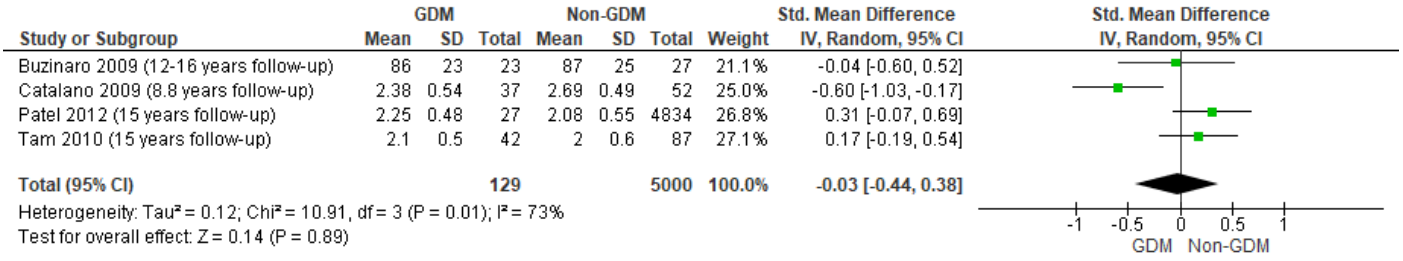
LDL cholesterol data were available from 10 studies (eight serum LDL cholesterol, two cord blood cholesterol).

Four studies on serum LDL cholesterol were included in the meta-analysis. The age of follow-up ranged from eight to 16 years of age. There was no difference in serum LDL cholesterol between those exposed to GDM and controls (SMD -0.03 95% CI -0.44-0.38; *n*(total)= 5,129, *n*(exposed to

GDM)=129; p=0.01, I^2 = 73%; Figure 4.5.5.2.1A)[231, 232, 235, 236]. Four studies that were not included in the meta-analysis showed no difference in LDL between GDM and control groups[226, 242, 244, 253] (Supplementary Table 4.8.1). Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

Two studies on cord blood LDL were included in the meta-analysis. Quantitative summary measures did not show a significant difference in cord blood LDL between GDM and control groups (SMD -0.60 95% CI -1.57-0.38; *n*(total)= 298, *n*(exposed to GDM)=126; p=0.01, I^2 = 84%; Figure 4.5.5.2.1B)[270, 271]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

A:



B:

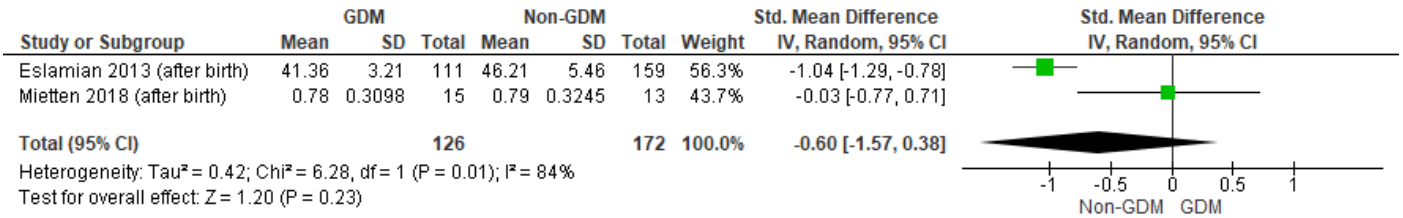


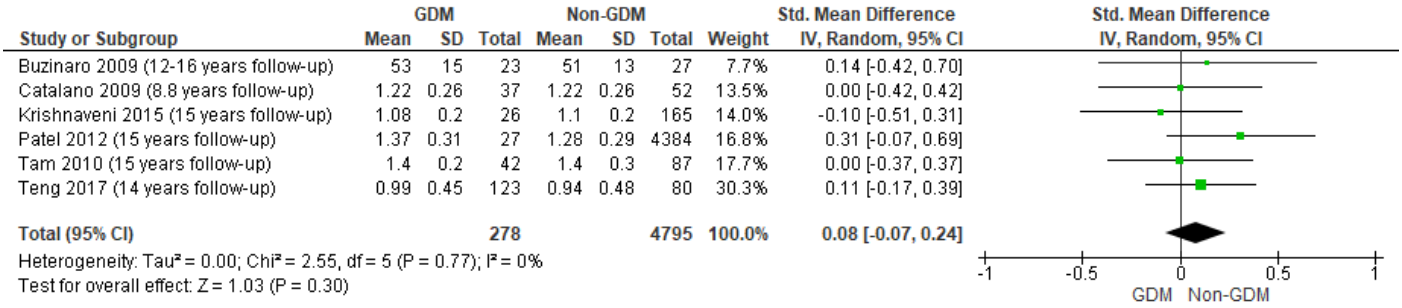
Figure 4.5.5.2.1(A) Standard mean difference in serum blood total cholesterol in those exposed to GDM *in utero* and controls (B) Standard mean difference in cord blood total cholesterol in those exposed to GDM *in utero* and controls

4.5.5.3. HDL

HDL cholesterol data were available from 15 studies (12 serum HDL cholesterol, three cord blood HDL cholesterol).

Six studies on serum HDL cholesterol were included in the meta-analysis. The age of follow-up ranged from eight to 16 years. Quantitative summary measures showed no significant difference in serum HDL cholesterol between those exposed to GDM and controls (SMD 0.08 95% CI (-0.07-0.24); *n*(total)= 5,073 *n*(exposed to GDM)=278; p=0.77, I^2 = 0%; Supplementary Figure 4.5.5.3.1B)[231, 232, 234-236, 269]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis. Six studies were not included in the meta-analysis[226, 239, 240, 242, 244, 253]. Of these, one reported lower serum HDL cholesterol in the GDM group compared to controls (Supplementary Table 4.8.1).[242]. Three studies on cord blood HDL were included in the meta-analysis. Quantitative summary measures showed no difference in cord blood HDL between GDM and controls groups. (SMD -0.13 95% CI -0.84-0.59; *n*(total)= 374 *n*(exposed to GDM)=164; p=0.0006, I^2 = 87%; Supplementary Figure 4.5.5.3.1B)[254, 270, 271]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

7A:



7B:

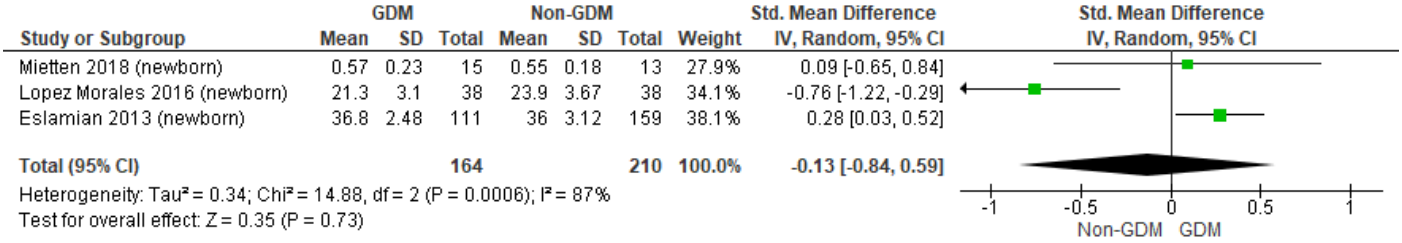


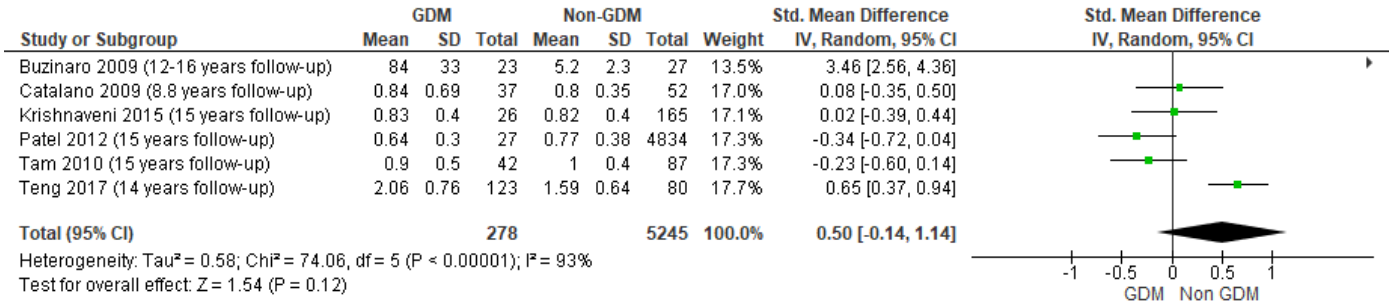
Figure 4.5.5.3.1: (A) Standard mean difference in serum blood HDL cholesterol in those exposed to GDM *in utero* and controls (B) Standard mean difference in cord blood HDL cholesterol in those exposed to GDM *in utero* and controls

4.5.5.4. Triglycerides

Triglyceride data were available from 14 studies (11 serum triglycerides, three cord blood triglycerides). Six studies on serum triglycerides were included in the meta-analysis. The age at follow-up ranged from seven to 16 years of age. Quantitative summary measures showed no difference in the level of serum triglycerides between GDM and control groups (SMD 0.50 95% CI -0.14-1.14; *n*(total)= 5,523 *n*(exposed to GDM)=278; p<0.00001, I^2 = 93%; Figure 4.5.5.4.1A[231, 232, 234-236, 269]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis. Five studies that were not included in the meta-analysis also showed no significant difference in serum triglycerides in GDM and control groups (Supplementary Table 4.8.1).[226, 239, 240, 242, 244]. Three studies on cord blood triglycerides were included in the meta-analysis. There was no difference in cord blood triglycerides in the GDM group compared to controls. (SMD 0.02 95% CI -

0.67- -0.71; *n*(total)= 374 *n*(exposed to GDM)=164; p=0.001, I^2 = 86%; Figure 4.5.5.4.1B)[254, 270, 271]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

8A:



8B:

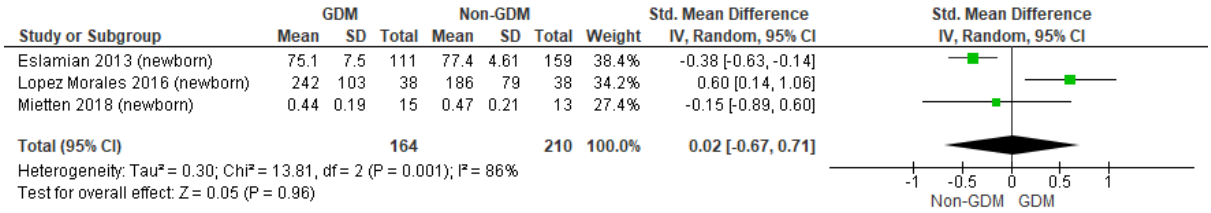


Figure 4.5.5.4.1 (A) Standard mean difference in serum triglycerides in those exposed to GDM *in utero* and controls (B) Standard mean difference in cord blood triglycerides in those exposed to GDM *in utero* and controls

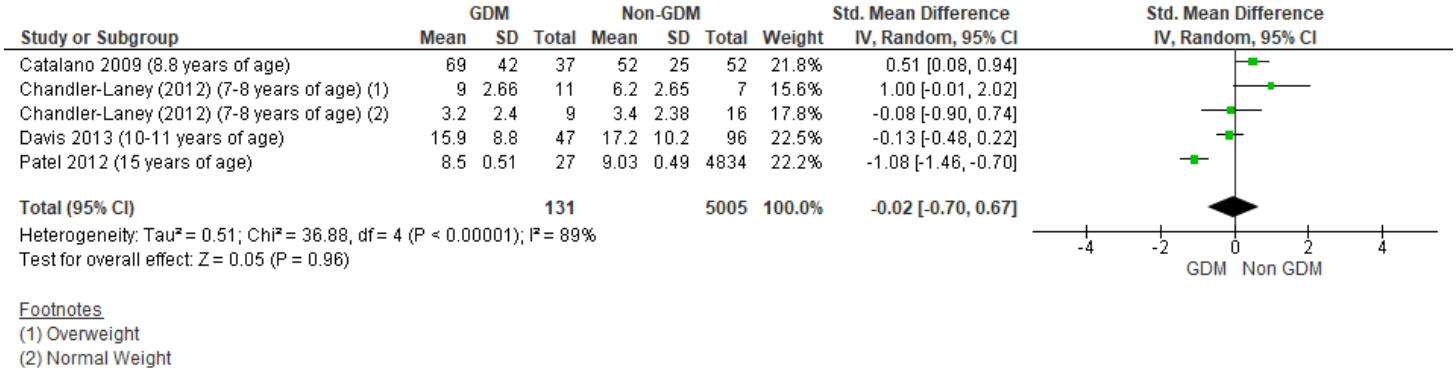
4.5.6. Serum Insulin

Data for fasting serum insulin were collected for 20 studies (16 serum insulin, four cord blood insulin).

Four studies on serum insulin were included in the meta-analysis. The age at follow-up ranged from eight to 15 years of age. The meta-analysis showed no difference in insulin between the two groups (SMD -0.02 95% CI -0.70-0.67, *n*(total)= 5,136 *n*(exposed to GDM)=131; p<0.00001, I^2 = 89%; Figure 4.5.6.1A)[232, 235, 245, 272]. Sensitivity analyses showed no difference in heterogeneity when poor quality studies were omitted (Table 4.5.6.1)

Twelve studies were not included in the meta-analysis[226, 234, 239-242, 244, 255, 272-276], of which five reported significantly elevated insulin levels in the GDM group compared to controls [234, 239, 255, 275, 276] (Supplementary Table 4.8.1). Two of these studies showed a significant difference in fasting insulin between offspring exposed to pre-GDM (i.e. diabetes diagnosed before pregnancy) and GDM[275, 276]. Two studies were included in a meta-analysis on cord blood insulin, however there was no difference between GDM and control groups (SMD -4.74 95% CI (-14.99-5.51), *n*(total)= 123 *n*(exposed to GDM)=60; p<0.00001, I^2 = 99%; 4.5.6.1B)[238, 270]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

A:



B:

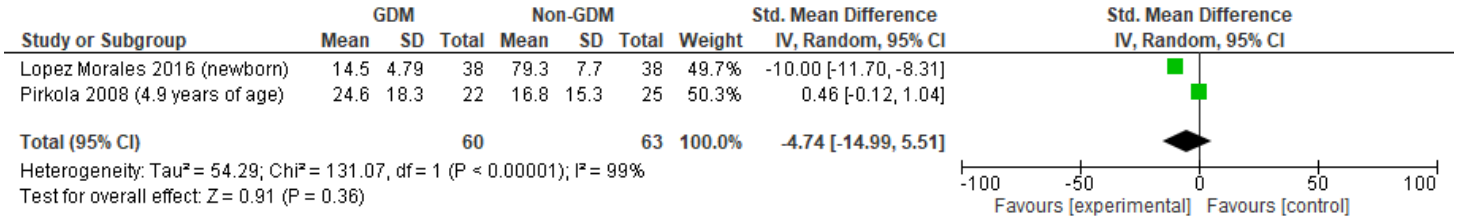


Figure 4.5.6.1 A) Standard mean difference in serum insulin in those exposed to GDM *in utero* and controls (B) Standard mean difference in cord blood insulin in those exposed to GDM *in utero* and controls

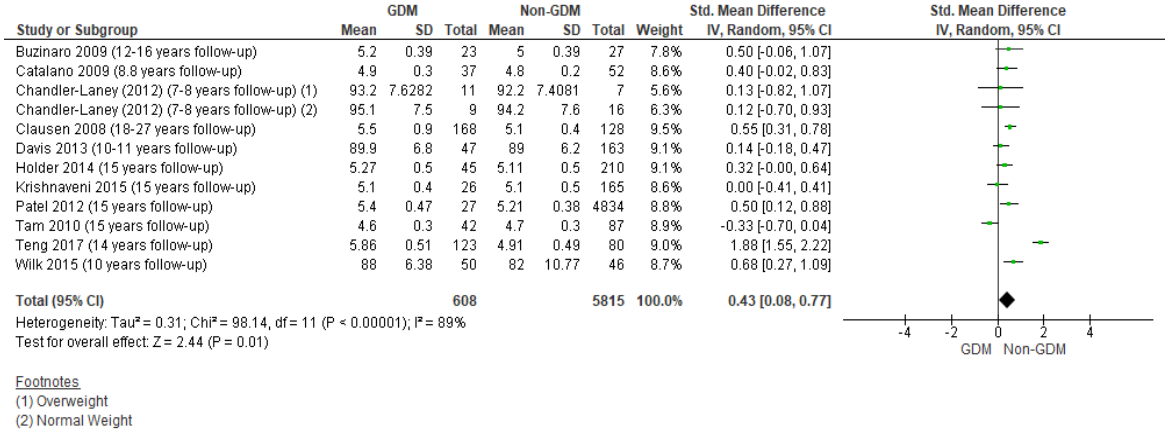
Table 4.5.6-1 Sensitivity analysis for serum insulin

Analysis	Studies	N=	SMD	95% CI	Chi^2 P=	I^2 (%)
Normal	4	5136	-0.02	-0.70,0.67	<0.00001	89
Sensitivity	3	5093	-0.24	-1.11,0.63	<0.00001	94

4.5.7. Blood Glucose

Glucose data were available from 25 studies (23 serum glucose, two cord blood glucose). Eleven studies on serum glucose were included in the meta-analysis, in which the age at follow-up ranged from eight to 27 years of age. Based on quantitative summary measures, the meta-analysis showed an increase in glucose in offspring exposed to GDM *in utero* compared to controls, demonstrating a 0.43 standard mean difference (95% CI 0.08-0.77; *n*(total)= 6,423 *n*(exposed to GDM)=608; p=0.00001, I^2 = 89% (Figure 4.5.7.1A)[231, 232, 234-236, 245, 246, 269, 272, 277, 278] Sensitivity analysis showed no difference in heterogeneity when removing low quality studies (Table 4.5.7.1). Twelve studies were not included in the meta-analysis[226, 239-242, 244, 253, 255, 259, 265, 273]. One study reported significantly higher serum glucose in the GDM group than controls[241]. One study reported a significantly lower serum glucose value in those exposed to GDM compared to controls[255]. Two studies assessed cord blood glucose with both newborn cohorts[254, 270] however no difference was seen between GDM and non-GDM groups (MD: -2.69 95% CI -5.80-0.42; *n*(total)= 346 *n*(exposed to GDM)=149; p=0.19, I^2 = 42%; Figure 4.5.7.1B)[254, 270]. Sensitivity analyses was not performed as no low-quality studies were included in the analysis.

A



B

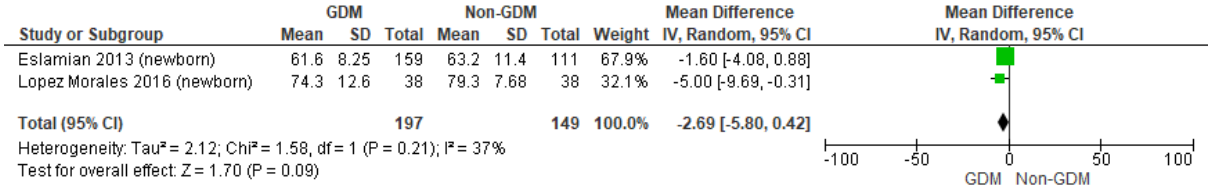


Figure 4.5.7.1 (A) Standard mean difference in fasting glucose in those exposed to GDM *in utero* and controls (B) Standard mean difference in cord blood glucose in those exposed to GDM *in utero* and controls

Table 4.5.7-1 Sensitivity analysis for serum glucose

Analysis	Studies	N=	SMD	95% CI	Chi² P=	I² (%)
Normal	11	6,423	0.43	0.08,0.77	<0.00001	89
Sensitivity	9	6,380	0.47	0.09,0.84	<0.00001	91

4.6. Discussion

This systematic review aimed to assess the prevalence of conventional cardiovascular risk factors in those exposed to GDM *in utero* compared to those not exposed to GDM. There is an established link between pregnancy complications and vascular outcomes such as elevated markers of inflammation and impaired fetal aortic intimal media thickness (aim)[279, 280]. Many reviews on GDM focus on cardiovascular endpoints including myocardial infarction and coronary heart disease. Identifying risk factors for CVD is vital in planning screening strategies to identify those at risk of future CVD with the aim of targeting preventive interventions. Hence, this review is a comprehensive synthesis of evidence from published studies comparing the main conventional cardiovascular risk factors in those born after pregnancies complicated by GDM compared to controls and includes outcomes that have not been recently reviewed in the literature such as serum and cord blood lipids.

Our meta-analysis showed that offspring exposed to GDM *in utero* have 1.75 mmHg higher systolic blood pressure than controls (95% CI 0.57-2.94, n=7,309, eight studies). Aceti *et al.* (2012) showed a similar association for offspring of GDM pregnancies (1.39 mmHg 95% CI, 0.00-2.77); 10 studies p=0.05)[52]. They also showed a smaller, non-significant increase in diastolic blood pressure for GDM offspring (0.75 mmHg (95% CI −0.47, 1.97); 9 studies p=0.23)[52].

This meta-analysis primarily consists of adolescent cohorts (i.e 10-19 years) with one 3 year old cohort. Therefore, the existing literature is not sufficient to show the trend in blood pressure throughout childhood and adolescence. These trends have been previously reported in a few large cohort studies. Krishnaveni *et al.*, demonstrated that systolic blood pressure remains elevated in those exposed to GDM compared to

unexposed controls throughout ages 5, 9.5 and 13.5 years[234, 239, 259]. A similar association was seen in another cohort at ages 8 and 15. [236, 242]. Therefore, it is important to assess childhood cohorts to affirm any trends seen in long term cohort studies.

Blood pressure that is elevated in childhood and adolescence is predictive of adult hypertension[281]. Raitakari *et al.* found a positive correlation between systolic blood pressure at 12-16 years with carotid artery intima medial thickness (C-IMT), which is a predictive factor of future CVD[282]. The association was weaker in males at 3-9 years age, but not among females. In a study by Oikonen *et al.*., two abnormal child or youth blood pressure observations were shown to predict risk for hypertension in adulthood[283]. While the effect size is our meta-analysis is small and blood pressure for all studies is generally within normal reference range, it is known that even a 2mmHg increase in systolic blood pressure is associated with 10% higher mortality from stroke, and 7% higher mortality from ischemic heart disease in middle age[284]. Therefore, offspring exposed to GDM may benefit from frequent blood pressure monitoring throughout childhood and adolescence. Dietary interventions during gestation, such as implication of a low GI diet, may benefit offspring and reduce the risk of high blood pressure. It has been demonstrated that children at 12 months old born to mothers at risk of GDM with a low GI diet have significantly thinner aortic IMT than those children whose mothers had a standard high fibre diet[285].

Among 31,485 participants it was shown that BMI Z-score is marginally higher in those exposed to GDM offspring compared to controls (MD: 0.11 95% CI 0.02-0.20, n=31,485, nine studies). We also observed a higher BMI in those exposed to GDM compared to controls (Supplementary Figure S2), however BMI is not an accurate predictor of childhood obesity. As an indicator of adiposity, BMI varies greatly based on fat and muscle mass, hence it may be accurate for fatter children but not those who are lean[286].

The findings of this meta-analysis on BMI z-scores are consistent with the findings reported in the review by Kawasaki *et al.* (pooled MD: 0.14 95% CI: 0.04–0.24, seven studies)[287].

Higher BMI in youth is associated with dyslipidaemia, hypertension and reduced insulin sensitivity[288]. Jago *et al.* showed that a change in BMI z-score at ages 11-14 was associated in a change in cardiovascular risk factors including an increase in systolic and diastolic blood pressure, HDL-C, LDL-C and triglycerides at the same age[288]. The results of this meta-analysis, support previous findings of higher BMI in those exposed to GDM *in utero* compared to controls.[226, 245, 266] Gestational diabetes mellitus is associated with newborn fat mass, indicative of the intrauterine environment in the final trimester of pregnancy. [289, 290] Higher birthweight is associated with markers of subclinical atherosclerosis such as mean carotid IMT. [291] Therefore, those who are exposed to GDM *in utero* appear to have risk factors for CVD very early in life. We could not assess the age distribution in very young children as majority of published studies were in adolescence. Hence, more studies among young children are required to support the association between gestational diabetes and increasing BMI z-score in offspring.

Our meta-analysis demonstrated that those exposed to GDM *in utero* have marginally higher fasting blood glucose levels (SMD 0.43 95% CI 0.08-0.77, n=6,423, 11 studies), but not fasting insulin compared to controls. Kawasaki *et al.* (2018) showed no difference in fasting plasma glucose among 7-10 and 15 year olds exposed to GDM compared to controls [287]. Plasma glucose was significantly higher at age 20 years among those exposed to GDM compared to controls (MD: 0.4 mmol/L; 95% CI: 0.25–0.55 seven studies) [287]. Our meta-analysis showed a similar association in predominantly childhood-adolescent cohorts, with one cohort during adulthood. We can support an

association between exposure to GDM *in utero* and impaired glucose tolerance in offspring, however as the effect size is minimal, further studies are required to support this association.

Abnormal plasma glucose is a requisite for pre-diabetes, and if untreated and coupled with increasing obesity may lead to early onset T2DM, which progresses at a faster rate in children and adolescence than in adults[292]. Adolescents diagnosed with T2DM are predicted to lose 15 years from their life expectancy compared to those without T2DM[293]. Hence, frequent fasting blood glucose monitoring in those exposed to GDM *in utero* may reduce the risk of T2DM in the future. Also, interventions during pregnancy may be beneficial as evidenced by studies showing that infants born to mothers with diet or insulin controlled GDM have lower fasting blood glucose than controls[255].

We acknowledge some limitations of our analyses. Both GDM and CVD are multifactorial diseases, influenced by genetic and environmental factors. Smoking during pregnancy is shown to have significant effects on childhood adiposity and elevated blood pressure[294, 295]. High pre-pregnancy BMI is associated with elevated systolic and diastolic blood pressure in offspring[296]. GDM is shown to cluster in families, and variants of different genes are associated with increased risk of GDM[297]. We could not adjust for such important covariates due to limitations in the data that was available. We were unable to examine female and male subgroups due to lack of power, however it may be of interest for future studies to consider this as Li *et al.* (2017) showed that male offspring of GDM pregnancy had higher BMI than male controls and an increased risk of obesity, while there was no significant association in the cohort of females exposed to GDM compared to female controls[258].

We did not identify any studies that looked at microvascular function in offspring of GDM. West and colleagues (2011) found offspring of diabetic pregnancies had increased levels of circulating cellular adhesion molecules such as E-selectin and VCAM1, even when adjusted for maternal pre-pregnancy BMI[298]. Therefore, further studies on this topic are required.

Most of the studies that we assessed in the meta-analysis are follow-up at adolescence, there were few studies that conducted follow-up during early childhood as well as in adulthood, therefore, we are unable to show age distributions in outcomes assessed.

Observational studies may be subject to publication bias, although visual analysis of funnel plots for BMI and glucose showed a low chance of publication bias (Supplementary Figure S9). However, these outcomes showed high heterogeneity based on I^2, and hence need to be interpreted with caution. We performed sensitivity analysis for relevant outcomes, however we observed no difference in heterogeneity for the outcomes assessed (Supplementary Table S3, S4, S5).

4.7. Conclusion

Offspring exposed to gestational diabetes mellitus *in utero,* demonstrate risk factors for cardiovascular disease in childhood and adolescence, including elevated systolic blood pressure, BMI z-score and fasting plasma glucose that are evident from early life. These outcomes at a young age, if not monitored, can lead to adverse vascular and metabolic health parameters resulting in CVD in adulthood. Regular blood pressure monitoring and weight control from a young age may benefit offspring exposed to GDM. Further long-term cohort studies also need to be established, which can adjust for important covariates and allow for affirmation of effect size.

4.8. Supplementary data

Supplementary Table 4.8 1 Studies not included in the meta-analysis

Study	**Results in GDM group**	**Results in control group**	**P**
SBP (mmHg)			
Krishnaveni 2010†	5 years (Girls): Mean (99.0) SD (8.2)	5 years (Girls): Mean (95.0) SD (8.1)	0.08
	5 years (Boys): Mean (95.4) SD (9.4)	5 years (Boys): 97.2 SD (8.9)	0.1
	9.5 years (Girls): Mean (103.8) SD (8.0)	9.5 years (Girls): Girls: Mean (99.4) SD (8.5)	0.02
	9.5 years (Boys): Mean (106) SD (12)	9.5 years (Boys): Mean (101.9) SD (8.9)	0.2
Lee 2007	Mean (93.3) SD (9.3)	IGT: Mean (92.3) SD (8.7)	NS
Page 2013∴ Ω	Mean (105.0) SEM (10.0)	Mean (100.0) SEM (10.0)	0.15
Tam 2008†	Mean (94) SD (9.5)	Mean (88) SD (8.9)	<0.001
Tam 2017Ω	Mean (104) SD (8.7)	Mean (102) SD (8.9)	0.01
Tsadok 2011 Ω	Mean (121.56) SD (12.30)	Mean (119.84) SD (12.06)	<0.05
Vaarasmaki 2009	Median 117 IQR (111–125)	Median 115 IQR (106–123)	NS
DBP (mmHg)			
Krishnaveni 2010†	Girls: Mean (59.8) SD (4.8)	Girls: Mean (57.9) SD (6.6)	0.09
	Boys: Mean (60.3) SD (7.6)	Boys: Mean (58.6) SD (6.9)	0.4
Lee 2007	Mean (59.6) SD (8.5)	IGT: Mean (59.0) SD (7.5)	NS
Page 2013∴ Ω	Mean (60) SEM (6)	Mean (60) SEM (9)	0.62
Tam 2008†	Mean (62) SD (6.3)	Mean (57) SD (6.0)	<0.001
Tam 2017 Ω	Mean (63) SD (8.1)	Mean (62) SD (7.9)	0.06
Tsadok 2011 Ω	Mean (75.12) SD (7.44)	Mean (73.47) SD (8.30)	<0.05
Vaarasmaki 2009	Median (68) IQR (65-73)	67 (62-72)	NS
BMI (kg/m2)			
Baptise-Roberts 2012#	Age 3: Mean (15.5) SD (1.65)	Age 3: Mean (15.4) SD (3.0)	0.721
	Age 4 Mean (15.67) SD (1.91)	Age 4: Mean (15.36) SD (3.54)	0.31
	Age 7: Mean (16.35) SD (2.57)	Age 7: Mean (15.64) SD (1.99)	<0.001
Krishnaveni 2005 *	1 year: Mean (15.6) SD (1.7)	1 year: Mean (15.7) SD (1.4)	0.9
	5 years: (14.0) SD (1.2)	5 years: Mean (13.6) SD (1.2)	0.03
Krishnaveni 2010 *	Girls: Median (16.4) IQR (14.8-17.8)	Girls: 14.3 (13.13-15.4)	<0.001
	Boys: Median (15.2) IQR (13.8-16.6)	Boys: Median (14.2) IQR (13.4-15.4)	0.07
Lee 2007	Mean (16.1) SD (1.9)	IGT: Mean (16.1) SD (1.7)	NS
Nehring 2013 Ω	Mean (16.1) 95% CI (15.8-16.4)	Mean (15.5) 95% CI (15.5-15.5)	NS
Nielsen Ω	Mean (26.2) SD (5.6)	Mean (23.3) SD (4)	NR
Page 2012∴ Ω	Mean (20.8) SD (1.3)	Mean (16.1) SD (1.4)	0.004

Pirokla 2010	Normal weight: Mean (24.3) 95% CI (23.4-25.1)	Control: Mean (23.7) 95% CI (23.6-23.8)	NR
	Overweight: Mean (26.7) 95% CI (25.3-28.1)		
Silverman 1998#	Mean (26.0) SD (5.5)	Mean (20.9) SD (3.4)	<0.001
Tam 2008†	Mean (16.2) SD (3.1)	Mean (16.2) SD (3.0)	0.86
Tam 2017 Ω	Mean (15.3) SD (2.1)	Mean (15.0) SD (2.3)	0.04
Tsadok 2011 Ω	Mean (22.47) SD (3.86)	Mean (21.18) SD (3.11)	<0.05
Vaarasmaki 2009	Median (20.8) IQR (19.4-23.8)	Mean (20.2) (18.8-22.1)	NS
Vohr 1995	AGA: Mean (12.5) SD (0.9)	AGA: Mean (12.6) SD (0.9)	NS
	LGA: Mean (14.1) SD (1.2)	LGA: Mean (14.2) SD (1.0)	NS
Vohr 1999	AGA: Mean (12.8) SD (1)	AGA: Mean (13.0) SD (1)	NS
	LGA: Mean (14.7) SD (1)	LGA: Mean (14.8) SD (1)	NS
BMI percentiles (Centiles highlighted next to author name)			
Boney 2005 (>85th)	LGA: 13/39 (33%)	LGA: 11/41 (27%)	NS
	AGA: 7/49 (14%)	AGA: 9/41 (22%)	NS
Baptise-Roberts 2012 (>85th)	Age 3: Mean (15) SD (11.7)	Age 3: Mean (724) SD (7.0)	0.041
	Age 4: Mean (29) SD (21.2)	Age 4: Mean (1063) SD (9.0)	<0.001
	Age 7: Mean (90) SD (23.3)	Age 7: Mean (2795) SD (12.6)	<0.001
Boerschmann 2010 (≥ 90th)	Pre-pregnancy BMI Overweight (BMI 25-29.9 kg/m^2): 18/49 Pre-pregnancy BMI Obese (≥ BMI 30 kg/m^2): 24/57	24/71	NR
Chandler Laney 2012 (≥ 95th)	Normal weight: Mean (55.3) SEM (5.3)	Normal weight: Mean (49.1) SEM (4.0)	NS
	Overweight: Mean (96.1) SEM (4.9)	Normal weight: Mean (94.2) SEM (6.2)	NS
Davis 2013 (≥85th)	Mean (97.3) SD (3.0)	Mean (97.3) SD (3.4)	NS
Gillman 2003(85th-95th)	Female: 35 (15.2%)	Female: 966 (13.1%)	NR
	Male: 37 (19.5%)	Male: 951 (15.6%)	NR
Farfel 2013 (≥85th)	Female (15.9%)	Female (15.6%)	<0.01
	Male (27.0%)	Male (16.1%)	0.01
Koing 2014 (>50th)	Female 40 (67.8%)	Female: 17 (53%)	0.18
Hammound 2017 (based on International Obesity Task Force cut-offs)	4/24 (17%)	T1D: 2/27 (7%) T2D: 8/22 (36%)	NR
	Male: 20 (55.56%)	Male: 13 (50%)	0.8
Lee 2007 (≥ 95th)	17 (8.5%)	4 (4.3%)	NS
Le Moullec 2018 (based on International Obesity Task Force cut-offs)	25.5	14.2	<0.001
Page 2014† (NR)	Mean (73.7) SEM (5)	Mean (52.5) SEM (6)	0.61
Page 2015† (NR)	Mean (63) SD (30)	Mean (61) SD (36)	0.87
Pham 2013 (>85th or >95th)	Mean (51.8) SD (33.1)	Mean (55.2) SD (30.6)	0.12
Rutwoska 2015 (>90th)	54.80%	29.00%	0.04

Tam 2008† (≥85th)	Mean (19) SEM (30.2)	Mean (26) SEM (25.5)	0.86
Tam 2017 (≥85th)	30 (22.7%)	121 (15.3%)	0.03
Wilk 2015 (≥85th)	38%	41%	0.19
Whitaker 1998 (≥85th)	11/58 (19%)	62/257 (24%)	NR
Wright 2009 (>95th obese, >85th-95th overweight)	Obese: 7 (14%) Overweight: 9 (18%)	Obese: 91 (9%) Overweight: 169 (17%)	NR
Zhao 2015Boys: Obese (⩾82nd) Overweight (⩾96.3) Girls: Obese (⩾87.4) Obese (⩾98th)	Obese: 115 (10.7%) Overweight: 178 (16.6%)	Obese: 212 (12.0%) Overweight: 222 (12.6%)	NR
BMI Z-Scores			
Baptise-Roberts 2012	Age 3: Mean (-0.51) SD (1.30)	Age 3: Mean (-1.29) SD (65.11)	0.892
	Age 4 Mean (-0.13) SD (1.44)	Age 4: Mean (-0.42) SD (1.71)	0.05
	Age 7: Mean (0.16) SD (1.16)	Age 7: Mean (-0.17) SD (1.16)	<0.001
Lawlor 2010^	Mean (0.302) SD (1.225)	Mean (-0.006) SD (0.991)	NR
Page 2012†	Mean (0.9) SD (0.4)	Mean (0.3) SD (0.4)	0.04
Page 2013†	Mean (0.7) SD (1)	Mean (0.4) SD (1)	0.37
Retnakaran 2013	Median (0.28) IQR (-0.37-0.75)	Median (-0.08) IQR (-0.58-0.55)	0.2
BMI SDS			
Bozkurt 2016	Mean (0.05) SD (1.1)	Mean (0.32) SD (1.0)	NR
BMI Peak			
Hakanen 2016	417 (17.9)	5688 (17.7)	NR
Total Cholesterol			
Serum			
Lee 2007	Mean (4.4) SD (0.7)	IGT: Mean (4.2) SD (0.8)	NS
Tam 2008†	Mean (0.83) SD (0.48)	Mean (4.6) SD (0.8)	0.62
Vaarasmaki 2009	Median (4.20) IQR (3.90–4.75)	Median (4.20) IQR (3.70–4.70)	NS
Tam 2017 Ω	Mean (4.52) [238-244, 250]SD (0.68)	Mean (4.47) SD (0.74)	0.41
LDL			
Cord Blood			
Elsamain 2013 Ω	Mean (2.3) SD (0.18)	Mean (2.6) SD (0.3)	0.08
Serum			
Retnakaran 2013	Median (2.60) IQR (2.15-3.15)	Median (2.60) IQR (2.30-3.20)	0.58
Tam 2008†	Mean (2.7) SD (0.8)	Mean (2.5) SD (0.8)	0.08
Tam 2017 Ω	Mean (2.53) SD (0.61)	Mean (2.47) SD (0.64)	0.33
Vaarasmaki 2009	Median (2.20) IQR (2.00–2.70)	Median (2.20) IQR (1.90–2.60)	NS
HDL			
Serum			
Krishnaveni 2010†	Girls: Mean (1.0) SD (0.2)	Girls: Mean (1.1) SD (0.1)	0.2
	Boys: Mean (1.2) SD (0.3)	Boys: Mean (1.1) SD (0.2)	0.4

Lee 2007	Mean (1.4) SD (0.3)	IGT: Mean (1.4) SD (0.3)	NS
Retnakaran 2013	Median (1.10) IQR (1.00-1.30)	Median (1.10) IQR (0.90-1.30)	0.54
Tam 2008†	Mean (1.58) SD (0.32)	Mean (1.71) SD (0.30)	0.019
Tam 2017 Ω	Mean (1.65) SD (0.31)	Mean (1.66) SD 0.35	0.73
Vaarasmaki 2009	Median (1.33) IQR (1.17–1.56)	Median (1.39) IQR (1.20–1.60)	NS
Triglycerides (mmol/L)			
Serum			
Krishnaveni 2010†	Girls: Mean (1.1) SD (0.5)	Girls: Mean (1.0) SD (0.4)	0.2
	Boys: Mean (0.8) SD (0.3)	Boys: Mean (0.8) SD (0.3)	0.6
Lee 2007	Mean (0.8) SD (0.3)	Mean (0.9) SD (0.4)	NS
Tam 2008†	Mean (0.83) SD (0.48)	Mean (0.92) Mean (0.4)	0.27
Tam 2017 Ω	Mean (0.78) SD (0.34)	Mean (0.74) SD (0.33)	0.24
Vaarasmaki 2009	Median (0.79) IQR (0.63–0.97)	Median (0.72) IQR (0.57–0.96)	NS
Glucose			
Cord blood			
Lopez Morales 2016	Mean (74.28) SD (12.58)	Mean (79.28) SD (7.68)	0.04
Serum			
Borgono 2012 ∞	Median (4.5) IQR (4.2–4.8)	Median (4.5) IQR (4.3–4.8)	0.67
Jaber 2006	Diet: Mean (2.82) SD (0.92)	Control: Mean (4.03) SD (0.35)	<0.001
	Insulin: Mean (3.23) SD (1.00)		<0.05
Krishnaveni 2005 *†	Mean (4.8) SD (0.5)	Mean (4.8) SD (0.5)	0.8
Krishnaveni 2010 *†	Girls: Mean (4.6) SD (0.4)	Girls: Mean (4.7) SD (0.4)	0.7
	Boys: Mean (4.7) SD (0.4)	Boys: Mean (4.7) SD (0.4)	0.6
Lee 2007	Mean (4.8) SD (0.5)	IGT: Mean (4.7) SD (0.5)	NS
Plagermann 1997	Mean (4.90) SD (0.20)	PreGDM: Mean (4.57) SD (0.09)	NS
Page 2013⁘Ω	Mean (93) SEM (6)	Mean (86) SEM (5)	<0.001
Retnakaran 2013 ∞	Median (4.5) IQR (4.2-4.8)	Median (4.5) IQR (4.3-4.8)	0.67
Tam 2008†	Mean (4.7) SD (0.48)	Mean (4.7) SD (0.4)	0.78
Tam 2017 Ω	Mean (4.64) SD (0.49)	Mean (4.57) SD (0.35)	0.12
Vaarasmaki 2009	Median (5.30) IQR (5.00–5.50)	Median (5.10) IQR (4.90–5.40)	NS
Vohr 1999	LGA: 95 ± 11	NR	NR
	AGA: 96 ± 15	NR	NR
Insulin			
Cord blood			
Jahan 2011	Mean (21) IQR (2.6-67.0)	Mean (8.03) IQR (2.1-29.7)	NR
Serum			
Borgono 2012	Median (7.5) IQR (5.0–14.0)	Median (7.5) IQR (3.5–13.5)	0.67
Bozkurt 2016	Median (4.1) IQR (2.1-5.9)	Median (3.15) IQR (1.0-4.7)	NR
Jaber 2006	Diet: Mean (6.23) SD (5.98)	Mean (4.65) SD (4.72)	<0.05
	Insulin: Mean (7.84) SD (5.45)		<0.05

Krishnaveni 2010 *	Girls: Median (35) IQR (25048)	Girls: Median (25) IQR (18-37)	0.003
	Boys: Median (25) IQR (18-37)	Boys: Median (26) IQR (18-34)	0.95
Krishnaveni 2015 *	Median (54.3) IQR (37.0, 73.3)	Median (42.5) IQR (30.7, 53.2)	0.02
Lee 2007	Mean (4.2) SD (1.1)	IGT: Mean (6.8) SD (3.5)	NS
Page 2013∴Ω	Mean (10) SEM (7)	Mean (12) SEM (10)	0.78
Plagermann 1997	Mean (64.2) SD (19.2)	PreGDM: Mean (118.3) SD (15.4)	<0.005
Plagermann 1997	Mean (40.3) SD (5.47)	PreGDM: Mean (78.1) SD (5.95)	<0.001
Tam 2008†	Mean (66.4) SD (52.5)	Mean (64.7) SD (51.2)	0.84
Tam 2017 Ω	Mean (3.77) SD (3.57)	Mean (4.07) SD (5.33)	0.53
Vaarasmaki 2009	Median (10.20) IQR (8.45–14.30)	Median (9.30) IQR (7.30–11.90)	NR

NR - not reported for a direct comparison between GDM and non-GDM exposed offspring

NS - not significant

^- *Lawlor and Patel studies of same cohort*

*- *Krishnaveni studies of same cohort*

∴ - *Page studies of the same cohort*

† - *the study with the oldest cohort was included in the meta-analysis*

\# - *sample size unknown for outcome*

Ω - *adjusted values*

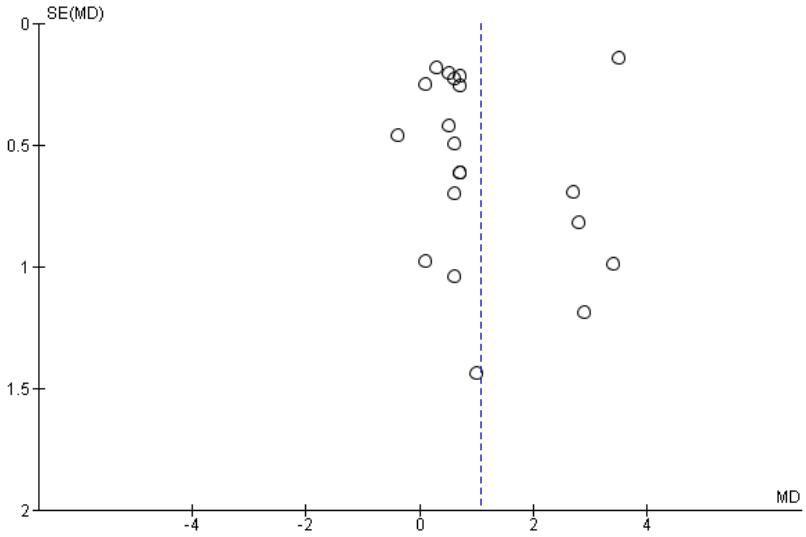
∞ - *Retnakaran study is a substudy of Borgono study*

Supplementary Table 4.8 2 Quality assessment of studies included in systematic review

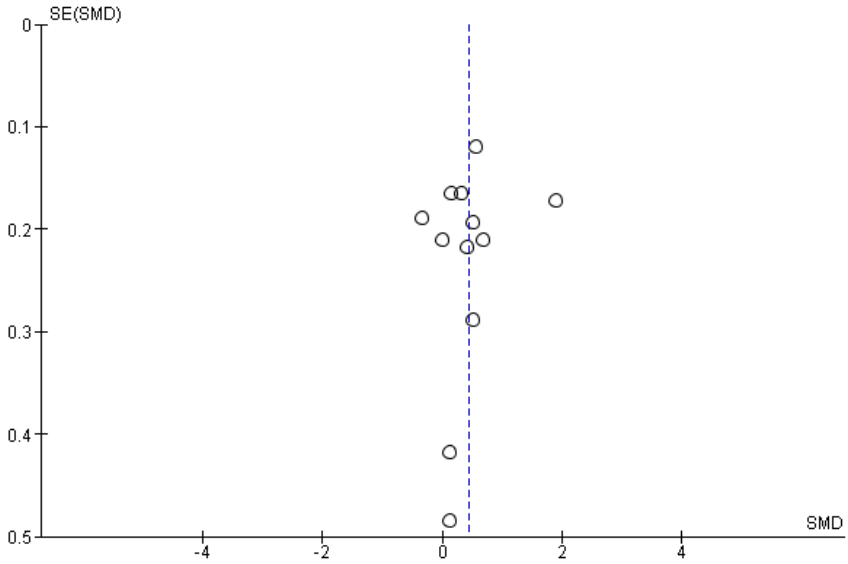
Quality assessment	Selection				Comparability	Exposure			Total Score
	1	**2**	**3**	**4**	**1**	**1**	**2**	**3**	
Baptise-Roberts	a	a	a	a	a	a	a	b	7
Boney	a	b	b	a	a	a	b	b	3
Borgono	a	a	a	a	a	a	a	c	7
Bozkurt	a	a	b	a	a	a	a	a	7
Boerschermann	a	a	c	b	a	a	a	c	5
Buzinaro	a	a	c	b	a	a	a	b	5
Catalano	a	a	a	a	a	a	a	a	8
Chandler-Laney	b	b	c	b	b	d	a	c	1
Chang	a	a	a	a	a	a	a	c	6
Clausen	a	a	a	a	a	a	a	b	7
Davis	b	b	a	b	not adjusted	d	a	a	3
Elsamian	a	a	b	a	a	a	a	a	7
Farfel	a	a	a	a	a	a	a	a	7
Gilliman	b	a	c	a	a+b	d	a	c	4
Hakanen	a	b	b	a	a	a	a	a	5
Holder	b	b	a	a	a	d	a	a	5
Jaber	a	a	a	a	a	a	a	a	8
Jahan	a	a	a	a	a+b	a	a	a	8
Kavesa	a	a	a	a	a	a	a	b	7
Kearney	a	b	a	a	a	a	a	c	6
Koing	a	b	a	a	a	a	a	a	7
Krishnaveni (2005)	a	a	a	a	a	a	a	b	7
Krishnaveni (2010)	a	a	a	a	a	a	a	c	7
Krishnaveni (2015)	a	a	a	a	a	a	a	b	7
Lawlor	a	a	a	a	a	a	a	c	7
Lee	a	a	c	a	a	a	a	b	6
Le Moullec	a	b	b	a	a	a	a	b	5
Li	b	a	c	a	a+b	d	a	c	b
Lopes-Morales	a	a	a	a	a+b	a	a	a	8
Mietten	a	a	a	a	a	a	a	b	7
Nehring	a	b	a	b	a	a	a	a	5
Nielsen	a	a	b	a	a	a	a	c	6
Page 2012	a	a	c	a	not adjusted	d	a	c	3
Page 2013	a	a	c	a	not adjusted	d	a	c	3
Page 2014	a	a	c	a	not adjusted	d	a	c	3
Page 2015	a	a	c	a	not adjusted	d	a	c	3
Patel	a	a	a	a	a	a	a	b	7
Pham	a	a	a	a	not adjusted	a	a	c	6
Pirkola (2008)	a	a	b	a	a	a	a	b	6
Piroka (2010)	a	b	a	a	a	a	a	b	6
Plagemann 1997	a	b	a	a	a	a	a	c	6

Plagemann 1997	a	b	a	a	a	a	a	c	6
Retnakaran	a	a	a	a	a	a	a	c	6
Rutowska	c	b	c	a	not known	e	b	a	2
Silverman	c	b	c	a	a	e	?	c	2
Tam (2008)	a	a	a	a	a	a	a	c	7
Tam (2010)	a	a	a	a	a	a	a	c	7
Tam (2017)	a	a	a	a	a	a	a	b	7
Teng	a	a	a	b	not adjusted	a	a	c	5
Tsadok	a	b	a	a	a	a	a	c	6
Vaarsamarki	a	a	a	a	a	a	a	c	7
Vohr 1995	a	a	a	a	not adjusted	a	a	a	6
Vohr 1999	a	a	a	a	not adjusted	a	a	c	6
Whitaker	a	a	a	a	a	a	a	b	6
Wang 2018	a	a	a	a	a	a	a	a	8
Wilk	a	a	a	a	not adjusted	a	a	a	7
Wright	a	a	a	a	a	a	a	b	7
Zhao	a	a	a	b	a	a	a	b	6
Zhao (2016)	a	b	a	b	not adjusted	a	a	b	4

(A)



(B)



Supplementary Figure 4.8 1 Funnel plots for (A) BMI (B) Blood glucose

Chapter 5

5. Author response: Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus: a systematic review and meta-analysis (2020)

Maleesa M Pathirana, Zohra Lassi , Claire T Roberts , Prabha H Andraweera

5.1. Statement of Authorship

Title of Paper	Author Response: Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: A systematic review and meta-analysis
Publication Status	Published – 2020
Publication Details	Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Author response: cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis. J Dev Orig Health Dis. 2020 Jun;11(3):244-245. doi: 10.1017/S2040174420000185. Epub 2020 Apr 13. PMID: 32279699.

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana	
Contribution to the Paper	Knowledge, drafting	
Overall Percentage (%)	70%	
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.	
Signature		**Date 14 Feb 2022**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Zohra S Lassi	
Contribution to the Paper	Knowledge, drafting	
Signature		**Date 14 Feb 2022**

Name of Co-Author	Claire Roberts	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Name of Co-Author	Prabha Andraweera	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Abstract

This commentary is an author response to Lu and Wang, regarding the manuscript entitled "**Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: Systematic review and meta-analysis".** We address their concern regarding duplication of studies in the meta-analysis and the quality of included studies

Letter

Dear editor,

We thank Dr. Lu and Dr. Wang for their comments regarding our systematic review and meta-analysis on cardiovascular disease in offspring exposed to gestational diabetes mellitus *in utero*[207]. Their comments highlight important considerations regarding study quality in systematic review and meta-analyses, and statistical methods put in place to address low quality studies.

Although we have already specified our methodology regarding including publications of multiple cohorts in the meta-analysis, we appreciate the opportunity to provide further clarity. There has been the understanding that the cohort publications published by Krishnaveni *et al.,* Tam *et al.,* and Vohr *et al.* that we have included in our systematic review, have been doubly reported in the meta-analysis[226, 234, 236, 239, 242, 259, 264, 265]. In our methods under the 'included studies' header, it states that "when the same cohort was reported in multiple publications at different ages, the study reporting on the older age group was included in the meta-analysis." We only used the publications of Krishnaveni *et al.* (2015) and Tam *et al.* (2010) in our meta-analysis as these studies have data on the most recent follow-up (i.e. 15 years of age for both cohorts)[236, 239]. The publications that have been mentioned in the previous commentary are only reported as supplementary data (Supplementary Table 1) but not in the meta analyses. The Vohr *et al.* studies are also only reported in the supplementary data. We included 59 studies from 54 cohorts in our systematic review, and only 25 studies were used in the meta-analysis (Figure 1). The reasons for not including 34 studies in the meta-analysis include but are not limited to; 1) reporting the cohort at an earlier follow-up and thus not being the most recent publication with the oldest follow-up age (in the case of Krishnaveni and Tam studies); 2) some studies not reporting a control group value (in the case of Vohr *et al.* 1999); 3) studies only including adjusted mean values that we could not incorporate in a meta-analysis due to

limitation in the number of studies; 4) being unable to include median and interquartile range values in the analysis. While we endeavoured to contact authors for unadjusted and unknown values in the meta-analysis, we received a 44% response rate. It would be counterintuitive to exclude these studies all together after trying to contact the authors for appropriate data, it seemed best to report this data in a supplementary table if it was not suitable for the analysis, thereby providing readers a more comprehensive review of the literature. Furthermore, in our protocol we were interested in subgroup analyses stratified by childhood, adolescence, and adulthood to determine if any of the cardiovascular risk factors appeared at certain points during the lifecourse in offspring exposed to GDM *in utero*. However, we did not have sufficient number of studies to complete any subgroup analyses. We have addressed this in our discussion.

The second point mentioned by Lu and Wang regarding using only high quality studies in a meta-analysis is an important one to address. While we have included studies of varying study quality, we must emphasize that our methods address how we handle low quality studies. All 59 included studies have been verified by two authors, and underwent quality assessment using the Newcastle-Ottawa Scale (NOS), which is a recommended quality assessment tool used for observational studies. The NOS broadly assesses study quality, including study selection, definition and comparability of cases and controls, assessment and reporting of outcome. We only found nine studies of low quality. We performed sensitivity analyses to omit all low quality studies from the meta-analysis, thereby assessing whether these studies would have influenced the effect size of the outcomes. Performing a quality assessment of studies and performing sensitivity analyses are common protocol for many meta-analyses [34, 52]. Sensitivity analyses were done for only four outcomes, as these were the only outcomes that included low quality studies. Our sensitivity analysis tables reported as supplementary data show that there was no significant difference between the effect estimates when removing the low quality

studies, based on I^2 and chi-square value. Therefore, the effect size of our meta-analysis are unaffected by these low quality studies. Henceforth, the heterogeneity in these analyses needs to be explored in other avenues, including through visual analysis of funnel plots for heterogeneity (which in our analysis were all standard), through performing analyses with values adjusted for important covariates, and subgroup analysis (both actions that we were unable to do).

Including all relevant studies and reporting them allows for an extensive scope of the literature, and it is important to assess and report which of this literature is high, moderate and low quality to ensure that clinical decision-making is based on the best quality evidence.

Chapter 6

6. Author response: Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus: a systematic review and meta-analysis (2022)

Maleesa M Pathirana, Zohra Lassi, Claire T Roberts , Prabha H Andraweera

6.1. Statement of Authorship

Title of Paper	Author Response: Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: A systematic review and meta-analysis
Publication Status	Accepted for publication in J Dev Orig Health (in press).
Publication Details	Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Author response: cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis. J Dev Orig Health Dis. 2020 Jun;11(3):244-245. doi: 10.1017/S2040174420000185. Epub 2020 Apr 13. PMID: 32279699.

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Knowledge, drafting
Overall Percentage (%)	70%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	**Date 14 Feb 2022**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

iv. The candidate's stated contribution to the publication is accurate (as detailed above);
v. Permission is granted for the candidate to include the publication in the thesis; and
vi. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Zohra S Lassi	
Contribution to the Paper	Knowledge, drafting	
Signature		**Date 14 Feb 2022**

Name of Co-Author	Claire Roberts	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Name of Co-Author	Prabha Andraweera	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Abstract

This commentary is an author response to Yu and colleagues regarding the manuscript entitled "**Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: Systematic review and meta-analysis".** We address their concern regarding minor errors in our manuscript, our search strategy and assessment of heterogeneity.

Letter

Dear editor:

We thank Yu and colleagues for their comments regarding our systematic review and meta-analysis on cardiovascular disease in offspring exposed to gestational diabetes mellitus *in utero* [299]. Their comments highlight important considerations regarding study quality, statistical analyses, and search strategy for systematic reviews and meta-analyses.

Thank you for the recommendation on databases that can be used in the process of literature retrieval in the future update of this review. We used PubMed CINAHL, SCOPUS, and EMBASE with an end of search date of April 18, 2018. Subsequently, we updated the literature search to include all relevant articles published until October 17, 2018. Our systematic review only had peer-reviewed full-text published papers. However, we will search the recommended databases, particularly grey literature databases, in our future update of this systematic review.

We thank Yu and colleagues for identifying two typographical errors, and we acknowledge that the total number of participants in the BMI Z score analysis is 31485 instead of 8759 as stated in the manuscript and that the chi-squared p-value in figure 4 is <0.00001 instead of 0.00001.

The heterogeneity of the analyses was indeed significantly high, and we did report this in our discussion section as a significant limitation. We could not perform subgroup analyses based on age in this review as there were not enough studies with varying follow-up times to assess this. However, we did plan a subgroup analysis of time to follow-up at <1 year postpartum, 1-5 years postpartum, 5-10 years postpartum, and 10+ years postpartum to assess heterogeneity. We proposed to perform subgroup analyses in our PROSPERO registration (CRD42018094983). However, these analyses were also not undertaken as there were insufficient publications to conduct meaningful comparisons. It would be beneficial to complete other subgroup analyses for future updates of this review. Other meta-analyses

completed by our research group with a greater number of studies and sample size included subgroup analyses stratified by age, ethnicity, the definition of GDM, and metabolic syndrome [36, 300]. We have planned for meta-regression in our next update of this systematic review.

We did perform sensitivity analyses for all the outcomes in which we removed low-quality studies and reported the outcomes before and after the sensitivity analyses in Supplementary Tables S3 to S5. We found no significant difference based on the sensitivity analyses, and heterogeneity remained high but the effect size of the outcomes remained unaffected. In our future update of this systematic review, we will consider other avenues, including meta-regression to explore heterogeneity in the data, as mentioned in a previous letter to the editor[301].

We appreciate the comment from Yu *et al.* regarding the use of "Begg's Test" or "Egger's Test" for publication bias. We assessed publication bias using Egger's test and prepared funnel plots for all of our outcomes and they are provided in the supplementary file.

Chapter 7

7. Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis.

Maleesa M Pathirana, Zohra S Lassi, Anna Ali , Margaret A Arstall, Claire T Roberts,

Prabha H Andraweera

7.1. Statement of Authorship

Title of Paper	Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis
Publication Status	Published – 2021
Publication Details	**Pathirana MM,** Lassi Z, Ali A, Arstall M, Roberts CT, Andraweera PH. Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis. Endocrine. 2021 Feb;71(2):310-320. doi: 10.1007/s12020-020-02492-1. Epub 2020 Sep 15. PMID: 32930949.

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana	
Contribution to the Paper	Acquiring data, knowledge, analysis, drafting	
Overall Percentage (%)	70%	
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.	
Signature		**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Zohra S Lassi	
Contribution to the Paper	Conceptualisation, acquiring data, analysis, drafting	
Signature		**Date 14 Feb 2022**

Name of Co-Author	Anna Ali	
Contribution to the Paper	Acquiring data, analysis	
Signature		**Date 14/02/2022**

Name of Co-Author	Margaret Arstall	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Name of Co-Author	Claire Roberts	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Name of Co-Author	Prabha Andraweera	
Contribution to the Paper	Conception, acquiring data, knowledge, drafting	
Signature		**Date 28/02/2022**

7.2. Abstract

Objective: The primary aim of this systematic review and meta-analysis was to determine the association between gestational diabetes mellitus (GDM) and metabolic syndrome (MetS) in women and children. Our secondary aim was to assess the development of MetS with respect to the elapsed time postpartum at which MetS was diagnosed.

Methods: This review is registered with PROSPERO (CRD42020173319). PubMed, CINHAL, SCOPUS, and EMBASE databases were searched. Studies reporting on the rate of MetS in pregnant women with GDM, the rate of MetS in women with a history of GDM, and the rate of MetS in offspring exposed to GDM *in utero* compared to healthy controls were selected.

Results: We identified 588 articles from the literature search. Fifty-one studies were included in the review and of those 35 were included in the meta-analysis. Quantitative summary measures showed that women with a history of GDM have an increased risk of developing MetS compared to those without a history of GDM (RR 2.36, 95% CI 1.77 to 3.14, 29 studies, 13,390 participants; heterogeneity: Chi^2 $P < 0.00001$; $I^2 = 93\%$). Those exposed to GDM *in utero* have an increased risk of developing MetS compared to those not exposed to GDM *in utero*. (RR 2.07, 95% CI 1.26 to 3.42, three studies, 4,421 participants; heterogeneity: Chi^2 $P = 0.33$; $I^2 = 12\%$). Women diagnosed with GDM have an increased risk of developing MetS during pregnancy (RR 20.51, 95% CI 5.04 to 83.55; three studies, 406 participants; heterogeneity: Chi^2 $P = 0.96$; $I^2 = 0\%$). Subgroup analysis revealed that MetS is diagnosed as early as <1 year postpartum in women with a history of GDM.

Conclusions/interpretation

Women with GDM in pregnancy have an increased risk of developing MetS during pregnancy. Women with a history of GDM and offspring exposed to GDM *in utero* have a higher risk of

developing MetS compared to those with no history of GDM. Metabolic syndrome in women with a history of GDM is seen as early as <1 year postpartum.

7.3. Introduction

Gestational diabetes mellitus (GDM) is impairment of glucose that is first diagnosed during pregnancy, hence different from both type I and II diabetes mellitus. GDM is estimated to affect one in seven pregnancies [79]. Women with a history of GDM are more likely to be obese, have dyslipidaemia and hypertension during the postpartum period [78]. These women also have an approximately seven-fold increased risk of developing type II diabetes mellitus (T2DM) later in life [34]. The diagnostic criteria for GDM have changed as of recent, being defined as fasting glycaemia ≥5.1mmol/L, or 1-h plasma glucose ≥10.0mmol/L and 2-hour plasma glucose: ≥8.5mmol/L with a 75g oral glucose tolerance test [302].

Metabolic syndrome (MetS) is defined as a cluster of metabolic disorders, conventionally defined as three or more of the following: central obesity, reduced high-density lipoprotein cholesterol, hypertriglyceridemia, hyperglycaemia and hypertension. However, the cut-offs for these individual components of MetS are different between definitions [303, 304]. Both GDM and MetS share a similar aetiology and both increase the risk of chronic diseases such as T2DM and cardiovascular disease (CVD) [34, 35, 305, 306].

GDM is promoted by an inability of β-cells to undergo expansion. Therefore, β-cells are unable to compensate for the highly insulin resistant state leading to the subsequent elevation of glucose during pregnancy [214]. Development of pregnancy complications, such as GDM is influenced by pre-pregnancy lifestyle and metabolic characteristics [307]. Women with MetS are already in a state of pro-inflammation and insulin resistance [308], therefore it is possible that when they become pregnant, they are more susceptible to developing GDM [309]. This association has not been explored in a systematic review and meta-analysis. Furthermore, GDM increases the risk of developing cardiovascular disease in later life and approximately 50% of women who develop GDM go on to develop T2DM later in life [212]. Therefore, women who may not have MetS in pregnancy or only present with one or two components of MetS

may be at risk of developing MetS postpartum. A meta-analysis in 2014, showed that women who experience GDM have a higher risk of developing MetS than women with a normal pregnancy [310]. However, the studies included in the above meta-analysis were conducted before the implementation of the new International Association of Diabetes in Pregnancy Study Group (IADPSG) guidelines that recommended a lowering of the glucose threshold for the diagnosis of GDM [80]. As the new guidelines are known to increase the number of women diagnosed with GDM, it is possible that the number of metabolic risk factors in women who had GDM will also increase. Children exposed to GDM *in utero* may also be more susceptible to developing MetS, as it has been shown that they have higher systolic blood pressure (SBP), body mass index (BMI), and blood glucose than those not exposed to GDM *in utero* [207]. To our knowledge, no systematic review has assessed the risk for MetS among children born to pregnancies complicated by GDM. Even small improvements in the components of metabolic syndrome such as hypertension and dyslipidaemia can significantly reduce the risk of ischemic heart disease in young and middle age adults [222, 311, 312] and reducing childhood adiposity can reduce the risk of CVD later in life [313].

Therefore, the objective of our systematic review and meta-analysis was to evaluate the association between GDM and MetS by determining 1) the risk of MetS in pregnancy among women who are diagnosed with GDM, 2) the risk for postpartum MetS among women who experienced GDM, and 3) the risk of developing MetS in children born to pregnancies complicated by GDM

7.4. Methods

The review protocol is registered in PROSPERO (CRD42020173319). The review was undertaken with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [84].

7.4.1. Search strategy

All studies describing the association between GDM and MetS were identified by searching the following electronic databases: PubMed, CINAHL, SCOPUS and EMBASE with an end search date of February 18th 2020. The search was conducted by ZL. The search strategy included the terms ("gestational diabetes*" OR "pregnancy induced diabetes") AND ("metabolic syndrome" OR "insulin resistance syndrome" OR "syndrome X") and is detailed in Appendix S1. We included observational studies (case-control, cross-sectional and cohort). Bibliographies of previously conducted systematic reviews and meta-analyses on closely related topics, and eligible studies were checked for additional studies. All identified studies were independently assessed for relevance by two authors (MP, AA). Two authors (MP, AA) independently extracted data, and discrepancies were resolved by discussion with ZL and PA.

7.4.2. Inclusion criteria

Studies were eligible for inclusion if they reported the number of cases of MetS in 1) pregnant women diagnosed with GDM, 2) women with a history of GDM, compared to women who did not experience/have a history of GDM 3) those exposed to GDM *in utero* compared to those not exposed to GDM *in utero*. We included studies that defined GDM based on the IADPSG guidelines [85]. However, since the diagnostic criteria have been revised recently, we included studies that used prior recommended diagnostic

criteria of GDM including the 1999 World Health Organization (WHO) definition [303], and other regional and study specific definitions as detailed in Table S1 [303, 314-321]. MetS was defined based on the definitions of the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP-III) [304], International Diabetes Federation [322] [323], the WHO [303], or the American Heart Association [324]. Because there is no validated definition of MetS in children and pregnant women, we accepted variations of current guidelines and study-specific definitions. The definitions of GDM and MetS of included studies are detailed in Table S1. Studies that did not include a definition of GDM or MetS, those that did not define the case and control groups, and those that compared women with GDM in pregnancy/postpartum, and those exposed to GDM *in utero* to another risk group were excluded.

7.4.3. Statistical analysis

Data were extracted independently and in duplicate for the number of MetS cases. We analysed all studies collectively as an overall analysis, and subsequently stratified into subgroups based on the time of follow up postpartum as: <1 year, 1-5 years, 5-10 years, and 10+ years from the index pregnancy. Some studies analysed the rate of MetS based on t multiple definitions. Therefore, when assessing data from those studies, the NCEP-ATP-III definition was used in the overall analysis as the majority of studies used this definition. However, we conducted subgroup analyses based on the rate of MetS defined according to the NCEP-ATP-III, IDF, and WHO guidelines. We performed an ad-hoc analysis based on ethnicity, but only for Asian and Caucasian ethnicities, as these were the most commonly reported ethnicities. When the same cohort was assessed multiple times during the postpartum period, the study with the largest sample size was used in the overall analysis. For the analysis on offspring exposed to GDM *in utero*, the

oldest cohort was used in the meta-analysis. We considered studies published in English. We did not need to contact any authors for additional information, as only one dichotomous outcome was evaluated, and only studies reporting on the outcome were eligible.

The following data were collected from each included study: definition of GDM, definition of MetS, time of postpartum follow up (number of years since index pregnancy for both women and children) *or* gestational age (week) at which MetS and GDM were diagnosed during pregnancy, number of cases (those who experienced GDM) and controls (those who did not experience GDM), birthweight of offspring and gestational age at delivery for both cases and controls.

The meta-analysis was performed using RevMan software (Review Manager Version 5.3) based on an inverse variance method. As per protocol, the random-effects model was selected to account for the differences in diagnostic criteria of GDM. For each outcome measure, the number of events and the total number of participants were used in the meta-analysis to analyse the risk difference. If the number was only reported as a percentage, then the number of participants/events was calculated based on the total sample size for each group. The analysis was cross-checked and discrepancies were resolved by discussion (PA, MP).

Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the Chi^2 P value was less than 0.1. Data from eligible studies that could not be included in the meta-analysis are included in Table S2. To assess publication bias, funnel plots were used for the primary outcome. The methodological quality was assessed using the National Heart, Lung and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and are presented in the

supplementary data (Table S3) [325]. Sensitivity analysis was performed to evaluate heterogeneity for outcomes after excluding low-moderate quality studies (i.e. studies that were considered of low-moderate quality in the NHLBI Quality assessment tool after discussion with authors).

7.5. Results

7.5.1. Search results

The literature search identified 588 articles. One hundred and ninety articles were eligible for full text review. Of these, 51 were included in the review and 35 were included in the meta-analyses (Figure 7.5.1.1) (Table 7.5.1.1). The reasons for excluding 139 studies are detailed in Figure 1. The quality assessment showed that all studies were of moderate to high quality (Supplementary Table 7.8.2)

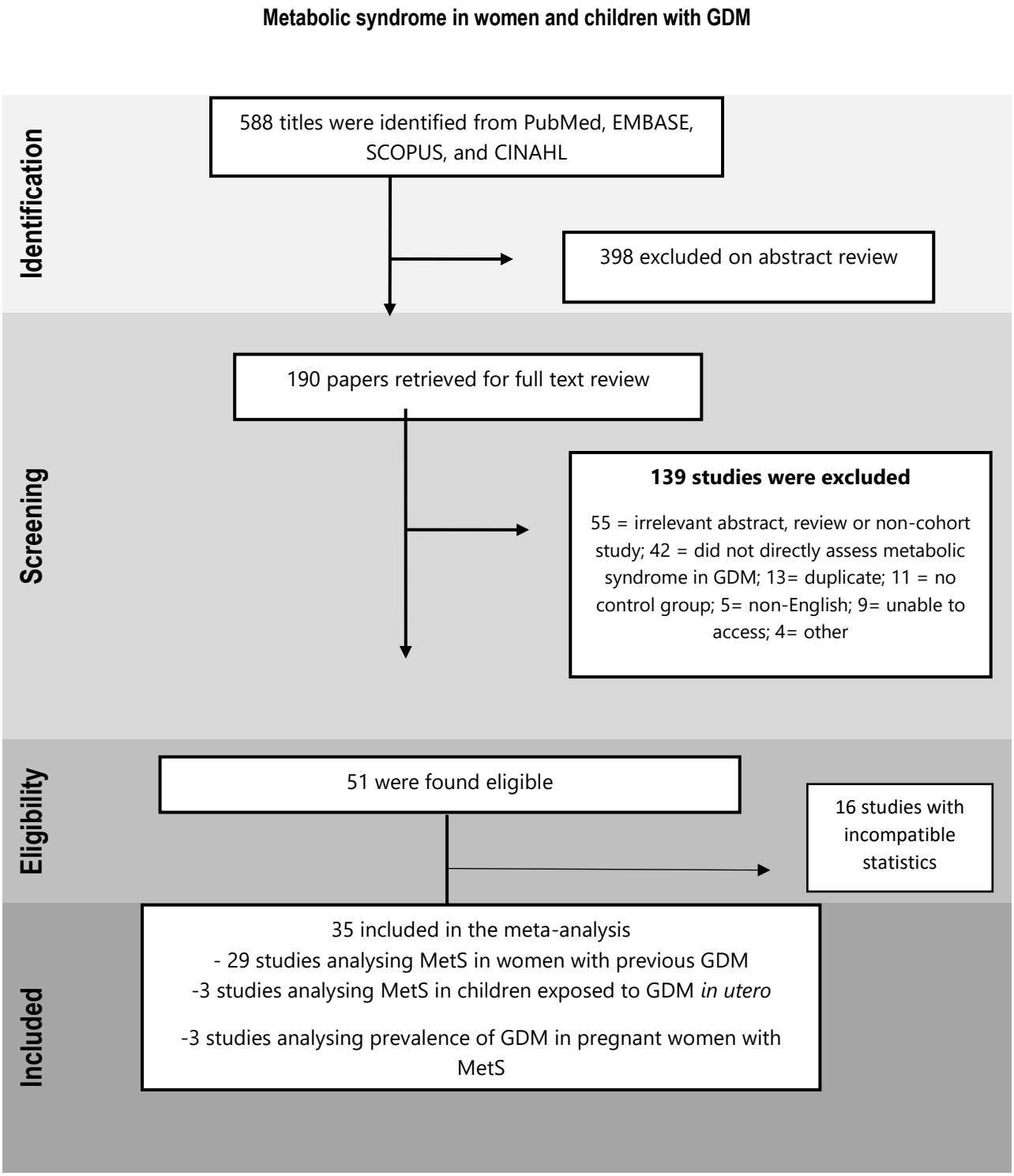


Figure 7.5.1.1 Flow Chart of selected studies for systematic review and meta-analysis of metabolic syndrome in women with a history of gestational diabetes mellitus and their children.

Table 7.5.1-1 Studies included in systematic review and meta-analyses

Study	Study design	Country	Exposed/Definition of GDM (n=)	Definition of MetS	Non exposed (n=)	Birthweight	Time of assessment
Risk of Gestational Diabetes Mellitus in pregnant women with MetS							
Bo 2004	Cross Sectional	Italy	150/ 50g OGTT - positive result followed by 3h OGTT 100g - Carpenter and Coustan	One abnormal value or GDM or hyperinsulinemia (2 SD above the mean for the 100 women with negative OGCTs, used as controls)], plus at least two of the following secondary criteria: arterial blood pressure 140/90; plasma triglycerides 2 SD above the mean of the controls and/or low HDL-cholesterol (<1.0 mmol/l); BMI>30 kg/m2 or waist 2 SD above the mean of the controls.	100	3174 (0.51)/3319 (0.48)	24-28 weeks
Chatzi 2009 †	Abstract - Prospective cohort	Greece	508 pregnant women without GDM diagnosis	NHLBI/AHA criteria	NA	Not reported	24-28 weeks gestation
Dane 2011	Prospective	Turkey	20/ 2 or more high values in 100g OGTT	NCEP-ATP III, WHO	40	Not reported	32-33 weeks
Grieger 2018 †	Prospective	Australia and New Zealand	410/WHO	IDF	681	39.6 ± 2.5 /39.3 ± 2.8 stratified by MetS status	MetS assessed at 15 weeks gestation
Midga 2016 †	Prospective	Poland	124 (MetS)/ Polish Gynecology Society Recommendations	IDF	30	Not reported	11-13 weeks gestation
Negrato 2008** †	Prospective	Brazil	50/ 100g OGTT - Carpenter and Coustan	Any one of the two primary criteria: Impaired glycemic profile and/or impaired OGTT, plus at least two of the following secondary criteria: hypertension (systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg on at least two occasions at least six hours apart); dyslipidaemia (plasma	46	Not reported	24-28 weeks

				triglycerides ≥ 2 SD above the mean of the control group and/or low HDL-C < 39 mg/dl) and obesity (BMI ≥ 30 Kg/m2 and/or waist ≥ 2 SD above the mean of pregnant women in the control group			
Negrato 2009**	Prospective	Brazil	50/ 100g OGTT - Carpenter and Coustain	Same as Negrato 2008	46	Not reported	24-28 weeks
Retnakaran 2019 †	Abstract	Canada	49 (MetS)/Not specified	Not specified	1134 (No MetS)	Not reported	Not specified
Zaman 2018 †	Case control	Iran	260/IADPSG	NCEP-ATP-III	260	Not reported	First visit of pregnancy

Study	**Study design**	**Country**	**Exposed/Definition of GDM (n=)**	**Definition of MetS**	**Non exposed (n=)**	**Birthweight cases/Controls (g)**	**Gestational age cases/controls (weeks)**	**Follow up (years)**
		Risk of MetS in women with previous GDM						
Akinci 2010* †	Prospective	Turkey	165/ 50g 1h OGTT - Carpenter and Coustan	NCE-PATP III and IDF	65	3426(664)/3228(590) stratified by MetS status	Not reported	40.54 months
Akinci 2011*	Prospective	Turkey	195/ 50g 1h OGTT - Carpenter and Coustan	NCE-PATP III and IDF	71	Not reported	Not reported	3 years
Akinci 2011* †	Prospective	Turkey	128/ 50g 1h GCT, then 100g OGTT - Carpenter and Coustan	AHA	67	Not reported	Not reported	3 years
Albareda 2004	Prospective	Spain	262/50-g, 1h GCT	NCEP 2001	66	Not reported	Not reported	5 years
Bo 2006	Prospective	Italy	182/ 50g Oral Glucose Test - positive result followed by 3h OGTT 100g -	NCEP-ATP III	161	Not reported	Not reported	6 years

			Carpenter and Coustan					
Carr 2006	Cross Sectional	USA	332/Self -reported	NCEP-ATP III	662	Not reported	Not reported	29.9 years
Costacou 2008	Prospective	USA	22/American Diabetes Association	NCEP-ATP III	29	Not reported	Not reported	1-2 years
Dehmer 2018 †	Prospective	USA	101/ Self report of GDM validated by medical record	Any of the following three: waist circumference > 88 cm, TG ≥ 150 mg/dl, HDL cholesterol < 50 mg/dl, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg or use of antihypertensive medications, and fasting glucose ≥ 100 mg/dl.	719	Not reported	Not reported	Over a period 25 years from baseline
Derbent 2011	Cross Sectional	Turkey	36/1979 NDDG	NCEP-ATP III	40	Not reported	Not reported	1-5 years
Di Canni 2007	Prospective	Italy	166/ Carpenter and Coustan	NCEP-ATPIII	98	Not reported	Not reported	16 months postpartum
Edalat 2013	Retrospective	Iran	77/ WHO	ATP III	67	Not reported	Not reported	2-3 years
Ferraz 2007 †	Prospective	Brazil	70/WHO	ATP III	108	Not reported	Not reported	6 years
Gunderson 2009^** †	Longitudinal	USA	259 (MetS)/Self report validated by medical records	NCEP-ATP III	1192 (non-cases)	Not reported	Not reported	0-7, 7-10, 10-15, 15-20 years
Gunderson 2010**	Longitudinal	USA	120 (cases of MetS)/Self report validated by medical records	NCEP-ATP III	584 (non-cases)	Not reported	Not reported	0-7, 7-10, 10-15, 15-20 years

Gunderson 2014*	Longitudinal	USA	119/ Self report validated by medical records	NCEP-ATP III	779	Not reported	Not reported	20 years
Hakkarainen 2016*	Cohort	Finland	489/ 2h OGTT (75g glucose after overnight fast) fasting, 1h, 2h capillary plasma glucose 4.8, 11.2 and 9.9 mmol/L	IDF	385	GDM 1 Abnormal OGTT 3637±571 GDM 2 Abnormal OGTT 3671±531/ 3581±571	GDM1 278±10 GDM 2 278±10/ 279±11	<5 years, 5-10 years, 10 years
Hakkarainen 2018*	Cohort	Finland	AGA (376) LGA (68)/ 75g-2h OGTT Fasting, 1h, 2h capillary plasma glucose 4.8, 11.2 and 9.9 mmol/L	IDF	AGA (286), LGA (48)	AGA 3596 ± 406/ 3595 ± 385, LGA 4421 ± 370/4365 ± 424	AGA 279 ± 9/280 ± 11 LGA 278 ± 8/279 ± 11	Mean 7 years
Iljas 2013	Prospective	Finland	61/ At risk women performed 75g OGTT 2h - one or more abnormal values: Fasting, 1h, 2h capillary - 4.8, 10.0, 8.7 mmol/L	NCEP-ATP III	55	Not reported	Not reported	18 years
Kousta 2005	Retrospective	UK	368/WHO	IDF	482	Not reported	Not reported	20 years
Krishnaveni 2007	Prospective	India	35/100g 3h OGTT - Carpenter and Coustan	IDF criteria recommended for South Asian women	489	Not reported	Not reported	5 years
Lauenborg 2005	Prospective	Denmark	481/Danish Criteria	WHO, ATP III, EGIR	100	Not reported	Not reported	9.8 years
Li 2018	Prospective	Singapore	123/1999 WHO	ATP-III	119	Not reported	Not reported	5 years
Madarasz 2009	Prospective	Hungary	68/ WHO	ATP III, WHO, IDF	39	Not reported	Not reported	4 years
Maghbooli 2010	Case Control	Iran	92/ Abnormal 50g OGCT prompting 100g OGTT,	WHO	100	Not reported	Not reported	6-12 weeks

			O'Sullivan and Mahan					
Mai 2014** †	Prospective	China	190/ADA	WHO	80	Not reported	Not reported	2.5 years
Mai 2015**	Prospective	China	453/ADA	WHO	1180	Not reported	Not reported	1.3 years postpartum
Noctor 2014	Prospective	Ireland	265/ 2h 75g OGTT IADPSG (WHO definition before 2010)	NCEP-ATP III	378	Not reported	Not reported	2-3 years
Noujah 2018	Population based prospective	Iran	176/IADPSG	NCEP-ATP-III, IDF	86	Not reported	Not reportd	6-12 weeks
Rukusakul 2016	Case Control	Thailand	56	AHA/NHLBI	51	Not reported	Not reported	3 years
Retnakaran 2010	Prospective	Canada	137/ NDDG	AHA/NHLBI, IDF	259	Not reported	Not reported	3 months postpartum
Roca-Rodriguez 2012	Case control	Spain	41/NDDG	WHO NCEP-ATP III	21	Not reported	Not reported	1 year
Shen 2019	Multi-centre	China	1263/ WHO	NCEP-ATP III, IDF	1263	Not reported	Not reported	3 years
Tam 2007 *	Prospective	Hong Kong	67/WHO	IDF	136	3230 ± 485 3272 ± 429	39.3 ± 2.1 39.5 ± 1.6	8 years
Tam 2012* †	Prospective	Hong Kong	45/WHO	IDF	94	3230 ± 485 3272 ± 429	39.3 ± 2.1 39.5 ± 1.6	15 years postpartum
Wender-Ozegowska 2007	Prospective	Poland	153/Polish Diabetic Society	NCEP-ATP-III	155	Not reported	Not reported	6 years study group 5.1 years control
Wijeyaratne 2006	Prospective	Sri-Lanka	274/ ACOG	IDF	168	Not reported	Not reported	3 years postpartum
Verma 2002	Longitudinal follow-up study	USA	58/Carpenter and Coustan modification of NDDG	NCEP-ATP-III	51	Not reported	Not specified	11 years
Vilmi- Kerala 2015	Hospital based cohort study	Finland	120/ Finnish Criteria	NCEP-ATP-III	120	Not reported	Not reported	2-6 years postpartum
Risk of MetS in those born to women with GDM								
Boney 2005	Observational Cohort	USA	LGA GDM (n=42) AGA GDM (n= 52)/ NDDG	NCEP-ATP III	LGA Control (n=43) AGA Control (n=42)	(LGA) 4107 (386)*† /4132 (285)*, (AGA)	Not reported	6, 7, 9, 11 years postpartum

						3316 (310)† 3370 (282)		
Clausen 2009	Cohort	Denmark	168/ At risk women performed 3h 50g OGTT. Two consecutive fasting blood glucose values of at least 4.1mmol/L tested	IDF 2006	141	3410 (530)/3492 (497)	273 (247–284)b,c 281 (254–302)	20 years postpartum
Maslova 2019 †	Prospective	Norway	608/ ICD classification and self-reported	MetS z score based on BMI, waist circumference, fasting blood glucose, insulin, triglycerides, HDL, systolic blood pressure	626	Not reported	Not reported	9-16 years
Vaarasmaki 2009	Population-Based	Finland	95/75g OGTT – one or more values: Fasting, 1h, 2h: 5.5, 11.0, 8.0mmol/L	IDF	3,909	Not reported	Not reported	16 years postpartum

*- studies are part of same cohort
** - studies report the same data, only one is included in meta-analysis
† - results included in the non-meta-analysis table (Supplementary Table 1)
OGTT – Oral Glucose Tolerance Test
GCT – Glucose Challenge Test
IADPSG – International Association of Diabetes in Pregnancy Study group
NDDG – National Diabetes Data Group
WHO – World Health Organization
LGA – large for gestational age **AGA –** average for gestational age
ICD - International Statistical Classification of Diseases and Related Health Problems
AHA/NHLBI – American Heart Association/National Heart Lung Blood Institute

ACOG – American College of Obstetrics and Gynaecology
NCEP-ATP-III - National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III
IDF – International Diabetes Federation

7.5.2. Risk of MetS during pregnancy in women with GDM

Eight studies were included in the assessment of this outcome [309, 326-332], of which three studies were included in the meta-analysis [326-328]. All three studies assessed GDM and MetS at the same time (i.e. approximately 24-32 weeks gestation). Pooled analysis showed that women diagnosed with GDM had an increased risk of MetS in pregnancy (RR 20.51, 95% CI 5.04 to 83.55; three studies, 406 participants; heterogeneity: Chi^2 P=0.96; I^2=0%) (Figure 7.5.2.1). Five studies were not included in the meta-analysis [309, 329-332], with four showing an increased risk of developing GDM in women who are diagnosed with MetS during pregnancy [330, 331, 333, 334] (Supplementary Table 7.8.1).

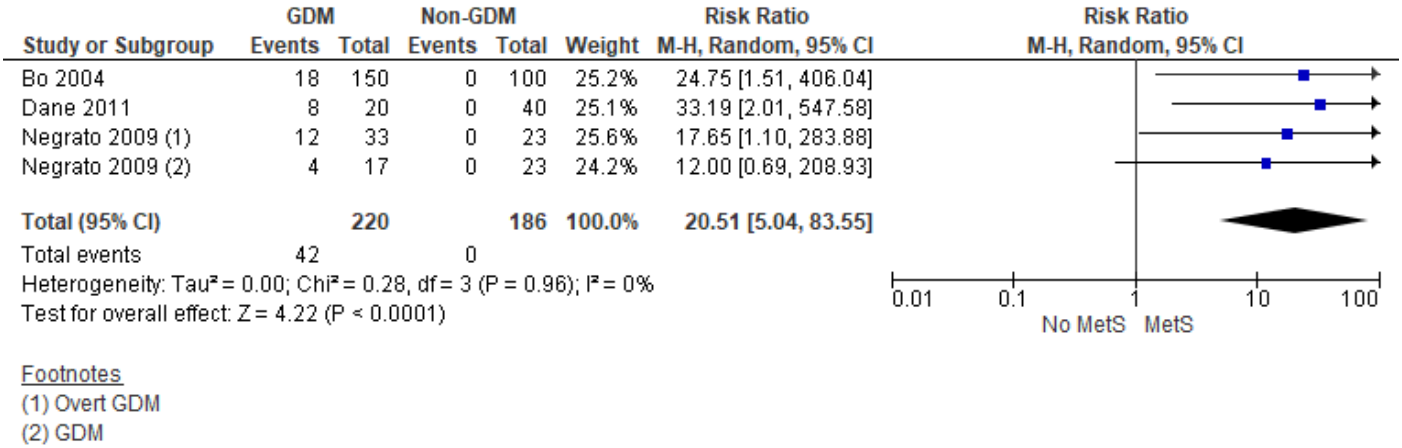


Figure 7.5.2.1 Meta-analysis showing the risk of developing MetS during pregnancy in women with GDM

7.5.3. Risk of MetS in women with a history of GDM

Thirty-five studies were included in the assessment of this outcome [97, 118, 135, 322, 333, 335-365], of which 29 studies were included in the meta-analysis [97, 118, 135, 320, 322, 333, 335-358]. Pooled analysis showed that women with a history of GDM had a significantly increased risk of developing MetS (RR 2.36, 95% CI 1.77 to 3.14; 29 studies, 13,390 participants; heterogeneity: Chi^2 P <0.00001; I^2=93%)(Figure 7.5.3.1). Of the six studies that were not included in the meta-analysis [359-365], one showed an increase in prevalence of MetS among women with a history of GDM compared to controls [341](Supplementary Table 7.8.1). Sensitivity analysis after excluding the studies of moderate quality resulted in a slight reduction in heterogeneity (Chi^2 P <0.00001; I^2=78%) (Supplementary Figure 7.8.1). Assessment of the funnel plot of the meta-analysis revealed moderate publication bias (Supplementary Figure 7.8.2).

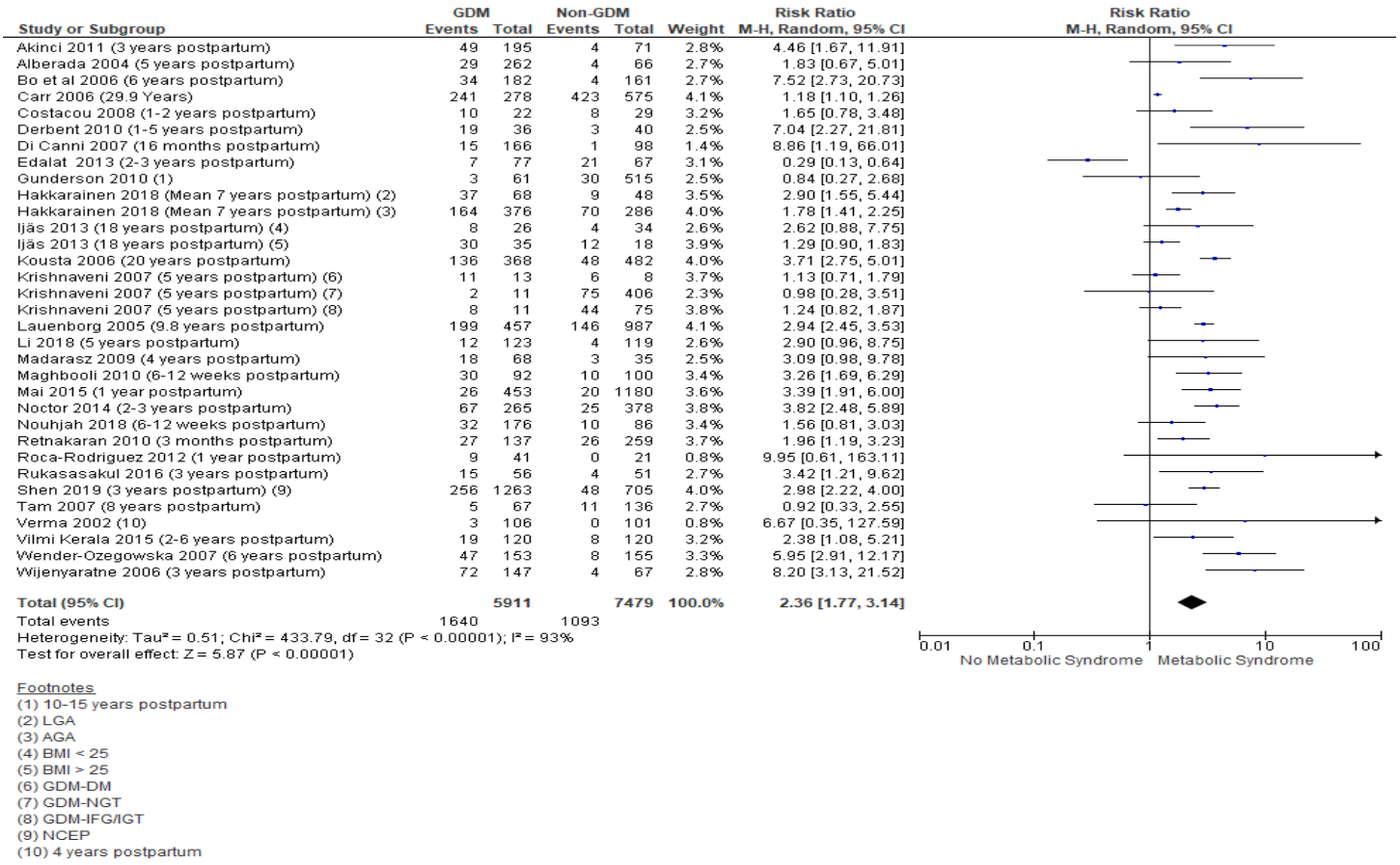


Figure 7.5.3.1 Meta-analysis showing the risk of developing metabolic syndrome in women with previous GDM

7.5.4. Risk of MetS in children exposed to GDM *in utero*

Four studies were included in the assessment of this outcome [366-369], of which three studies were included in the meta-analysis [366-368]. Pooled analysis showed that offspring exposed to GDM *in utero* had a significantly increased risk of developing MetS (RR 2.07, 95% CI 1.26 to 3.42; three studies, 4,421 participants; heterogeneity: Chi^2 P 0.33; I^2=12%) (Figure 7.5.4.1). The study that was not included in the meta-analysis showed an increased MetS severity Z-score in those exposed to GDM *in utero* compared to controls [369]. (Supplementary Table 7.8.1).

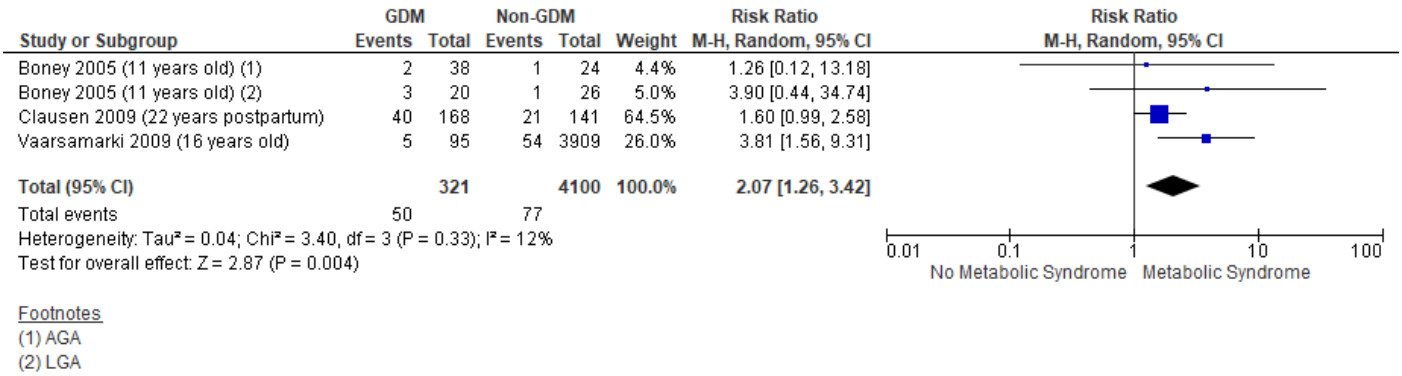


Figure 7.5.4.1 Meta-analysis showing the risk of developing GDM in those born to women with GDM

7.5.5. Subgroup analyses

We conducted subgroup analyses based on the time of postpartum follow up among women with a history of GDM. The results are shown in Table 7.5.5.1. The risk of developing MetS was significantly increased in women with a history of GDM at <1 year postpartum (RR 1.95, 95% CI 1.15 to 3.28, three studies, 850 participants; heterogeneity Chi^2 P=0.09 I^2=59%), 1-5 years postpartum (RR 2.99, 95% CI 2.14 to 4.18, eighteen studies, 7.328 participants; heterogeneity Chi^2 P <0.00001 I^2 = 70%), 5-10 years postpartum (RR 2.29, 95% CI 1.62 to 3.25, nine studies, 4,518 participants; heterogeneity Chi^2 P< 0.0001 I^2=79%), and >10 years postpartum (RR 2.07 95% CI 1.22 to 3.50, six studies, 3,037 participants; heterogeneity Chi^2 P<0.00001 I^2=94%).

Table 7.5.5-1 Subgroup analysis for metabolic syndrome in women with previous GDM stratified by time of MetS assessment.

Time of MetS assessment	RISK DIFFERENCE (RR M-H, 95% CI)	(N=) Studies	(N=) GDM	(N=) TOTAL	HETEROGENEITY
<1 YEAR	1.95 (1.15-3.28)	3	405	850	P= 0.09 I^2 = 59%
1-5 YEARS	2.99 (2.14-4.18)	18	3,716	7,328	P<0.00001 I^2 = 70%
5-10 YEARS	2.29 (1.62-3.25)	9	1,595	4,518	P<0.00001 I^2 = 79%
10+ YEARS	2.07 (1.22-3.50)	6	966	3,037	P<0.00001 I^2 = 94%

We conducted a subgroup analysis to evaluate the risk of developing MetS in women with a history of GDM based on the three most common definitions of MetS (i.e. NCEP-ATP-III, IDF, and WHO). A significantly increased risk of MetS was demonstrated for women with a history of GDM compared to women without a history of GDM, irrespective of the definition used to diagnose MetS (NCEP-ATP-

III: RR 2.58 95% CI 1.72 to 3.87, 20 studies, 8,768 participants; heterogeneity Chi^2 P <0.00001 I^2=94%; IDF: RR 2.15 95% CI 1.60 to 2.90, 11 studies, 5,615 participants; heterogeneity Chi^2 P <0.00001 I^2=79%; WHO: RR 2.99 95% CI 2.51 to 3.57, 5 studies, 3,433 participants; heterogeneity Chi^2 P=0.69 I^2 =0%) (Table 7.5.5.2).

Table 7.5.5-2 Subgroup analysis for metabolic syndrome in women with previous GDM stratified by MetS definition.

Definition of MetS	RISK DIFFERENCE (RR M-H, 95% CI)	(N=) Studies	(N=) GDM	(N=) TOTAL	HETEROGENEITY
NCEP-ATP-III	2.58 (1.72-3.87)	20	4,145	8,768	P<0.00001 I^2 = 94%
IDF	2.15 (1.60-2.90)	11	2,922	5,615	P<0.00001 I^2 = 79%
WHO	2.99 (2.51-3.57)	5	1,107	3,433	P=0.69 I^2 = 0%

We performed ad-hoc analysis based on ethnicity (Asian and Caucasian) and found that there was a similar increased risk of MetS for women with a history of GDM for both ethnicities. (Table 7.5.5.3).

Table 7.5.5-3 Ad-hoc analysis for metabolic syndrome in women with previous GDM stratified by ethnicity.

Ethnicity	RISK DIFFERENCE (RR M-H, 95% CI)	(N=) Studies	(N=) GDM	(N=) TOTAL	HETEROGENEITY
Asian	2.15 (1.32-3.51)	7	2,144	4,891	P<0.0001 I^2 =81%
Caucasian	2.72 (2.04-3.63)	11	2,232	4,549	P<0.0001 I^2 = 70%

7.6. **Discussion**

Our meta-analysis revealed that women with a history of GDM are at a significantly increased risk of developing MetS later in life, and that this risk is seen as early as <1 year postpartum. Our results also demonstrate that the risk for MetS in pregnancy is higher among women diagnosed with GDM and that children born to women who experience GDM have an increased risk of developing metabolic syndrome in later life.

This systematic review and meta-analysis was a comprehensive review of the literature on the association between gestational diabetes mellitus and metabolic syndrome, among women and their offspring. There has not been a systematic review and meta-analysis that investigated the association between GDM and MetS in pregnant women and offspring, and no review has evaluated the association between GDM and MetS in women with a history of GDM after the change of guidelines in 2013[310].

Many environmental and genetic factors contribute to the risk for GDM. There are certain candidate genes that are associated with T2DM and GDM, that mainly influence insulin secretion [216]. Obesity and GDM share the same causal pathway, through elevation of free fatty acids and dysregulation of cytokines to promote insulin resistance [7, 370]. Common risk factors such as advanced maternal age, familial history of T2DM or GDM in a first-degree relative (either mother or sister) also contribute to a higher risk for GDM [371]. Therefore, it is unclear whether MetS in overweight/obese women with a history of GDM is due to the disease phenotype, or due to a pre-existing predisposition. Asian ethnicity is a significant risk factor for GDM [371] and diagnosis of MetS can also vary based on ethnicity. Therefore, we assessed the influence of ethnicity through an ad-hoc analysis and found that both Caucasian and Asian ethnicities conferred similar increased risks for MetS in women with a history of GDM. Women and men have different CVD risks, particularly with regard to obesity, as men generally have greater muscle mass and women have higher fat mass. Research into a modified

female definition of metabolic syndrome may be important, considering the differences in body composition and conventional risk factors between males and females and the higher risk of CVD among women who experience major pregnancy complications [372].

Our results on the risk for MetS among women with a history of GDM showed substantial heterogeneity However, when we performed subgroup analyses based on the time of diagnosis of MetS, definition of MetS and ethnicity, heterogeneity was substantially reduced. Sensitivity analysis also showed a reduction in heterogeneity after removing studies of moderate quality. Funnel plot assessment revealed a moderate degree of publication bias. It is difficult to elucidate the reason for heterogeneity in aggregate data, but it is typically due to differences in study design, differences in definitions (i.e. MetS and GDM definitions), years of postpartum follow-up and study populations. The heterogeneity that was observed in our analysis could also be attributed to genetic and environmental factors . Large, well characterised longitudinal cohort studies will contribute to further evidence and help reduce overall heterogeneity.

Our meta-analysis revealed that women with a history of GDM are at significantly increased risk for developing MetS later in life (RR 2.48). Women who experience GDM have a reduction in insulin sensitivity in the third trimester, to support an increase in glucose transfer to the fetus. This is promoted by an increase in fetal and placental factors [7, 373]. However, if women are insulin resistant prior to pregnancy and fail to increase β-cell capacity during pregnancy, maternal glucose levels are unlikely to return to normal after pregnancy [374]. Considering the increased risk for cardiovascular risk factors and T2DM in women with a history of GDM [34, 307], it is not surprising that these women are at a higher risk for developing MetS later in life. Intervention trials to reduce the development of T2DM are known to be successful during the early period after pregnancy, but compliance in exercise and weight loss are shown to decrease over time [219, 375, 376]. This is likely due to the difficulty in changing behavioural patterns and individual circumstances. It may be more beneficial to intervene

before a diagnosis of GDM, as both diet and physical activity changes have been shown to result in an 18% reduction in the risk for GDM among women with a pre-pregnancy BMI <25kgm^2 as well as ≥ 25kgm^2; and this intervention was shown to be most effective before 15 weeks' gestation [377]. The prevalence of obesity in women of reproductive age is around 15-18% in Australian women [378]. Therefore, it is necessary to identify women who are at increased risk of developing GDM and implement interventions as soon as practical (either during pre-conception planning or in early pregnancy) with the aim of reducing the risk of development of GDM. This is especially important, as our results showed that women who experience GDM are at increased risk of being diagnosed with MetS, as early as <1 year postpartum.

Our study also demonstrated that offspring exposed to GDM *in utero* have a two-fold increased risk of developing MetS. GDM promotes a hyperinsulinemic environment to allow increased nutrient delivery to the fetus, thereby increasing fetal growth and body mass resulting in macrosomia which may persist as obesity throughout childhood and adolescence [373]. This idea pertains to "The Barker Hypothesis" which states that adverse nutrition in early life increases the likelihood of developing metabolic risk factors [379]. We have recently shown in a meta-analysis that those exposed to GDM *in utero* have higher SBP, BMI z-score, and blood glucose compared to those not exposed to GDM *in utero* [207]. Previous studies have also shown that juvenile T2DM is significantly associated with exposure to GDM *in utero* [380, 381], therefore highlighting the need for weight management and lifestyle guidance throughout childhood and adolescence for this group. It is important to note that there were only four eligible studies for the meta-analysis on offspring of pregnancies complicated by GDM. We believe this is influenced by the lack of consensus on a definition of MetS in childhood. An IDF recommended definition for the diagnosis of MetS in children older than six years of age does exist, but this definition is not universally used [382]. Furthermore, obesity as measured by BMI is not an accurate measure, as BMI varies greatly based on the muscle mass and fat mass, hence it is accurate for fatter children but not for those who are lean. BMI z-score is a more

appropriate measure as it adjusts for age and gender[286]. Only one study assessed the metabolic syndrome z-score, which adjusts for age and gender[369]. Considering the increasing rate of childhood obesity, a clear definition of MetS is required that can accurately account for childhood adiposity and adjust for important factors such as age, gender, weight distribution, and puberty.

We also observed that the risk for MetS in pregnancy was increased among women who were diagnosed with GDM compared to normoglycaemic women (RR 20.51). There are studies that have investigated the association between individual components of MetS including dyslipidaemia and obesity and the risk of developing GDM [383-385]. Gunderson *et al.*. (2010) showed that BMI and waist circumference were associated with increased risks for GDM after adjusting for lipids, fasting glucose and insulin [385]. Studies by Grieger and Chatzi showed a 3-fold increased risk of GDM for women diagnosed with MetS in early pregnancy [309, 330]. It is difficult to diagnose metabolic syndrome in pregnancy due to hemodynamic and inflammatory changes that occur during the first trimester of pregnancy, as SBP and maternal lipids decrease during this time [334, 386] Furthermore, placental and maternal hormones during pregnancy promote weight gain and also result in altered fat distribution in both healthy pregnancies and those complicated by GDM[387]. Therefore, these results signify a need for further research in large pregnancy cohorts.

7.7. **Conclusion**

Pregnant women with GDM are at a higher risk of developing MetS during pregnancy. Furthermore, women who experience GDM have an increased risk of developing MetS later in life. They may develop MetS as early as <1 year postpartum. Children born to pregnancies complicated by GDM are also at increased risk of developing MetS in later life. This review signifies the importance of considering GDM in CVD risk stratification, thus allowing an opportunity for primordial prevention. Based on our findings,, pre-conceptional management

of cardio-metabolic risk factors may be useful to reduce the risk of both GDM and MetS. Furthermore, it will be beneficial to screen women who experience GDM and children born to pregnancies complicated by GDM to detect modifiable CVD risk factors

7.8. Supplementary Data

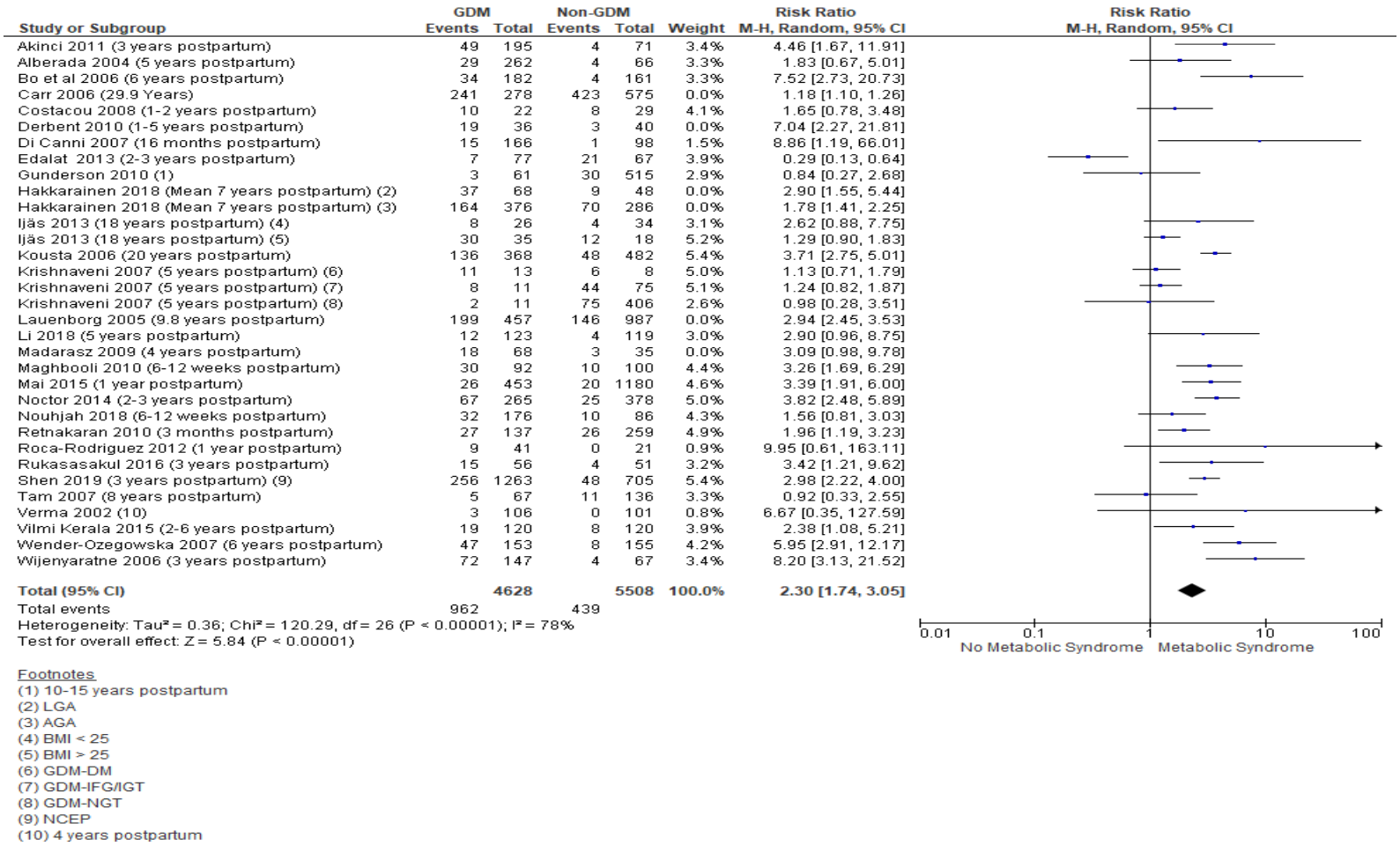
Supplementary Table 7.8 1 Studies not included in meta-analysis

Study	Case	Control	Significance
MetS and risk of GDM			
Chatzi 2009 (abstract) (GDM risk in MetS women) [388]	Risk of GDM in MetS women – RR: 3.17, (95% CI: 1.06, 9.50)	-	-
Migda 2016 (Rate of GDM in MetS participants) [331]	12/124 with MetS (9.6%)	0/30 without MetS	**0.019**
Grieger 2018 (MetS assessed at 15 weeks, GDM assessed at 24-28 weeks) [309]	50/410 Risk for GDM in women with MetS (RR 3.71 (95% 2.42 to 5.67)	314/681	-
Zaman (MetS assessed at first pregnancy visit, GDM assessed at 24-32 weeks) [329]	44/260 aOR: 2.34 (95% CI 1.03 to 5.30) p = 0.04	18/260	<**0.001**
Retnakaran 2019 (abstract) (Rate of GDM in MetS participants) [332]	2.0% (MetS n=49)	2.1% (No MetS n=1134)	0.99
MetS in women with GDM postpartum			
Akinci 2010 (Rate of GDM in MetS participants) [359]	6/43 GDM with MetS	11/121 GDM without MetS	0.389
Akinci 2011 [360]	43 (33.59%)	0	-
Dehmer 2018 (Metabolic Syndrome in GDM participants (HR 95%) [361]	Yes: 1.55 (0.55-4.35)	No: 2.50 (1.15-5.43)	0.5
Ferraz 2007 (Mean SD) [362]	1.71 (0.12)	1.50 (0.11)	0.1747
Gunderson 2009 (Rate of GDM in MetS participants) [363]	24/ 259 (9.3%)	64/1192 (5.4%)	**.02**
Mai 2014 [364]	38/ 190 (20%)	0/80	-
Tam 2012 [365]	10/45 (22.2%)	14/94 (14.9%)	0.41
Verma 2002 [355]	5 years postpartum: 3/88 (4.8%) 6 years postpartum: 8/87 (11.6%) 9 years postpartum: 8/57 (14.6%)	5 years postpartum: 1/79 (1.8%) 6 years postpartum:1/79 (1.8%) 9 years postpartum: 2/50 (4.1%)	0.11 **0.03** **0.007**
MetS in offspring exposed to GDM *in utero*			
Maslova 2018 (Mets z-score) [369]	1.3 (7.7)	-0.7 (3.7)	-

Supplementary Table 7.8 2 Quality assessment of included studies using the National Institute of Health Quality Assessment for cohort and case-control studies

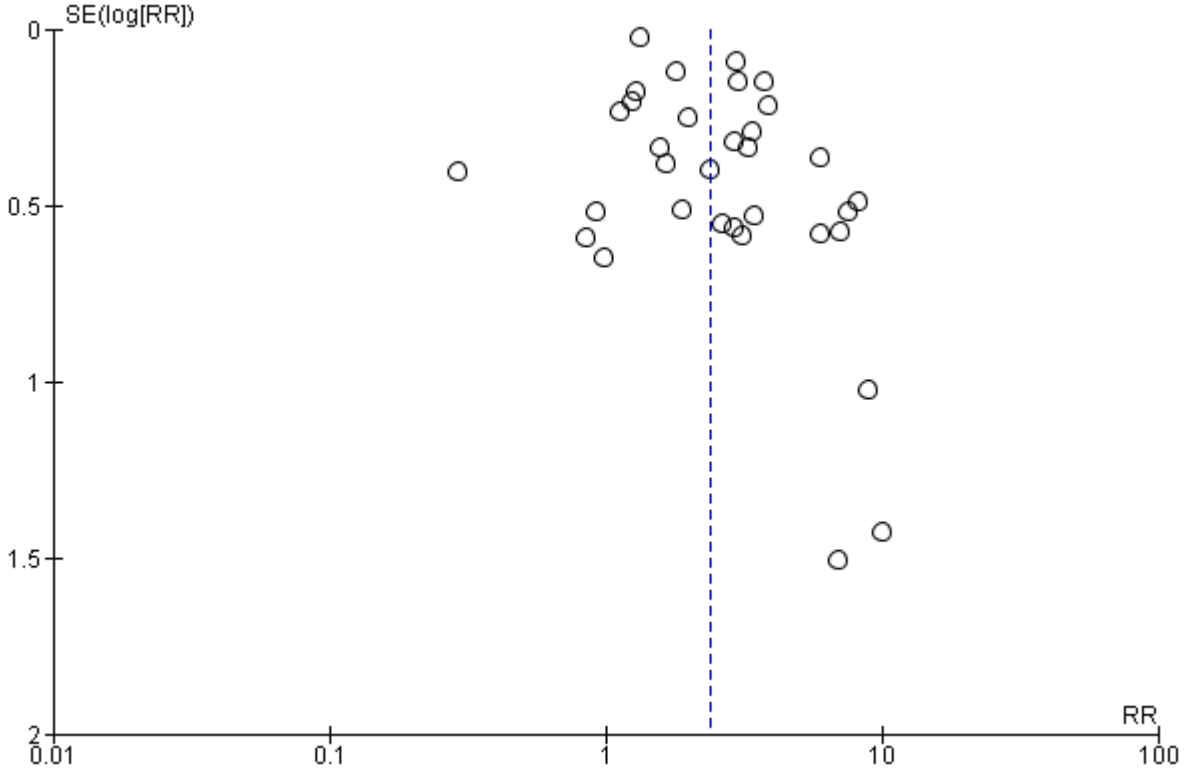
Quality assessment	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	TOTAL
Akinci 2010* [359]	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	✓	✗	NR	✗	9
Akinci 2011* [335]	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	✓	✗	NR	✓	10
Akinci 2011* [360]	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	✓	✗	NR	✓	10
Albareda 2004 [336]	✓	✓	✗	✓	✓	✓	✓	NA	✓	NA	✓	✗	NR	✓	9
Bo *et al.* 2004 [326]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✓	✓	✗	9
Bo *et al.*. 2006 [338]	✓	✓	✓	✓	✗	✓	✓	NA	✓	✓	✓	✓	✓	✓	12
Boney 2005 [366]	✓	✓	✓	✗	✓	✓	✓	NA	✓	NA	✓	✗	✗	✓	9
Carr 2006 [97]	✓	✓	✓	✗	✓	✗	✗	NA	✓	NA	✓	✗	NR	✓	7
Clausen 2009 [367]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✗	✓	9
Costacou 2008 [333]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✗	✓	9
Dane 2011 [327]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✗	NR	✗	7
Dehmer 2018 [361]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✗	✓	✓	9
Derbent 2010 [339]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✗	NR	✓	8
Di Canni 2007 [340]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Edalat 2013 [337]	✓	✓	✗	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	9
Ferraz 2007 [362]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Grieger 2018 [309]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✗	NA	✓	8
Gunderson 2010* [341]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✗	✓	✓	9
Gunderson 2014* [389]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✗	✓	✓	9
Hakkarainen 2016* [390]	✓	✓	✗	✓	✗	✓	✓	NA	✓	NA	✓	✗	✗	✓	8
Hakkarainen 2018* [342]	✓	✓	✗	✓	✗	✓	✓	NA	✓	NA	✓	✗	✗	✓	8
Iljas 2013 [343]	✓	✓	✗	✓	✗	✓	✓	✓	✓	NA	✓	✗	✗	✓	9
Kousta 2005 [344]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Krishnaveni 2007 [345]	✓	✓	✗	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Lauenborg 2005 [135]	✓	✗	✓	✗	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	8

Li 2018 [346]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Madarasz 2009 [347]	✓	✗	✗	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	8
Maghbooli 2010 [322]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Mai 2014* [364]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Mai 2015* [348]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Maslova 2019 [369]	✓	✓	✗	✗	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	8
Midga 2016 [331]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✗	9
Negrato 2008** [391]	✓	✓	✓	✓	✗	✗	✓	NA	✓	NA	✓	✗	NR	✗	7
Negrato 2009** [328]	✓	✓	✓	✓	✓	✗	✓	NA	✓	NA	✓	✗	✓	✗	8
Noctor 2014* [349]	✓	✓	✗	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	9
Noujah 2018 [118]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Retnakaran 2010 [350]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Roca-Rodriguez 2012 [351]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Shen 2019 [353]	✓	✓	✗	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	9
Tam 2007 * [354]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Tam 2012* [365]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Vaarasmaki 2009 [368]	✓	✓	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	10
Vilmi Kerala 2015 [356]	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	✓	✗	✓	✓	11
Verma 2002 [355]	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓	✓	✗	✗	✓	11
Wender-Ozegowska 2007 [392]	✓	✗	✓	✓	✗	✓	✓	NA	✓	NA	✓	✗	✓	✓	9
Wijeyaratne 2006 [358]	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	✓	✗	✓	✓	11
Zaman 2018 [329]	✓	✓	✓	✓	✗	✗	✗	NA	✓	NA	✓	✗	✓	✓	8



Footnotes
(1) 10-15 years postpartum
(2) LGA
(3) AGA
(4) BMI < 25
(5) BMI > 25
(6) GDM-DM
(7) GDM-IFG/IGT
(8) GDM-NGT
(9) NCEP
(10) 4 years postpartum

Supplementary Figure 7.8 1 Sensitivity analysis of MetS after a GDM pregnancy omitting moderate quality studies



Supplementary Figure 7.8 2 Funnel plot analysis

Chapter 8

8. Protective influence of breastfeeding on cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: A systematic review and meta-analysis

Maleesa M Pathirana, Anna Ali , Zohra S Lassi , Margaret A Arstall, Claire T Roberts,

Prabha H Andraweera

8.1. Statement of Authorship

Title of Paper	Protective influence of breastfeeding on cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: A systematic review and meta-analysis
Publication Status	Published – 2021
Publication Details	**Pathirana MM,** Ali A, Lassi ZS, Arstall M, Roberts CT, Andraweera PH. Influence of Breastfeeding on Cardiovascular Risk Factors in Women With Previous Gestational Diabetes Mellitus and Their Children: A Systematic Review and Meta-Analysis. J Hum Lact. 2021 Oct

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Acquiring data, knowledge, analysis, drafting
Overall Percentage (%)	70%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Anna Ali	
Contribution to the Paper	Acquiring data, analysis	
Signature		**Date 14/02/2022**

Name of Co-Author	Zohra S Lassi	
Contribution to the Paper	Conceptualisation, acquiring data, analysis, drafting	
Signature		**Date 14 Feb 2022**

Name of Co-Author	Margaret Arstall	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Name of Co-Author	Claire Roberts	
Contribution to the Paper	Conception, knowledge, drafting	
Signature		**Date 28/02/2022**

Name of Co-Author	Prabha Andraweera	
Contribution to the Paper	Conception, acquiring data, knowledge, drafting	
Signature		**Date 28/02/2022**

8.2. Abstract

Background: There is evidence that breastfeeding may provide protection against cardiovascular risk factors in mothers with a history of gestational diabetes mellitus and their children who were exposed *in utero*. We aimed to perform a systematic review and meta-analysis of observational studies to ascertain the effects of breastfeeding on cardiovascular risk factors in women with previous gestational diabetes mellitus and their children exposed *in utero*.

Methods: Studies assessing conventional cardiovascular risk factors in women with previous gestational diabetes mellitus and children exposed *in utero* stratified by breastfeeding/no breastfeeding or breastfed/not breastfed were included. Gestational diabetes mellitus was defined based on the International Association of Diabetes in Pregnancy Study Group definition or previous accepted definitions. Breastfeeding was defined as reported in each study.

Results: The literature search yielded 260 titles, of which 17 studies were selected to be in the review. Women with previous gestational diabetes mellitus who did not breastfeed had higher blood glucose (*SMD:* 0.32, 95% CI 0.12, 0.53) and a greater risk of developing type 2 diabetes mellitus (*RR:* 2.08 *95% CI* 1.44 to 3.00) compared to women with no history. There were not enough studies to conduct a meta-analysis on the effects of breastfeeding on risk factors for cardiovascular disease among children exposed to gestational diabetes mellitus *in utero*.

Conclusion: Breastfeeding appears to be protective against cardiovascular risk factors among women who experience gestational diabetes mellitus.

8.3. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is initially diagnosed during pregnancy and affects one in seven pregnancies globally [393]. Women with previous GDM have an approximately seven-fold increased risk of developing type II diabetes mellitus (T2DM) later in life [34]. Furthermore, women with previous GDM are more likely to be hypertensive, obese, and have dyslipidaemia postpartum[300]. These metabolic and vascular morbidities promote the development of metabolic syndrome, which is a significant global concern and important risk factor for CVD [394]. It has been reported in a previous systematic review and meta-analysis, that women with a history of GDM are at a higher risk of developing metabolic syndrome later in life [395]. Furthermore, women with a GDM history have a 2-fold- increased risk of developing cardiovascular disease (CVD), irrespective of disease progression to T2DM [396]. It has also been reported that children exposed to GDM *in utero* also exhibit higher systolic blood pressure, obesity, and higher blood glucose throughout life compared to children born to non-GDM pregnancies; thereby significantly increasing their risk of T2DM and CVD at an earlier age [207]. Therefore, preventative strategies are necessary to reduce CVD risk in both mothers and children exposed to GDM.

Human milk is "the gold standard for infant feeding", with lactation being mutually beneficial for both mother and child [397]. Breastfeeding over 12 months promotes a significant reduction in both chronic hypertension and T2DM in women [59]. Furthermore, children who are breastfed are less likely to develop obesity and T2DM compared to those who are not breastfed [60]. Breastfeeding for 6 months exclusively, and for up to 2 years as complementary to other nutritional sources is encouraged in women [397]. Two reviews have assessed breastfeeding and metabolic risk factor reduction in women with previous GDM [398, 399] but these studies have not reported on all conventional cardiovascular risk factors, such as blood pressure and lipids. Having a comprehensive assessment of the effects of breastfeeding on all major cardiovascular risk factors can aid treatment strategies and disease mitigation. These reviews also did not assess the effects of breast-feeding on all major CVD risk factors in children exposed to GDM *in utero*. Therefore, our aim was to perform a systematic review and meta-analysis to determine the effects of breastfeeding on cardiovascular risk factors in women with previous GDM and their exposed children.

8.4. Methods

8.4.1. Search strategy

We undertook a systematic review of the literature and meta-analysis of observational studies in order to assess the effects of breastfeeding on cardiovascular risk factors in mothers with previous GDM and children exposed to GDM *in utero*. The review was undertaken with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [84]. The protocol of this review is registered in PROSPERO (CRD42020190529)

Studies eligible for the meta-analyses included women who had a history of GDM/those exposed to GDM *in utero*, the intervention assessed was breastfeeding/being breastfed compared to not breastfeeding/not being breastfed, and the outcomes of interest were conventional cardiovascular risk factors. Observational studies (i.e. cross-sectional, case-control and cohort) were included. Studies that did not include a definition of GDM, those that did not define the breastfeeding and non-breastfeeding groups or did not include participants with GDM, were excluded. We assessed the following in our review (1) CVD risk factors in women with previous GDM who breastfed compared to women with previous GDM who did not breastfeed (2) CVD risk factors in those exposed to GDM *in utero* who were breastfed compared to those exposed to GDM *in utero* who were not breastfed. We included studies of CVD risk assessment at any point in the postpartum period. Key search terms included (gestational diabetes OR pregnancy-induced diabetes) AND (breast feeding OR breastfeeding OR breastmilk OR human milk OR lactat*) AND (formula fed OR infant formula) AND (blood pressure OR hypertension OR cholesterol OR lipids OR body mass index OR glucose OR diabetes OR metabolic syndrome).

As different definitions of breastfeeding were used among studies, breastfeeding was considered as exposure to human milk (either exclusive or mostly breastfed), as defined in the study or feeding at hospital discharge, and not breastfeeding was considered as feeding predominantly or exclusively using other sources (i.e. formula, animal milk, solids and other

liquids) that were not human milk, as well as those reporting on "not breastfeeding at hospital discharge". The definitions of breastfeeding that were reported in the studies are specified in Table 1. GDM is currently defined based on the International Association of Diabetes in Pregnancy Study Group (IADPSG) guidelines[400]. However, since GDM diagnosis has been revised recently, we included studies defining GDM based on prior recommended diagnostic criteria such as the 1999 World Health Organization (WHO) definition [303], and other regional and study specific definitions. All GDM definitions reported for each study are detailed in table 1. The literature search generated 260 titles, of which 233 were identified through electronic search and 27 were found through bibliographic search of similar reviews [398, 399]. Of these, 39 papers were assessed in full text and 18 were found to be eligible. Figure 1 describes the reasons for excluding studies. Overall, nine studies were included in the meta-analysis. The 10 studies that were not included in the meta-analysis are reported in Table 8.4.4.1.

8.4.2. Inclusion criteria

All studies describing the effects of breastfeeding on conventional CVD risk factors in women with previous GDM and those exposed to GDM *in utero* were identified by searching electronic databases PubMed Medical Subject Headings [401], CINAHL, and EMBASE, including all studies up until May 26th 2020. MP conducted the search. The complete search strategy is included in Appendix 1. Bibliographic search of previous observational studies, and systematic reviews and meta-analyses on similar topics were cross-checked for additional studies. All identified studies were independently assessed for relevance by two authors (MP, AA). Data was independently extracted by two authors (MP, AA) and discrepancies were resolved by discussion with ZL and PA.

For each study, the following data were extracted: author's last name, study year, country, study design, definition of GDM, assessment of breastfeeding (i.e. how breastfeeding was assessed and how breastfeeding and not breastfeeding were defined), number of women

breastfeeding/non-breastfeeding or children who were breastfed/not breastfed, years of postpartum follow-up/age at assessment, outcome measures, and significant findings.

Data extraction was completed independently and in duplicate for the following cardiovascular outcomes: systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI), serum lipid levels (low density lipoprotein (LDL) high density lipoprotein (HDL), total cholesterol, and triglycerides), blood glucose, fasting insulin and incidence of T2DM. If the same cohort was assessed in different studies, the meta-analysis would include the study with the largest sample size. The oldest cohort was used for the analysis of children born to pregnancies complicated by GDM. We considered studies published in English. Authors of studies were contacted for data clarification (i.e. any missing data) and additional data, when required. If missing or unclear data could be not clarified, these studies were included in the review and reported in Table 1 but not the meta-analysis.

The National Heart, Lung and Blood Institute [402] Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to assess the methodological quality of each study[402]. Studies were assessed for internal validity and study quality was decided between authors. Two authors (MP and AA) assessed all eligible studies based on this criteria. Study quality (i.e. high, medium and low quality) was ascertained based on the authors scoring and after discussion. The quality assessment is graphically illustrated in the supplementary data.

8.4.3. Statistical analysis

All conventional cardiovascular risk factors were assessed including blood pressure, serum lipids, blood glucose, insulin, and type II diabetes mellitus. The random-effects model was selected as per protocol, in order to account for variability in GDM diagnosis, and differences in breastfeeding practices. For continuous outcomes, mean and standard deviation (SD) were reported in the meta-analyses. Standard Error of Mean [403] was converted to *SD* on RevMan software if Mean and *SD* were not reported. The Standardized Mean Difference (*SMD*) was used when individual studies reported outcome in different units, and Mean Difference [404] was

used when units were consistent. For dichotomous outcomes, the (*n*=) of events and (*n*=) of participants were used in the meta-analysis to analyse the Risk Ratio (RR) and the associated 95% confidence intervals (CI). The number of participants/events would be calculated based on the total sample size for breastfeeding and not breastfeeding groups, if the numbers were only reported as a percentage. All analyses were cross-checked and discrepancies were resolved by discussion (ZL, MP). The effects of breastfeeding compared to not breastfeeding for all outcomes were considered significant if there was a difference of $p<0.05$. All test values were two-tailed.

When the I^2 statistic exceeded 50%, and the Chi^2 *P* value was less than 0.1, substantial heterogeneity was considered. Data that was unable to be reported in the meta-analyses, but still reported an association between breastfeeding and CVD risk in women with GDM history and exposed children were included in Table 1 under significant findings. The meta-analysis was performed using Review Manager Version 5.3, based on inverse variance. Sensitivity analyses were conducted to ascertain heterogeneity for each outcome after excluding studies classified as of low to moderate quality in the NHLBI Quality assessment, as determined after author discussion. Five authors were contacted for additional data, of whom one responded (20% author response rate). Assessment of publication bias by funnel plot analysis was not required for any of the meta-analysis, as there was an inadequate amount of studies in the meta-analysis to perform a sufficient assessment.

8.5. Results

8.5.1. Search results

Table 8.4.4.1 highlights the details of each study. Overall, majority of studies defined GDM based on the previous criteria, only three studies in the review defined GDM based on definitions influenced by IADPSG guidelines. Most studies were conducted in Caucasian populations, with two studies conducted in Asian populations. The age range of participants across studies was wide, with participants as young as <25 years to >40 years of age. Follow-up assessment varied between less than one month postpartum to 24 years postpartum.

Quality assessment of studies based on the NHLBI tool revealed that nine studies were of high quality, ten studies were of moderate quality, and none of the studies were of poor quality (Supplementary Table 8.8.1).

Table 8.5.1-1 Published studies of the effects of breastfeeding on cardiovascular disease risk factors among women with previous GDM and children exposed to GDM *in utero*

Study	Study Design	Definition of GDM	Assessment and definition of breastfeeding	(n=) breastfed/not breastfed or did not breastfeed	Follow-up assessment time or age at follow up	Outcomes of interest	Significant findings
Studies assessing offspring of mothers with previous GDM							
Hui 2018 Hong Kong[405]	Prospective cohort	Self-reported (WHO 1999 definition at time)	Self-administered questionnaire assessing formula feeding, mix feeding or breastfeeding only	464/4,143	0-3 months	BMI Z-Score, Glucose	Those exposed to GDM *in utero* who were breastfed had significantly lower BMI than those who were not breastfed at 3 months only. Infant glucose levels were lower in those who were breastfed than those who were not (3.17mmol/L (0.65) vs. 2.86 (0.57) p=0.03). Breastfed infants had higher mean blood glucose compared to those who were formula fed for their first feed (3.20(0.63) vs. 2.68mmol/L (0.58), p=0.002
Martens 2016** Canada[406]	Retrospective database linkage	Hospital diagnosis at 21 weeks gestation	Medical records on breastfeeding	42,332/208,060	24 years	Type II Diabetes	Unadjusted pooled analysis showed that breastfeeding initiation was associated with a 17% reduced risk of youth onset type 2 diabetes in all offspring, including those exposed to GDM *in utero* (HR 0.83, CI 0.69–0.99, P5.038).
Studies assessing mothers with previous GDM							
Chamberlain 2015 Australia[407]	Retrospective database linkage	ADIPS definition	Discharge medical records on breastfeeding fully, partially or never	Fully: 217 (75%) Partial: 51 (18%) Never: 17 (6%)	3, 5, 8 years postpartum	Type II Diabetes	Combined analysis (i.e. indigenous and non-indigenous women) showed that there was an increased rate of progression to type 2 diabetes among women who partially breastfed compared to those who fully breastfed at

							discharge from hospital (HR 2.34 95% CI 1.23–4.47 p=0.009)
Corrado 2019 Italy[408]	Retrospective cohort	Italian Institute of Health	Interviewed at OGTT about frequency of breastfeeding	81/16	3 months	BMI, Lipids, Glucose Insulin	HOMA-IR is significantly associated with breastfeeding (OR 0.370 95% CI 0.170-0.805 p <0.01)
Chouinard-Castonguay 2013[409]	Retrospective follow-up	Medical records	Self-reported through questionnaires. Total duration of lactation was sum of months of lactation, either exclusive or mixed.	116/28	4 years	BMI Glucose Insulin	Women who lactated had higher HOMA-IS than those who did not lactate (Mean (SD)) 0.064(0.044) vs. 0.045(0.021), p=0.01) Lactation duration is an independent predictor of insulin sensitivity indices (i.e. HOMA and Matsuda index (beta coefficient -0.02 p=0.03 for both). However, it was not a predictor of fasting and 2-h post OGTT glucose concentrations, 2-h post OGTT insulin concentrations, AUC for insulin and secretion of insulin.
Dijigow 2015[410]	Retrospective cohort	IADPSG	Medical records – yes/no to breastfeeding	114/18	40 days postpartum	Glucose	Breastfeeding was a protective factor against development of glucose intolerance in the postpartum OGTT (OR: 0.27)
Gunderson 2011** USA[411]	Prospective Observational Cohort	Carpenter and Coustan	Self-reported at 6-9 weeks postpartum and based on previous telephone interaction and monthly questionnaires. Exclusive lactation: no formula food or liquid, mostly lactation, (0-6 oz of formula per 24h) Mostly formula: >17oz per 24 hours Mixed: (7-17 oz of formula per 24h) Exclusive formula: formula only, no breastfeeding or breastfeeding <3 weeks since birth	Exclusively BF: 211 Mostly: 99 Mixed: 77 Exclusively FF: 135	6-9 weeks	BMI, Glucose	Plasma glucose and insulin in unadjusted and fully adjusted means (95% CI) were significantly lower among exclusive breastfeeding compared to formula feeding. Glucose (Mean Difference -6.1 (-9.0 to -3.1) p<0.001). Insulin (Mean Difference -6.3 (-10.1 to -2.4) p<0.001) Fully adjusted for race, baseline parity, age, BMI, education, weeks'

							postpartum and hours of fasting before test.
Gunderson 2015** USA[412]	Prospective Observational Cohort	Carpenter and Coustan	Same as 2011	Exclusively BF: 205 Mostly: 387 Mixed: 214 Exclusively FF: 153	Same as 2011	Same as 2011	Multivariable regression showed that higher lactation intensity and longer duration of lactation is associated with lower adjusted rates of incident diabetes. Exclusive lactation (HR 0.47 (95% CI 0.23-0.82) Exclusive formula (HR 0.72 (0.41-1.28) Lactating 0-2 months (HR 0.48 95% CI (0.25-0.90), >2-5 months (HR 0.65 95% CI (0.33-1.24), >5-10 months (HR 0.65 95% CI (0.33-1.24), > 10 months (HR 0.47 95% CI (0.24-0.91) Adjusted for age, maternal and perinatal risk factors, newborn outcomes and postpartum lifestyle behaviours
Kim 2011 South Korea[413]	Prospective Observational	Carpenter and Coustan	Self-reported	GDM-NGT: 52% BF 32.3% Mixed 15.6 Not BF GDM-prediabetes: 47% BF 44% mixed 8.3 % not BF GDM-T2DM: 50% BF 50% mixed 0% not	6-12 weeks	Type II diabetes	Lactation and duration of lactation have no significant effect on postpartum glucose status (beta coefficient -0.016 p=0.25)
Kjos 1993 U.S.A[414]	Prospective Observational	NDDG 1979	Self-reported 4-12 weeks after delivery "Are you nursing your infant?" (yes or no)	404/405	44-45 days postpartum	BMI, Lipids, Glucose Type II Diabetes mellitus	When stratified for diet and insulin treated GDM, women who lactated with either diet or insulin therapy had significantly lower fasting serum glucose and higher HDL cholesterol.

Martens 2016** Canada[406]	Retrospective database linkage	Hospital diagnosis at 21 weeks gestation	Medical records on breastfeeding	7,510/3,040	5, 10, 15, 20, 24 years	Type II Diabetes	Initiating breastfeeding was inversely related to postpartum T2DM among mothers with and without GDM
McManus 2011 Canada[415]	Prospective Observational	ADA	Not specified	Lactation for 3 months: 14 Did not lactate past discharge: 12	3 months	Blood pressure BMI Lipids Glucose Insulin	Women with previous GDM who were lactating had higher β-cell function for the degree of insulin resistance based on disposition index (129.9 (SD 26.0) vs. 53.4 (SD 18.0 x 10^4 min^1 (p=0.03)
Nelson 2007 Niger[416]	Retrospective cohort	Not specified	Self-reported	36% of n=193 women in cohort were breastfeeding at 1 year	1 year postpartum	Blood glucose	Women who had normal glucose tolerance postpartum were more likely to be breastfeeding (p=0.005) but breastfeeding did not protect women from deteriorating glucose tolerance
Saucedo 2014 Mexico[417]	Prospective Observational	ADA	Not specified	Lactation < 6 weeks Lactation >6 weeks-6 months	6 months postpartum:	Lipids, Glucose, Insulin	Women who lactated longer than 6 weeks had greater weight loss postpartum and lower leptin levels, even after adjustment for weight.
Shub 2019 Australia[418]	Secondary analysis of cohort study	ADIPS	Women were asked whether they exclusively BF, exclusively formula fed or a mixture of both methods.	GDM group: Exclusively BF: 106 Non-BF: 53 Controls: BF: 65 Non BF: 19	6-10 weeks postpartum	Lipids, Glucose	After adjusting for BMI, age and ethnicity, women with GDM that were breastfeeding had significantly lower fasting glucose 0.22 (95% CI 0.39 to 0.05, p=0.12). No difference was seen in fasting lipids (i.e. HDL, LDL, triglycerides) between women with previous GDM who breastfeed and those who did not.
Yashui 2017 Japan[419]	Retrospective	Japan Society of Obstetrics and Gynaecology	Posted questionnaire or telephone interview asking about breastfeeding practices at 6-8 weeks, 6 months and 12 months postpartum. High intensity breastfeeding defined as	High intensity: 70, non high intensity: 18	6-8 weeks, 6-8 months, 12-14 months	BMI, Glucose, Insulin	High intensity breastfeeding was significantly associated with abnormal glucose tolerance (crude OR 0.24, 95% CI 0.06 to 0.75; p=0.013). HOMA-IR is significantly

			infants being fed by breastfeeding alone or roughly 80% of volume at 6-8 weeks and 6 months postpartum, and if mothers continued to breastfeed at 12 months regardless of the volume. Non-high intensity was classified as not following this criterion.				lower in high intensity breastfeeding group than non-high-intensity breastfeeding group (unadjusted Mean (SD): 1.41 ± 1.02 vs. 2.28 ± 1.05, p = 0.035). The difference was the same after adjusted for maternal age, pre-pregnancy BMI, familial diabetes history, 2-h plasma glucose at diagnosis of gestational diabetes, pregnancy weight gain and postpartum weight loss.
Ziegler 2012 Germany[420]	Prospective Observational	German Diabetes Association	Self-reported questionnaire asking on lactation (yes/no) duration and full lactation at 9 months postpartum	201 women breastfed their child, 109 continued breastfeeding >3 months postpartum. Full breastfeeding was practiced by 62% of mothers	15 years postpartum	Type II diabetes	Lactation was associated with a marked delay in diabetes development in women who did lactate compared to those who did not breastfeed. Duration of lactation is inversely associated with postpartum diabetes risk (p=0.002) and longer diabetes free duration. However, lactation did not significantly affect the trend of post-pregnancy BMI.

Abbreviations: BMI – Body Mass Index; **WHO –** World Health Organisation **IADPSG –** International Association of Diabetes in Pregnancy Study Group; **ADIPS –** Australian Diabetes in pregnancy study; **ADA –** American Diabetes Association; **NDDG –** National Diabetes Data Group

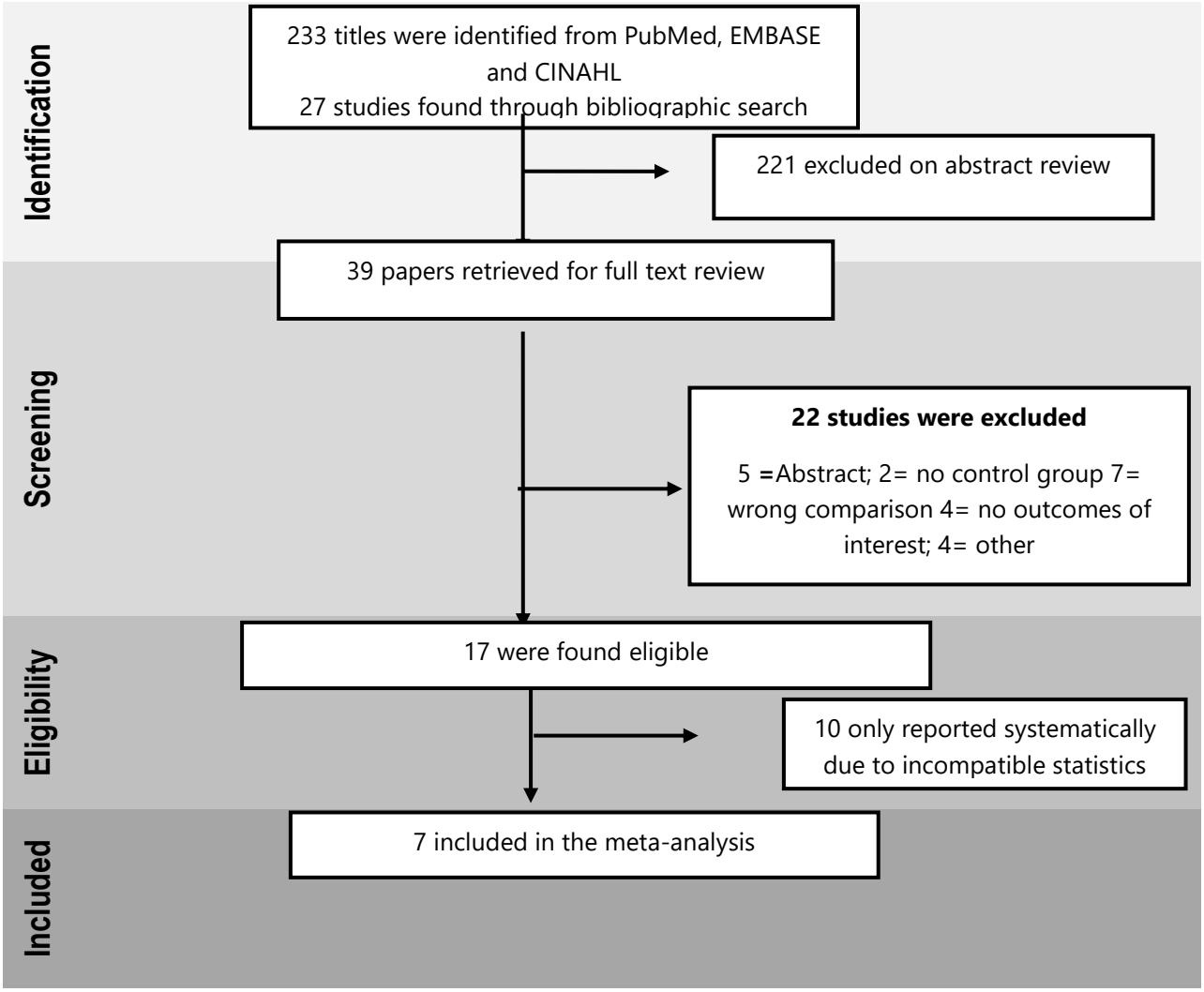


Figure 8.5.1.1 Flow chart of study selection

8.5.2. Breastfeeding in women with a history of GDM

8.5.2.1. Blood pressure

Blood pressure data was reported in one study [415, 421]. The study showed that systolic and diastolic blood pressure was lower in women with a history of GDM that breastfed compared to those who did not (Table 8.4.41).

8.5.2.2. Body Mass Index

Body Mass Index (BMI) data was reported in five studies [408, 409, 411, 414, 415, 419, 421]. BMI was not different in women with previous GDM who did not breastfeed compared to those who breastfed based on quantitative summary measures (Figure 8.4.2.2.1).

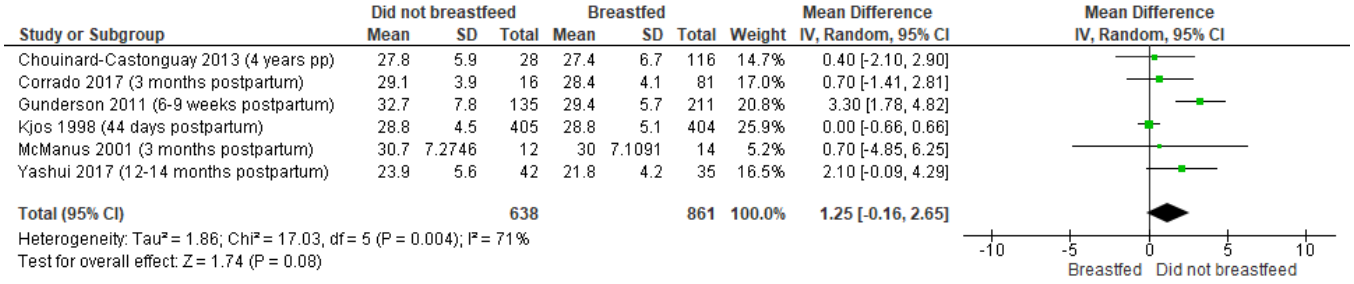


Figure 8.5.2.2.1 Mean difference in BMI (kg/m2) in women with previous GDM who did not breastfeed compared to those who breastfed.

8.5.2.3. Lipids

8.5.2.3.1. Total cholesterol

Total cholesterol data was reported in five studies [408, 414, 415, 421]. Total cholesterol levels were not different between women with previous GDM who did not breastfeed in comparison to those who did breastfed (Figure 8.4.2.3.1).

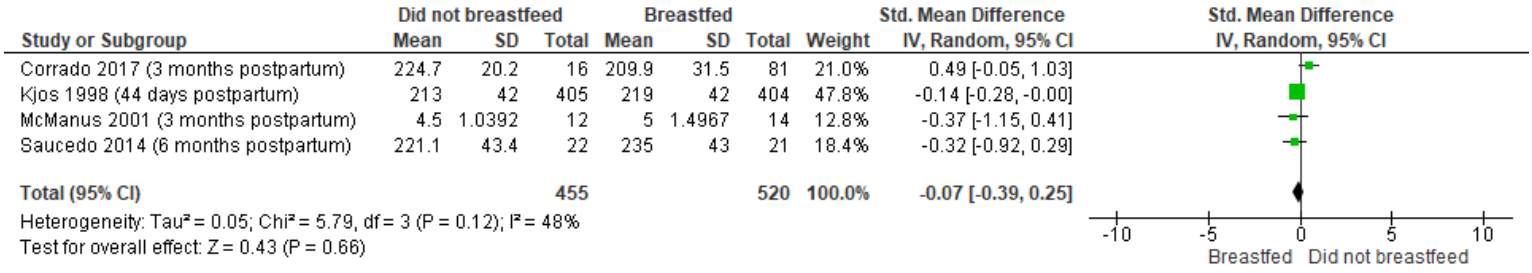


Figure 8.5.2.3.1.1 Standard mean difference in total cholesterol in women with previous GDM who did not breastfeed compared to those who breastfed.

8.5.2.3.2. **Triglycerides**

Serum triglyceride data were available from five studies [408, 414, 415, 417, 418, 421], Four studies were reported in the meta-analysis [408, 414, 415, 417, 421].Serum triglycerides were not different between women who have a history of GDM who did not breastfeed compared to those who did breastfeed(*SMD* 0.23 *95% CI* -0.01 to 0.47, *p*=.06 I^2 = 26%) (Figure 8.5.2.3.2.1). The authors of the one study not reported in the meta-analysis found that serum triglycerides were not significantly different between women who had a history of GDM who breastfed compared to women with previous GDM who did not breastfeed [418].

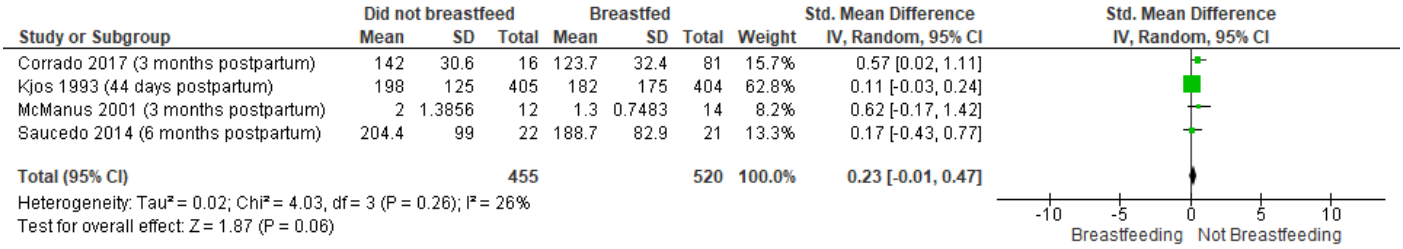


Figure 8.5.2.3.2.1 Standard mean difference in serum triglycerides in women with previous GDM who did not breastfeed compared to those who breastfed.

8.5.2.3.3. **HDL and LDL cholesterol**

Two studies reported on LDL and HDL cholesterol [414, 418, 421]. Both studies showed that serum LDL-C levels were not different between women who had a history of GDM who did not breastfeed compared to those who breastfed. However the study by Kjos *et al.*. 1993 demonstrated that HDL-C was lower in those with a history of GDM that were non-lactating compared to those were lactating (Table 8.5.1).

8.5.2.4. **Serum Insulin**

Fasting insulin data were available from five studies [408, 409, 415, 417, 419]. There was no significant difference in fasting insulin between women with previous GDM who did not breastfeed compared to those who breastfed, based on quantitative summary measures (Figure 8.5.2.4.1).

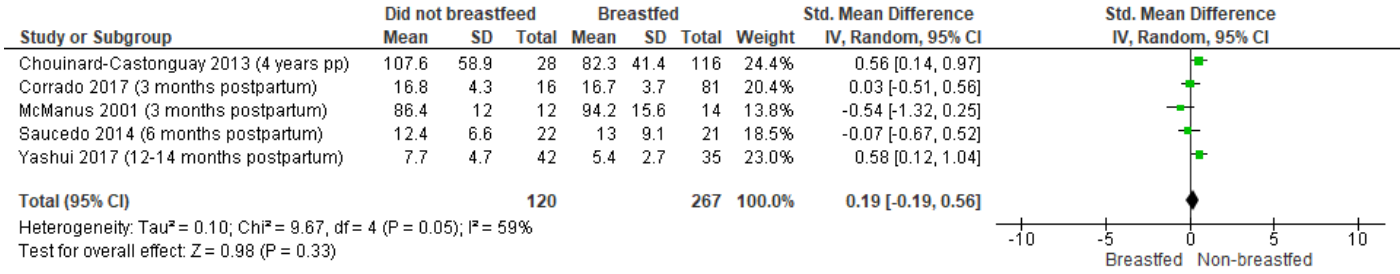


Figure 8.5.2.4.1 Standard mean difference in insulin in women with previous GDM who did not breastfeed compared to those who breastfed.

8.5.2.5. **Glucose**

Serum glucose data were available from eleven studies [408-412, 414-419, 421], of which eight were included in the meta-analysis [408-410, 412, 414, 415, 417, 419, 421]. Based on quantitative summary measures, there was a 0.34 SMD higher serum glucose level among women with previous GDM who did not breastfeed compared to those who breastfed (*SMD* 0.32 *95% CI* 0.12 to 0.57, p=.003 I^2 = 66%) (Figure 8.5.2.5.1). The authors of two studies that were not included in the meta-analysis reported that women with previous GDM who breastfed had significantly lower blood glucose compared to those who did not breastfeed in both unadjusted and adjusted models [411, 418]. However, Nelson *et al.* (2008) reported that breastfeeding was not protective against deteriorating glucose tolerance in women with previous GDM [416].

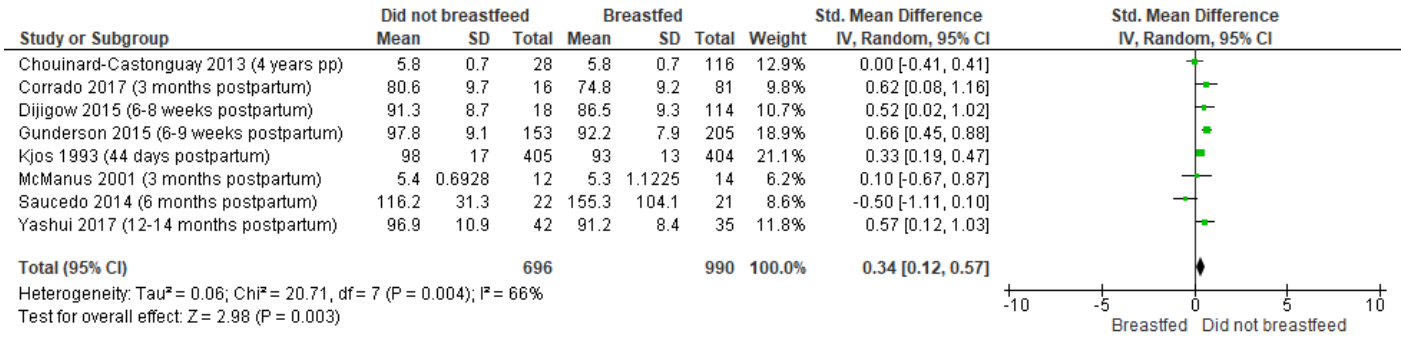


Figure 8.5.2.5.1 Standard mean difference in insulin in women with previous GDM who did not breastfeed compared to those who breastfed.

8.5.2.6. Incidence of type II diabetes mellitus

Type II diabetes mellitus incidence was reported in seven studies [406, 407, 412-415, 420], of which four were reported in the meta-analysis [407, 412, 414, 415]. Based on quantitative summary measures, women with previous GDM who did not breastfeed were at a significantly higher risk of developing T2DM compared to women who breastfed (*RR* 2.21 *95% CI* 1.50 to 3.27, *p*<.0001 I^2 = 0%) (Figure 8.4.2.5.1). From the results of the three studies that were not reported in the meta-analysis, authors of two studies reported that breastfeeding was associated with a reduction in T2DM [406, 407, 420]. However, Kim *et al.* reported that lactation and duration of lactation had no significant effect on postpartum glucose status, including progression to T2DM [413].

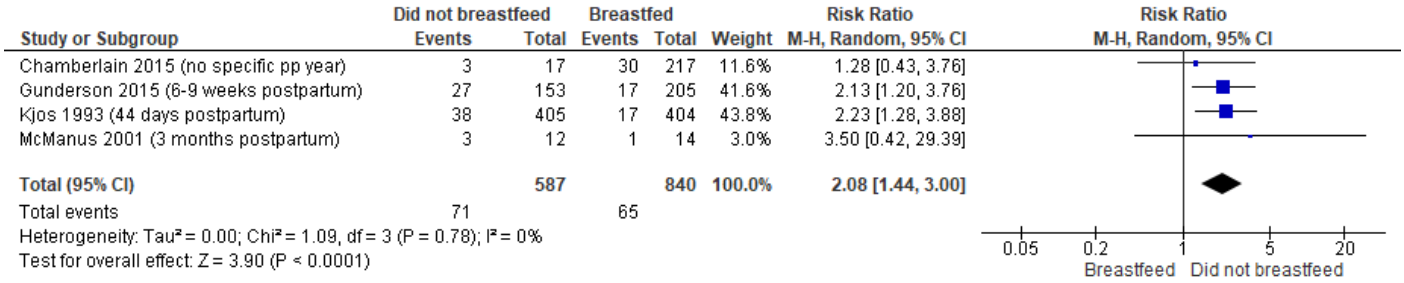


Figure 8.5.2.6.1 Difference in risk of developing type II diabetes mellitus in women with previous GDM who did not breastfeed compared to those who breastfed.

8.5.2.7. **Sensitivity analyses**

The results of sensitivity analyses including moderate quality studies showed a significant decrease in heterogeneity for outcomes BMI, triglycerides and total cholesterol. However, there was an increase in heterogeneity for outcomes blood glucose and insulin. (Supplementary Table 8.8.1).

8.5.3. Effect of breastfeeding on cardiovascular risk factors among children exposed to GDM *in utero:*

Two studies were eligible for inclusion [405, 406]. The details for both studies are included in Table 1.

8.5.3.1. **BMI:** One study reported on BMI z-score. Hui *et al.*. in a prospective birth cohort reported that breastfeeding does not attenuate the association between GDM exposure *in utero* and BMI in the offspring at 3 months of age (Table 8.4.1.1)[405].

8.5.3.2. **Type II diabetes mellitus:** Martens *et al.* reported that breastfeeding initiation before hospital discharge was associated with a reduced risk of T2DM at a 24 year follow up in those who were exposed to GDM *in utero,* (*overall HR*: 0.83, *95% CI* 0.69–0.99, *P*=.038)[406].

8.6. Discussion

This systematic review comprehensively assessed the effects of breastfeeding on all conventional risk factors for CVD in women with previous GDM, and among children born to pregnancies complicated by GDM. The results of the meta-analysis demonstrated that women with previous GDM who breastfed their infants at any stage had a decrease in some cardiovascular risk factors compared to those who did not breastfeed. There were not enough studies to conduct meta-analyses on the effects of breastfeeding on cardiovascular risk factors in children exposed to GDM *in utero*. Longitudinal studies with sufficient power are required to ascertain the effects of breastfeeding on cardiovascular risk factors in children exposed to GDM *in utero.*

Pregnancy complications, including GDM, may confer risk for development of CVD in women with a predisposition to poor life-long cardiovascular health, due to either genetics or poor lifestyle (or both) [396]. GDM occurs when β-cells fail to undergo sufficient expansion resulting in inadequate compensation for placental induction of a hyperinsulinemic state, which promotes elevation of blood glucose [7]. This may lead to long-lasting β-cell damage following pregnancy. The growing fetus is also affected as GDM causes an excess of nutrient transport from the maternal to fetal circulation via the placenta. The fetus adapts epigenetically in response to this adverse intrauterine environment and is said to be programmed, which affects growth and long term metabolic health [422]. Therefore, mothers and their children are at higher risk of metabolic and cardiovascular diseases later in life. Preventive strategies and treatments to reduce development of obesity are required to significantly reduce development of CVD in women with a history of GDM and their offspring.

Evidence strongly suggests that changes in body adipose tissue content and reducing hyperglycaemia can promote disease mitigation [413]. While lifestyle changes can promote a

significant risk reduction, compliance drops after one year postpartum [219]. Physiological preparation for breastfeeding occurs during pregnancy and initiation of breastfeeding after birth aids maternal recovery and is mutually beneficial for both mother and baby [423]. Authors of various studies have reported that mothers who breastfeed for a period of 6-12 months are leaner with a lower BMI than those who do not[424]. Those who are breastfed are also less likely to be overweight or obese than those who are formula fed [60, 425]. Therefore, good quality evidence on the effects of breastfeeding on women with a history of GDM and their children is necessary to support updates to guidelines regarding breastfeeding in women with previous GDM and the benefits for long-term cardiovascular health.

Overall, women with previous GDM have a higher cumulative incidence of hypertension and ischemic heart disease compared with controls [426]. Breastfeeding may mitigate the risk of hypertension in all mothers, as it has been reported that women who breastfed are less likely to be hypertensive in comparison to those who did not [59]. It is thought that the increase in oxytocin and prolactin in breastfeeding mothers influences blood pressure regulation and furthermore promote positive changes to vascular remodelling [427]. This concept supports the hypothesis that breastfeeding may cause a physiological reset to the adverse effects that occur due to pregnancy [397]. While our values are within a healthy range, it is important to note that a 1-2mmHg decrease in blood pressure is linked with a clinically relevant lower mortality from stroke and coronary heart disease [284]. Further research are required to understand the effects of breastfeeding on systolic and diastolic blood pressure in women with a history of GDM

Women who breastfeed have a higher metabolic expenditure and increased rate of lipolysis than those who do not breastfeed [428]. Previous studies have reported that breastfeeding duration is associated with a reduction of dyslipidaemia in young women, including a reduction in the level of serum triglycerides. Furthermore, triglycerides make up the majority of fats in human

milk [58]. Therefore, more research may be needed to investigate an association between breastfeeding and reduction in serum triglycerides in mothers.

There is strong evidence to suggesting that breastfeeding reduces the risk of T2DM [59, 429]. It has been reported that women who have never breastfed have a 50% higher risk for developing T2DM than women who breastfed for as little as 1-3 months postpartum [430]. Our results support an association between breastfeeding and a reduced risk of T2DM in women with previous GDM. Considering the significantly higher risk of developing T2DM among women with previous GDM, many of who also exhibit a pre-diabetic phenotype [431], breastfeeding should be highly encouraged in this population to reduce the risk of T2DM later in life.

The literature suggests that breastfeeding can reduce the risk of non-communicable disease in children. Human milk is composed of long-chain polyunsaturated fatty acids, which can promote blood pressure reduction, and changes in skeletal muscle allowing for protection against insulin resistance and development of T2DM [429]. Whereas, formula fed or mixed fed infants are reported to present with higher levels of insulin resistance and atherosclerotic markers, and exhibit poor β -cell function [432, 433]. Breastfeeding may also promote a healthier diet, as those who are breastfed are more likely to have a higher intake of fruits and vegetables than those who are not [434]. This may be also influenced by the fact that women who choose to breastfeed may be more likely to have a high quality diet and promote this lifestyle in their children. As obesity and metabolic risk factors manifest as young as 3 years old in offspring exposed to GDM *in utero* [207], breastfeeding may be protective against early life obesity. Only two studies in the review assessed cardiovascular risk factors in those exposed to GDM *in utero* who were and were not breastfeed. Based on current literature longitudinal studies that assess long-term cardiovascular benefits of breastfeeding among children exposed to GDM *in utero* are warranted

Based on the qualitative assessment, many of the studies were of high to moderate quality. Due to the observational and retrospective design of the studies included in the review, it was not possible for majority of authors of studies to assess the frequency and volume of human milk fed to infants exposed to GDM *in utero*. A qualitative study design renders it difficult to assess outcomes continuously; rather a randomised control trial design would be more effective to account for variables in a controlled manner. However, studies by Gunderson and Yashui utilized a design in which women were contacted via telephone over the study period and interviewed about their current breastfeeding routine, therefore enabling less change of recall bias.

Some outcomes in the meta-analysis exhibited higher heterogeneity. However, sensitivity analysis resulted in reduced heterogeneity on outcomes of BMI, total cholesterol and triglycerides but a moderate increase in heterogeneity for the other outcomes. Funnel plot analysis was not required, as the number of studies for each outcome did not exceed ten. Heterogeneity in aggregate data is hard to ascertain. It can be due to study specific differences, such as diversity in population, age of assessment, definition of disease etc. We attribute some heterogeneity in these analyses to the different definitions of breastfeeding, particularly as lactation was defined in some studies as >=6 months of exclusive breastfeeding, and in some others it was defined as breastfeeding at hospital discharge. Majority of the studies used definitions of GDM that were prior to the new IADPSG definition, which has a lower cut-off for GDM diagnosis, and thereby is thought to increase the number of women being diagnosed with GDM. Therefore this may affect the assessment of cardiovascular outcomes and representation of women with GDM as studies with the old definition were used primarily in the meta-analysis. Presentation of CVD risk factors in these women may be affected by the time of postpartum assessment. We were unable to complete subgroup analyses stratified by time of risk factor assessment due to the low number of available studies. However, previous

reviews we have completed have demonstrated that cardiovascular risk factors are seen as early as<1 year postpartum in women with previous GDM[36, 395].

8.7. Conclusion

Women with previous GDM should be encouraged to breastfeed to reduce their risk of CVD later in life. More research in this area is required in order to integrate it fully for clinical use and disease mitigation strategies. Lactation specialists should promote breastfeeding in women with previous GDM through integrating what is known about the benefits of breastfeeding on cardiovascular disease risk factors. More research is needed to determine the effects of breastfeeding on cardiovascular risk factors in children exposed to GDM *in utero,* but the limited literature reports protective effects

8.8 Supplementary data

Supplementary Table 8.8 1 Quality assessment of studies included in the systematic review and meta-analyses

Quality assessment	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q1 0	Q1 1	Q1 2	Q1 3	Q1 4	TOT AL
Chamberlain 2015	✔	✔	✔	✔	✔	✔	✔	✘	✔	✘	✔	NA	NA	✔	10
Chouinard-Castonguay 2013	✔	✔	✔	✔	✘	✔	✔	✘	✔	✔	✔	NA	✔	✔	11
Corrado 2019	✔	✔	✘	✔	✘	✔	✔	✘	✔	✘	✔	NA	✔	✔	9
Dijigow 2015	✔	✔	✔	✔	✘	✔	✔	✘	✔	✔	✔	NA	✔	✔	11
Gunderson 2011	✔	✔	✔	✔	✘	✔	✔	✔	✔	✔	✔	NA	✔	✔	12
Gunderson 2015	✔	✔	✔	✔	✘	✔	✔	✔	✔	✔	✔	NA	✔	✔	12
Hui 2018	✔	✔	✔	✔	✘	✔	✔	✘	✔	✔	✔	NA	✔	✔	11
Kim 2011	✔	✔	✘	✔	✘	✔	✔	✔	✔	✘	✔	NA	✔	✔	10
Kjos 1998	✔	✔	✔	✔	✘	✔	✔	✘	✔	✘	✔	NA	✔	✔	10
Martens 2016	✔	✔	✔	✔	✘	✔	✔	✘	✔	✘	✔	NA	NA	✔	9
McManus 2001	✔	✔	**NR**	✔	✘	✔	✔	✘	✔	✘	✔	NA	NR	✔	8
Nelson 2008	✔	✔	✔	✔	✘	✔	✔	✘	✔	✔	✔	NA	✘	✔	10
Saucedo 2014	✔	✔	✔	✔	✘	✔	✔	✘	✔	✔	✔	NA	✔	✔	11
Shub 2019	✔	✔	✘	✔	✔	✔	✔	✘	✔	✔	✔	NA	✔	✔	11
Yasuhi 2017	✔	✔	✔	✔	✘	✔	✔	✘	✔	✔	✔	NA	✔	✔	11
Ziegler 2012	✔	✔	✔	✔	✘	✔	✔	✔	✔	✔	✔	NA	✘	✔	11

Supplementary Table 8.8 2 Sensitivity analysis for the meta-analyses that assessed cardiovascular risk factors in women with previous GDM who did not breastfeed compared to those who breastfed

Analysis	Studies	N=	MD	95% CI	Chi^2 P=	I^2 (%)
BMI						
Normal	7	1,580	1.11	-0.13, 2.35	0.0009	65
Sensitivity	4	593	2.14	0.73, 3.55	0.0003	29
TC						
Normal	5	1,056	-0.00	-0.30, 0.29	0.09	51
Sensitivity	2	69	-0.34	-0.81, 0.14	0.91	0
TG						
Normal	5	1,056	0.33	0.06, 0.61	0.12	45
Sensitivity	2	69	0.33	-0.14, 0.81	0.37	0
Insulin						
Normal	5	387	0.19	-0.19, 0.56	0.05	59
Sensitivity	4	290	0.21	-0.25, 0.68	0.03	65
Glucose						
Normal	9	1,767	0.32	0.12, 0.53	0.006	63
Sensitivity	6	780	0.27	-0.08, 0.63	0.002	74

Discussion of systematic review series

The findings of the systematic review and meta-analyses series have demonstrated an association between GDM and development of cardiovascular risk factors in both mothers and their offspring exposed to GDM *in utero.*

Women who are exposed to GDM are at an increased risk of developing high blood pressure, high BMI, impaired lipid profile, elevated blood glucose and elevated serum insulin. The risk of developing elevated blood pressure, impaired triglycerides, elevated blood glucose and overall risk of developing metabolic syndrome (MetS) is seen as early as <1 year postpartum. This finding is in line with research that suggests that 50% of women develop type II diabetes mellitus and are at risk of experiencing cardiovascular events within one year postpartum[34, 35]. The elevation in systolic blood pressure seen as early as <1 year postpartum reflects the vascular modifications that occur during gestation to women who experience GDM. Osman *et al.* have demonstrated that pregnant women at risk of GDM demonstrate increased augmentation index, which is an indicator of early arterial stiffness[435]. Therefore, investigation of supra-systolic vascular markers during early and late gestation may be important to ascertain what vascular changes during pregnancy promote ongoing vascular dysfunction in women during the postpartum period. Furthermore, while it is clear that peripheral blood pressure is elevated in women with a history of GDM throughout various timepoints, it is less understood whether these supra-systolic vascular markers are also seen during the postpartum as well. Mean arterial pressure is the average pressure through one cardiac cycle. Women with GDM during pregnancy have higher mean arterial pressure compared to women without GDM in pregnancy[436], however there is less evidence on whether it remains after pregnancy. In individuals with type II diabetes mellitus, there is

an increased in arterial stiffness due to vascular damage from pro-inflammatory markers insulin growth factor-1 (IGF-1) and a reduction in adiponectin[437]. Furthermore, a study by Yu and colleagues in 2016 found that mean arterial pressure was a predictive marker of CVD hospitalisation in patients with T2DM. There is inflammation of these markers in women with GDM, and therefore it may be likely that vascular damaging is occurring during gestation that leads to long-term arterial stiffness in the postpartum.[438]

The systematic review and meta-analyses of offspring risk for cardiovascular disease in those exposed to GDM *in utero* revealed that GDM exposed offspring present with higher blood pressure, BMI z-score, and blood glucose compared to those who were not exposed. Offspring who are exposed to GDM *in utero* are also more likely to develop childhood metabolic syndrome compared to children who were not exposed to GDM *in utero.*

An elevation in blood pressure throughout childhood may indicate vascular changes *in utero.* It has been shown that those born large for gestational age to diabetic mothers demonstrate a higher aortic intima medial thickness (aIMT) to birthweight ratio than those born both large for gestational age to uncomplicated pregnancies, and those born a normal birth weight[439]. It has been shown that children aged 5-16 who are obese have higher aIMT than non-obese controls. Covariates such as serum glucose, BMI and systolic blood pressure influenced this association[440]. As offspring exposed to GDM *in utero* are already at a higher risk of developing MetS at a younger age, and have been shown to have higher systolic blood pressure, it will be necessary to understand whether there are any markers of vascular dysfunction, particularly at a young age. This may indicate that exposure to GDM *in utero* could cause intrauterine changes providing a

structural vascular foundation for early onset atherosclerosis and heart disease later in life.

It has been established that offspring born to mothers with GDM are more likely to exhibit neonatal outcomes such as hyperglycaemia and hyperinsulinemia at birth. These offspring are more susceptible to juvenile type II diabetes and obesity[441]. Furthermore, an elevation in BMI z-score is indicative of changes in adiposity, however BMI as a measure in children and adolescence may not be as predicative of changes in total body fat[286]. Abdominal obesity, measured by waist circumference, can indicate many markers of poor metabolic health, such as poor physical inactivity, insulin resistance, elevation in cytokines etc[442]. Therefore, assessing abdominal obesity in tie with adjusted BMI may provide a clearer indication of risk of metabolic disorders and insulin resistance in offspring exposed to GDM *in utero*, later in life.

The findings of the systematic review and meta-analysis on the effect of breastfeeding on cardiovascular risk factors in women with a history of GDM and offspring exposed to GDM *in utero* revealed that breastfeeding in women with a history of GDM reduced the risk of developing both elevated serum glucose and T2DM. However, there was not enough evidence throughout the literature to support an association for other cardiovascular risk factors, and there were no observational studies seen that showed an association between better metabolic health in children who were exposed to GDM *in utero* who were breastfed.

Therefore, the findings of these systematic reviews and meta-analysis will form a basis into investigating the effect of gestational diabetes mellitus on vascular

and metabolic health at 3 years postpartum in the STOP cohort of women and their children.

SECTION 3: The STOP study and 3 year follow-up

This section begins with observational analysis of anxiety and depression in women in the STOP cohort during pregnancy. The following chapters have been written on the STOP 3 year follow-up study in women and children. All of the papers have been submitted for consideration of publication. Therefore, there may be repetition in the methodology sections across chapters.

Chapter 9

9. Anxiety and depression in early gestation and the association with subsequent gestational diabetes mellitus in a disadvantaged population

Maleesa M Pathirana, Prabha H Andraweera, Shalem Leemaqz, Emily Aldridge,

Margaret A Arstall, Gustaaf A Dekker, Claire T Roberts.

9.1. Statement of Authorship

Title of Paper	Anxiety and depression in early gestation and the association with subsequent gestational diabetes mellitus in a disadvantaged population.
Publication Status	Submitted for publication in *Journal of Diabetes Research*
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Ethics submission, recruitment, site specific administration, undertaking assessments with participants, data collection, analysis of results, interpretation of results, writing of manuscript.
Overall Percentage (%)	80%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature	**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Prabha H Andraweera
Contribution to the Paper	Designed protocol, ethics submission, contributed to manuscript and supervision
Signature	**Date 28/02/2022**

Name of Co-Author	Emily Aldridge
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, contributed to manuscript and technical advice.
Signature	**Date 14/02/2022**

Name of Co-Author	Shalem Leemaqz
Contribution to the Paper	Statistical analysis assistance, contributed to manuscript and technical advice.
Signature	**Date 23/02/2022**

Name of Co-Author	Margaret A Arstall
Contribution to the Paper	Conceived and designed protocol, assisted with data interpretation, contribute to manuscript and technical advice.
Signature	**Date 28/02/2022**

Name of Co-Author	Gustaaf A Dekker.

Contribution to the Paper	Conceived and designed protocol, recruited women into original STOP study, contributed to manuscript.	
Signature		**Date 28/02/2022**

Name of Co-Author	Claire Roberts	
Contribution to the Paper	Conceived and designed protocol and original STOP study, contributed intellectually to manuscript and supervised.	
Signature		**Date 28/02/2022**

9.2. Abstract

Objective: Evaluate the association between poor mental health and risk of developing gestational diabetes mellitus (GDM) in a cohort of women from a socioeconomically disadvantaged community.

Methods: This is a cohort study of nulliparous women with singleton pregnancies recruited to the Screening Tests to Predict Poor Outcomes of Pregnancy study in Adelaide, Australia. Women were assessed for mental health in the first trimester, including likelihood of depression, high functioning anxiety, perceived stress and risk of developing a mental health disorder. GDM was diagnosed based on the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria. Socioeconomic status of women was measured using the New Zealand Socioeconomic Index (SEI).

Results: There were 1,363 participants in the STOP study, with complete mental health data for 1,281 participants. There were 196 women diagnosed with GDM and 1,085 women who experienced a non-GDM pregnancy, encompassing women with an uncomplicated pregnancy and participants experiencing other major pregnancy complications. Over a quarter of women in the cohort had a history of depression, and nearly 50% were at high risk of developing a mental health disorder during pregnancy. There was no statistically significant difference in SEI, depression, risk of mental health issues, high functioning anxiety and perceived stress between women who developed GDM and those who did not. There was no difference in history of depression nor risk of developing a high mental health disorder in first trimester after adjusting for SEI, BMI in first trimester, smoking status in first trimester and maternal age between women with a GDM pregnancy and those who did not.

Conclusion: There was no difference in markers of poor mental health in early pregnancy between women who subsequently did or did not develop GDM. Cohort participants were

socioeconomically disadvantaged, potentially contributing to the lack of apparent differences in depression observed between groups.

9.3. Introduction

Gestational diabetes mellitus (GDM) is defined as hyperglycaemia in pregnancy, which is first diagnosed during pregnancy and affects 1 in 7 pregnancies in Australia[307, 443]. GDM poses a myriad of risks to both mother and child both during the perinatal period (macrosomia, birth injury, caesarean section, neonatal hypoglycaemia) and later in life when it is associated with poor metabolic and cardiovascular health[36, 207, 300, 307]. Women with previous GDM are at a 7.5 fold increased risk of developing type 2 diabetes mellitus compared to those with no history of GDM[34]. Conventional risk factors for GDM include, but are not limited to, family history, age and ethnicity[215]. While these risk factors are not modifiable, other conventional risk factors such as obesity and hypertension are primary targets for GDM prevention strategies.

Common mental disorders (CMD) including anxiety and depression are significant maternal health problems. It has previously been shown that 7-20% of women in high-income countries experience antenatal depression, and 20-25% of women have an anxiety disorder during pregnancy [444]. Previous systematic reviews and meta-analyses have demonstrated a bi-directional association between type 2 diabetes mellitus and major depressive disorder[445, 446]. This association is thought to be instigated by hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA), which causes an increase in circulating cortisol and insulin resistance [43, 447]. However, evidence in the literature is inconsistent regarding an association between CMD and development of GDM[448-450]. Furthermore, pertinent studies have not assessed this association against important covariates such as obesity and low socioeconomic status (SES), which contribute to both depression and diabetes [451]. Socioeconomic status is important in the context of understanding the association between maternal depression and GDM. In Australia SES significantly impacts burden of mental health disorders, and those who are disadvantaged often experience difficulty finding effective help for their mental health problems which may lead to poor physical health outcomes overall[452]. Hence, understanding whether there is an

association between depression and pregnancy complications may aid in improving access to clinical services for disadvantaged pregnant women.

Therefore, the aim of our study was to determine the association between markers of poor mental health and subsequent development of GDM in a cohort of pregnant women from a metropolitan socioeconomically disadvantaged community.

9.4. Methods

9.4.1. Study population

The Screening Tests to predict poor Outcomes of Pregnancy [1] study was a prospective cohort study, where 1,383 nulliparous women with singleton pregnancies were recruited from three major hospitals in Adelaide, Australia. Ethics approval was obtained from the Women's and Children's Hospital Human Research Ethics Committee (HREC/14/WCHN/90). Majority of the participants were recruited from the Lyell McEwin Hospital, which serves one of the lowest socioeconomic regions in urban Australia. Residents in this region experience some of the highest levels of chronic disease and mental illness across urban Australia[453]. Women were excluded if they were at high risk for preeclampsia or delivering a small for gestational age baby or delivering preterm due to gynaecological history or underlying medical conditions (including known pre-existing chronic hypertension, being on hypertensive medication or having blood pressure >160/100 mmHg at 15 weeks' gestation) or if they had three or more miscarriages or terminations. Couples who received medical or surgical interventions that could modify pregnancy outcome were also excluded. These exclusions enabled assessment of novel risk factors for pregnancy complications in a cohort of healthy, young women without known predisposing risk factors.

Consenting pregnant women were recruited into the STOP study between 2015 and 2017. Research and clinical midwives collected information from women including demographics, smoking status, and family, medical and gynaecological history. At the first antenatal visit (between 9-16 weeks' gestation) anthropometric data including height, weight and waist circumference were collected. Socioeconomic status was ascertained using the New Zealand Socioeconomic Index (SEI), calculated based on

the participant's occupation, producing a score between 10 and 90, with a lower score reflecting greater disadvantage. Smoking status was classified as a binary variable both in the 3 months prior to pregnancy and in the first trimester (yes/no).

As part of routine clinical care, women completed the following questionnaires to ascertain their mental health status at the first trimester visit:

- Antenatal (psychosocial) Risk Questionnaire (ANRQ)[454]
- Edinburgh Postnatal Depression Score (EPDS)[455]
- Perceived Stress Questionnaire (PSS) [456]
- State and Trait Anxiety score-6 (STAI-6) [457]

GDM was diagnosed at 24-28 weeks of gestation according to the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria (i.e. one or more values equal to or exceeding: fasting plasma glucose of 5.1mmol/L, and/or a 2h plasma glucose level of 8.5mmol/l following a 75g Oral Glucose Tolerance Test (OGTT)[400]. We also included women who, due to pre-existing risk factors, were diagnosed with GDM at 12 weeks' gestation. This decision was made as descriptive analysis showed no difference in baseline parameters and mental health markers when excluding women diagnosed with GDM earlier than 24 weeks' (data not shown).

9.4.2. Statistical analysis

Anxiety in pregnancy was defined using the STAI-6 score, where a score below 30 was defined as "low to no anxiety", 31-49 "normal level of anxiety" and a score of 45-80 was defined as a participant having an "elevated state of anxiety". Likelihood of depression was assessed using the EPDS, where "low risk" of depression was scored 0-9, "moderate risk" of depression in the following year score 10-12, and "likely depressed" score 13-30. Risk of perinatal mental health morbidity was assessed using the ANRQ, with a score >22. Women were considered at high risk when answering yes

to any of the following questions: 2A ("have you ever had 2 weeks or more where you felt particularly worried, miserable or depressed?), 2B (do you have any other history of mental health problems?) 8 (were you emotionally abused growing up?), 9 (have you ever been sexually or physically abused?). Stress was assessed using the PSS, whereby a score between 0-13 was considered "low" stress, 14-26 "moderate" stress and 27-40 "high" perceived stress. History of depression was defined as variable coded 'yes' to the question "do you have a history of depression?". Medication history was reported and data was analysed according to which participants were taking antidepressants.

Data were analysed using IBM SPSS Version 26. Univariate analyses were undertaken to assess women with GDM compared to women with non-GDM pregnancies for baseline variables, using Chi-squared test for categorical variables and *t*-test for continuous variables. Logistic regression analyses assessed the effect of having a history of depression (dichotomous grouping i.e. yes or no) on the risk of GDM, and having a high risk of having a mental health disorder (i.e. scoring high risk on the ANRQ) controlling for maternal age, BMI in first trimester, smoking status in first trimester and SEI, with data presented as odds ratio (95% CI). Variables were selected for logistic regression based on stepwise regression analysis and whether the variable was clinically associated with both depression and GDM. Data are presented as Mean (SD) or N (%).

9.5. Results

9.5.1. Participant demographics

The STOP study recruited 1,383 pregnant women from 2015 to 2018. Some women were excluded from this analysis due to miscarriage, loss to follow-up, or twin pregnancy. Of those recruited, there are data available and analysed for 1,300 with known pregnancy and birth outcomes. (Figure 9.5.1.1). Of these, 198 women were diagnosed with GDM and 1,102 experienced a non-GDM pregnancy. The participants in the latter group were women with an uncomplicated pregnancy and those who experienced pregnancy complications (but not including GDM) such as gestational hypertension, preeclampsia, spontaneous preterm birth and delivery of a small for gestational age (SGA) baby.

Descriptive statistics are highlighted in Table 9.5.1.1. Caucasian ethnicity was lower in women diagnosed with GDM than those with a non-GDM pregnancy. Furthermore, BMI in first trimester was significantly higher in women later diagnosed with GDM compared to women with a non-GDM pregnancy. There was no significant difference in maternal age, SEI nor smoking status between women diagnosed with GDM and those with a non-GDM pregnancy. The mean age, BMI and SEI score were similar for the cohort overall (Table 9.5.1.1). There was no significant difference in history of depression nor use of antidepressants between women diagnosed with GDM compared to those with a non-GDM pregnancy. History of depression was reported in 27.3% of the whole cohort, and antidepressant use was recorded for 13.5% (Table 9.5.1.1).

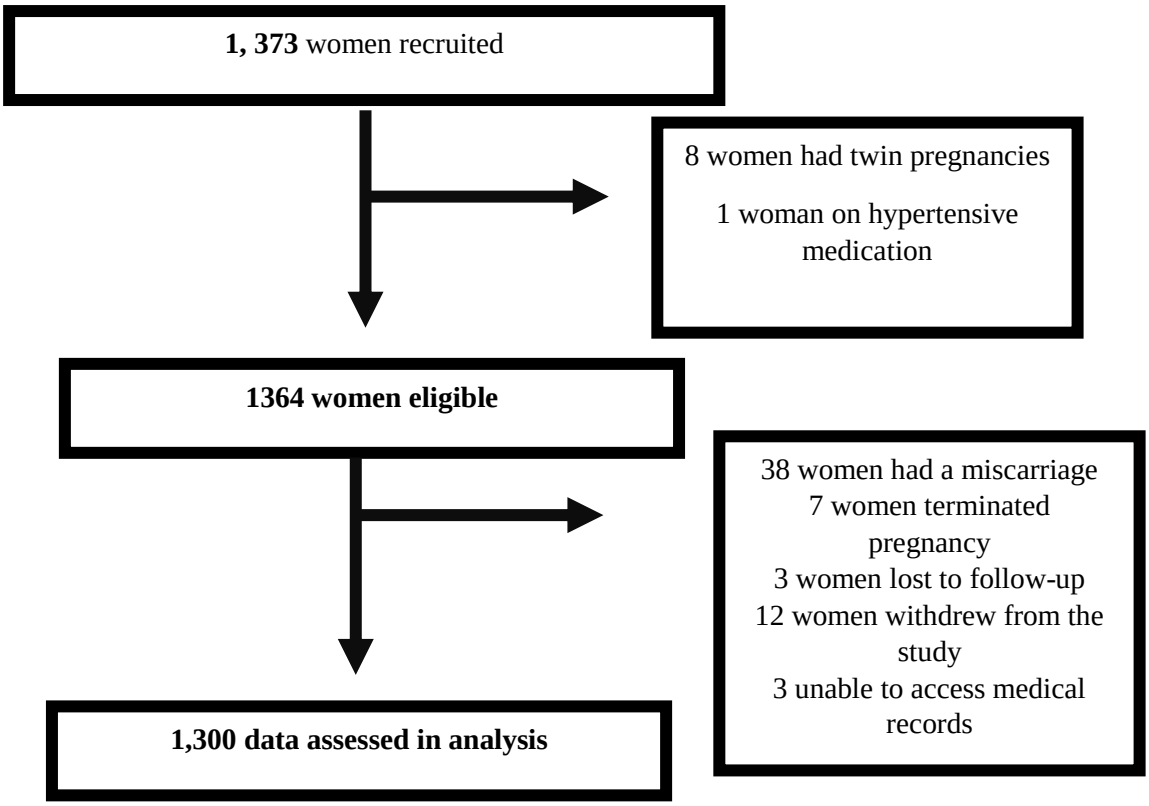


Figure 9.5.1.1 Flow chart of STOP study participants

Table 9.5.1-1 Characteristics of participants in early pregnancy

	Total (n=1300)	**GDM (n=198)**	**Non-GDM (n=1102)**	**P-value**
Caucasian ethnicity (N (%))	1077 (82.8%)	142 (71.9%)	935 (84.8%)	**0.000**
Maternal age (Median years range)	30 (15-45)	26.1 (5.1)	26.1 (5.1)	0.627
Maternal Education (N (%))*				0.127
Did not complete year 10	27 (2.1%)	4 (2.0%)	23 (2.1%)	
Year 10	247 (19%)	27 (13.6%)	220 (20%)	
Year 12	295 (22.7%)	42 (21.1%)	253 (23.0%)	
Certificate	462 (35.5%)	76 (38.2%)	386 (35.0%)	
Bachelor	193 (14.8%)	20 (20.1%)	153 (13.9%)	
Higher degree	72 (5.5%)	10 (5%)	62 (5.6%)	
*NZSEI (Median and IQR)	29 (24)	34.1 (13.5)	32.4 (13.6)	0.262
BMI in first trimester (Median and range)	26.3 (15.8-61.4)	31.7 (8.7)	27.3 (6.6)	**0.000**
***Other pregnancy complications (n=) (%)				
Preeclampsia	121 (9.4%)	18 (9.1%)	103 (9.4%)	0905
Gestational Hypertension	88 (6.8%)	21 (10.7%)	67 (6.1%)	**0.020**
Small for gestational age	153 (11.9%)	20 (10.1%)	133 (12.2%)	0.420
Maternal tobacco smoking (N (%))				
First trimester	265 (20.4%)	38 (19.1%)	227 (20.6%)	0.923
History of depression (N (%)) Yes	357 (27.5%)	62 (31.3%)	295 (26.8%)	0.187
History of antidepressant use for CMD (N (%)) Yes	175 (13.5%)	37 (18.7%)	138 (12.5%)	0.065

**NZSEI a scale of 10-90 based on occupation. A lower score indicates increasing disadvantage.
***Pregnancy complications are not mutually exclusive and one woman can experience more than one pregnancy complication. Missing data for 10 participants.

9.5.2. Mental health in women in pregnancy

Associations of mental health markers in early pregnancy between women later diagnosed with GDM and those with a non-GDM pregnancy are shown in Table 9.5.2.1. More women had a high risk of mental health disorder assessed by ANRQ and later developed GDM than those who did not (47.2% vs. 42.3%) but this was not statistically significant. Of the total cohort, 42.2% were at high risk of developing a mental health disorder. There was no statistically significant difference between groups for a higher likelihood of depression and perception of stress as assessed by PSS. There was a greater proportion of women in the GDM group who experienced an elevated state of anxiety in early pregnancy (14.4%) compared to those with a non-GDM pregnancy (10%) but this was not statistically significant.

Table 9.5.2-1 Association of mental health, likelihood of depression, stress perception and anxiety status in women with gestational diabetes in pregnancy compared to women with a non-GDM pregnancy

	Whole cohort N (%)	**Gestational Diabetes N (%)**			**Non-GDM N (%)**			**P-value**
	High	**Low**	**Moderate**	**High**	**Low**	**Moderate**	**High**	
Risk of mental health disorder (ANRQ)*^	548 (42.2%)	103 (52.3%)	-	94 (47.5%)	638 (57.9%)	-	455 (41.3%)	0.243
Likelihood of depression (EPDS)* **	101 (7.8%)	170 (85.9%)	13 (6.6%)	14 (7%)	910 (82.6%)	93 (8.4%)	87 (7.9%)	0.646
Stress perception (PSS)* ***	38 (3.1%)	91 (48.9%)	89 (47.7%)	6 (3.2%)	573 (54.1%)	454 (42.9%)	32 (3%)	0.424
		None-low anxiety	**Normal level of anxiety**	**Elevated state of anxiety**	**None-low anxiety**	**Normal level of anxiety**	**Elevated state of anxiety**	
Anxiety Status (STAI)* ***	139 (10.8)	129 (66.2%)	38 (19.5%)	28 (14.4)	783 (71.8%)	197 (18.1%)	111 (10.2%)	0.165

*High risk of mental health disorder was based on an ANRQ score > 22 or answering yes to questions 2A, 2B, 8 or 9 (specified in methods). Low risk of depression was scored 0-9, moderate risk of depression was scored 10-12, likely to be depressed scored 13-30. Low perceived stress was scored as 0-13, moderate perceived stress was scored 14-26 and high perceived stress was scored 27-40. A score below 30 denotes "low to no anxiety", 31-49 "normal level of anxiety" and 48-80 an "elevated state of anxiety"

^ANRQ assessed as high or low risk only.

** EPDS missing data for 13 participants

*** PSS missing for 15 participants, STAI missing for 15 participants

We performed a logistic regression analysis to determine the association between having a history of depression or having a high risk of developing a mental health disorder in first trimester and the risk of subsequent development of GDM, adjusting for SEI, BMI in first trimester, smoking status in first trimester, and maternal age. There was no significant association between having a history of depression and GDM after adjusting for covariates [aOR 0.15 (-0.2 to 0.5)]. Having a high risk for a mental health disorder in first trimester was not associated with GDM after adjustment for covariates [aOR -0.4 (-1.5 to 0.6))] (Table 9.5.2.2).

Table 9.5.2-2 Association between history of depression and high risk of mental health disorder with risk of GDM

	Unadjusted	Adjusted[#]
History of depression	**-1.0 (-1.1 to -0.9)**	0.15 (-0.2 to 0.5)
High risk of mental health disorder	-0.14 (-0.42 to 0.71)	-0.4 (-1.5 to 0.6)

[#]Adjusted for SEI, BMI in first trimester, smoking status in first trimester, and maternal age

9.6. Discussion

In this cohort study in a socioeconomically disadvantaged population, we did not find a statistically significant association between parameters of women's mental health during pregnancy and development of GDM. Furthermore, the prevalence of a history of depression, and that of being at high risk for mental health disorders, were not significantly different between women in the GDM and non-GDM groups after adjustment for covariates.

Approximately 50% of women with GDM in pregnancy scored at high risk of developing a mental health disorder in their first trimester. This was also similar in the non-GDM group. The ANRQ assesses an individual's psychosocial risk. A score of 23 or more is considered to be a clinically significant predictor of postpartum depression [458]. We sought to determine if there was an association between a high ANRQ score and risk of developing GDM. However, after adjusting for covariates such as age, BMI, smoking status and SEI there was no difference between groups.

Women from the STOP cohort were recruited from a community that is among the most severely disadvantaged in urban Australia[452]. Mean SEI, as assessed on the basis of occupation, confirmed the high level of deprivation among many women in the cohort. Reports of psychological distress in the northern Adelaide region (i.e. a score of >= 10 or more on the K10 depression scale) are 20% higher than the national average, and mental health and behavioural problems are 5% higher than the national average[72]. Women in this community predominantly have low levels of formal education, social support and income which all contribute to a higher risk of mental health disorders. Individuals with low social support and low SES have been shown to have a higher EPDS score, and higher rates of antepartum and postpartum depression than those who received adequate social support in a community of higher SES[459]. The majority of the literature that has found an association between antenatal depression and risk of GDM

assessed women from communities with an average or high SES. This is likely due to the difficulty in engaging those from low SES populations in clinical research. However, a very pertinent study that assessed women from an area of severe disadvantage found that depression was not associated with GDM. Therefore, it is likely that any association between depression and subsequent GDM in a low SES community is masked due to the high risk of mental health disorders across all pregnant women in that community. Furthermore, associations between depression and GDM may be more confounded in our cohort because rates of obesity and other factors such as smoking, alcohol consumption, reduced exercise and diabetes are higher than the state and national averages[72].

The northern Adelaide region experiences higher rates of domestic violence and other offences than other regions of Adelaide[460]. The ANRQ assesses health history and social determinants of health such as physical, sexual and/or emotional abuse, and emotional and or practical support from a partner. It is quite likely that an association between mental health risk status and GDM could be masked in our cohort due to the high rate of poor social support seen in both GDM and non-GDM groups. Furthermore, psychosocial risk affects both physical health and diet, which would place these women at risk of obesity and development of diabetes [461].

Reports in the literature are inconsistent regarding the association between depression and subsequent GDM. Depression alters metabolism, specifically by elevating oxidative stress and cortisol which drive insulin resistance and elevations in blood glucose[462]. Similar to depression, anxiety and stress can promote increased HPA activity, thereby promoting higher cortisol and arginine vasopressin secretion which subsequently impact insulin levels in the body and promote insulin resistance [463]. Some studies suggest an association, while others do not. Hinkle *et al.* assessed depression scores based on the EPDS in first trimester and found that depression in early pregnancy was associated with a two-fold increased risk of developing GDM after adjusting for relevant covariates [464]. Wilson *et al.* found no evidence of an association between

common mental disorders in the pre-natal period and GDM, for which depression and anxiety were diagnosed based on ICD diagnostic scoring [450]. However, Byrn *et al.* (2015) showed a significant association between depression/mood disorder and subsequent GDM in multivariate analyses [465]. A very recent meta-analysis also showed that GDM is associated with depressive symptoms. However, the analysis was highly heterogeneous due to variation of how depression and anxiety were diagnosed[466]. In our study, depression was self-reported and not clinically assessed. Therefore, the severity of depression between participants may vary. Other studies assessed depression in different ways including retrospective data linkage and EPDS [465, 467, 468]. It may be important to consider severity of depression for future studies, as this may influence the severity of maternal metabolic dysfunction and insulin resistance and thereby influence glucose tolerance in pregnancy.

There is still discrepancy in the literature regarding the association between anxiety and GDM. Our study showed that high functioning anxiety was more common, but not statistically significant, in women with GDM compared to non-GDM. Mishra *et al.*, found a significant association between high-perceived stress and GDM[463] while Silveria *et al.* showed no association between perceived stress during early or mid-pregnancy and subsequent GDM [469]. However, these studies did not find a direct correlation between perceived stress and diagnostic OGTT glucose levels. Therefore, it may be important to examine glycaemic levels and perceived stress, particularly as the HAPO study has shown that glucose levels below conventional diagnostic criteria at the time for GDM were associated with poor antenatal maternal and neonatal outcomes[225].

The strengths of our study include the large cohort with 15% of women with GDM, which is comparable to the national average of approximately 15% of pregnant women[470]. Our study also captures one of the lowest socioeconomic urban regions of Australia, where chronic diseases such as type 2 diabetes and cardiovascular disease are highly prevalent. We assessed

many risk factors, such as stress perception, anxiety and risk of common mental disorders. Our limitations include not having a clinical diagnosis of depression. In our cohort, nearly half of the participants were considered at high risk of developing a mental health disorder at their antenatal booking visit. Furthermore, the prevalence of antenatal depression is significantly higher in disadvantaged communities. In this cohort, we report low social support, lower education status and psychological factors such as stigma attached to mental health disorders that impact maternal mental health.

Furthermore, as this population is very disadvantaged (median SEI score of 29) it may be difficult to detect differences between GDM and non-GDM participants regarding mental health outcomes. Our population was primarily Caucasian. Therefore, our results may not be generalizable to women of other ethnicities.

9.7. Conclusion

We did not find a significant difference between women with GDM in pregnancy and women with a non-GDM pregnancy for history of depression and markers of depression, anxiety and stress in early pregnancy. This may be due in part to the low SES in our cohort. Future research should aim to assess risk of GDM in women with clinically diagnosed depression and assess different levels of obesity and socioeconomic disadvantage to explore these associations further

Chapter 10

10. Gestational diabetes mellitus and cardio-metabolic risk factors in women and children at 3 years postpartum

Maleesa M Pathirana, Prabha H Andraweera, Emily Aldridge, Shalem Y Leemaqz , Madeline Harrison, Jade Harrison, Petra E Verburg, Margaret A Arstall, Gustaaf A Dekker, Claire T Roberts

10.1. Statement of Authorship

Title of Paper	Gestational diabetes mellitus and cardio-metabolic risk factors in women and their children at 3 years postpartum
Publication Status	Submitted for publication in *Acta Diabetologica*
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Ethics submission, recruitment, site specific administration, undertaking assessments with participants, data collection, analysis of results, interpretation of results, writing of manuscript.
Overall Percentage (%)	80%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature	**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Prabha H Andraweera	
Contribution to the Paper	Designed protocol, ethics submission, contributed to manuscript and supervision	
Signature		**Date 28/02/2022**

Name of Co-Author	Emily Aldridge	
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, contributed to manuscript and technical advice.	
Signature		**Date 14/02/2022**

Name of Co-Author	Shalem Leemaqz	
Contribution to the Paper	Statistical analysis assistance, contributed to manuscript and technical advice.	
Signature		**Date 23/02/2022**

Name of Co-Author	Madeline Harrison	
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, reviewed manuscript	
Signature		**Date 15/02/2022**

Name of Co-Author	Jade Harrison
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, reviewed manuscript

Signature		**Date 15/02/2022**

Name of Co-Author	Petra E Verburg	
Contribution to the Paper	Conceived and designed protocol, recruited women into original STOP study, contributed to manuscript and provided technical advice.	
Signature		**Date 15/02/2022**

Name of Co-Author	Margaret A Arstall	
Contribution to the Paper	Conceived and designed protocol, assisted with data interpretation, contribute to manuscript and technical advice. Provided clinical guidance from cardiology perspective	
Signature		**Date 28/02/2022**

Name of Co-Author	Gustaaf A Dekker.	
Contribution to the Paper	Conceived and designed protocol, recruited women into original STOP study, contributed to manuscript and provided clinical guidance from obstetrics perspective	
Signature		**Date 28/02/2022**

Name of Co-Author	Claire Roberts
Contribution to the Paper	Conceived and designed protocol and original STOP study, contributed intellectually to manuscript and supervised.

Signature		**Date 28/02/2022**

10.2. Abstract

Introduction: Gestational diabetes mellitus (GDM) is thought to be associated with future development of cardio-metabolic risk factors in women and their children, with evidence of these risk factors seen in the early postpartum period and early childhood. We hypothesized that women with a history of GDM, and their children exposed to GDM *in utero,* would exhibit an increase in persistent abnormal cardiovascular and metabolic risk factors three years after the pregnancy, compared to women with normoglycemic pregnancies and those with uncomplicated pregnancies within the same cohort.

Methods: Women from the Screening Tests to Predict Poor Outcomes of Pregnancy study were invited to attend a follow-up with the child from their index pregnancy at 3 years postpartum. Women and children were assessed for anthropometric measures and haemodynamic function non-invasively with the USCOM BP+ device. Fasting blood samples were obtained from women to assess lipid and glucose status.

Results: Of the 1,363 STOP study participants recruited in pregnancy from 2015 to 2017 with complete pregnancy data, 281 woman-child dyads participated in the 3 year follow-up, of whom 40 women had developed GDM during their index pregnancy. At 3 years postpartum, fasting serum insulin was significantly higher in women with a history of GDM compared to those with an uncomplicated pregnancy. However, this association was mediated by BMI in early index pregnancy and socioeconomic index [471]. The rate of metabolic syndrome at 3 years postpartum was significantly higher in the GDM group than in those who had an uncomplicated pregnancy (65% vs 2% p=0.000). A history of GDM was associated with elevated maternal fasting serum triglycerides at 3 years after adjustment for BMI in index pregnancy and SEI [aMD 0.30 (0.07 to 0.6)]. At age 3 years, children exposed to GDM *in utero* had higher waist

circumference compared to children born after an uncomplicated pregnancy. However, this was also mediated by maternal early pregnancy BMI and SEI.

Conclusion: Exposure to GDM is associated with elevated serum triglycerides in women at 3 years postpartum but other perturbed cardiometabolic outcomes in women and their offspring at this time appear to be mediated largely by early pregnancy BMI and SEI.

10.3. Introduction

Cardiovascular disease (CVD) is the number one cause of global mortality, with 17.9 million deaths in 2016, representing 31% of all global deaths in that year[472]. The Australian Institute of Health and Welfare reported that 78% of CVD burden for females in 2015 was considered 'fatal' death due to premature death[470]. Therefore, it is important to understand causes and risk factors for CVD that put women at an increased risk.

Gestational diabetes mellitus (GDM) is defined as *de novo* diagnosis of diabetes during pregnancy[473]. It is commonly diagnosed at 24-28 weeks' gestation but prior risk factors including family history and obesity can qualify a woman to be tested earlier[3]. Having GDM increases risk of developing type 2 diabetes mellitus (T2DM) by 50% within five years post pregnancy, placing young women at increased risk of premature coronary heart disease[34]. Understanding the absolute cardiovascular risk (where T2DM is one of these risk factors) for this group of women allows for early intervention and merits further research. A recent meta-analysis showed that women with a history of GDM have an increased risk of developing cardiovascular risk factors in the future. Elevated blood pressure, serum triglycerides, blood glucose, which together are part of the diagnostic criteria for metabolic syndrome, have been detected within the first 12 months postpartum[36]. Furthermore, metabolic syndrome (MetS), which is a risk factor for CVD is seen in women and children exposed to GDM[300]. Elevated peripheral blood pressure very early after pregnancy, may indicate that permanent physiological and vascular changes have already occurred, thereby increasing the risk of hypertension and premature atherosclerosis.

Offspring who are exposed to GDM *in utero* exhibit higher systolic blood pressure than their counterparts who were not exposed[299]. Staley *et al.* demonstrated blood pressure differences between offspring of women who developed hypertensive disorders of pregnancy compared to

those from normotensive mothers consistently throughout childhood and adolescence[474]. Therefore, offspring exposed to GDM *in utero* may exhibit anthropometric and/or cardiovascular changes at an earlier age.

Our primary aim was to assess cardiovascular risk factors in women with and without a history of GDM recruited from a socioeconomically disadvantaged community. Our secondary aim was to assess these risk factors in their children at age 3. As an exploratory aim, we assessed the effect of maternal early pregnancy obesity on these cardiovascular risk factors in both women with a history of GDM and their children at 3 years postpartum.

10.4. Methods

10.4.1. **Study population**

The study participants included women and their children from the Screening Tests to Predict Poor Outcomes of Pregnancy [1] study recruited in pregnancy in 2015 to 2017[1]. The STOP study was a prospective cohort study that aimed to assess and predict the risk for pregnancy complications. A total of 1,363 nulliparous women, their partners and babies were originally recruited. Majority of the participants were recruited from the Northern Adelaide Local Health Network which serves a community resident in one of the most socioeconomically disadvantaged regions in metropolitan Australia[452]. This community harbours some of the highest rates of chronic disease including diabetes, heart disease and mental illness. Women of the STOP follow-up study were contacted using phone numbers provided during the STOP study, or from hospital records. If women could not physically attend an appointment, an external participation package was posted to their address and returned via pre-paid postage. Ethics approval was granted by the Central Adelaide Local Health Network, and site-specific ethics approval was received by the Northern Adelaide Local Health Network (STOP study: (HREC/14/WCHN/90) (ACTRN12614000985684), STOP follow-up study: HREC 18/CAHLN/318).

STOP study included data of only nulliparous women collected at 9-16 and 32-36 (mean 34) weeks' gestation and following delivery of the baby. The maternal data included demography, medical history, fertility history, information on previous pregnancies, diet, exercise, work, smoking, intake of alcohol and recreational drugs, measures of stress, anxiety and depression. Socioeconomic index (SEI) was assessed using the New Zealand Socioeconomic Index

(NZSEI)[475]. Physical measurements including height, weight, waist and hip circumference, BMI and haemodynamic measurements were performed. GDM was diagnosed at 24-28 weeks' gestation according to the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria [i.e. one or more values equal to or exceeding: fasting plasma glucose of 5.1mmol/L, and/or a 2h plasma glucose level of 8.5mmol/l following a 75g Oral Glucose Tolerance Test (OGTT)][400]. Women who were at high risk of GDM also completed a 75g OGTT in their first trimester. Data collected at birth included newborn weight, length, arm circumference, birthweight centile, and data on complications during the neonatal period and type of feeding at discharge from hospital.

Women were recruited into the STOP follow-up study within 3 months (either side) of when their first child turned 3 years old. Women who lived regionally or interstate were able to consent remotely to participating in the follow-up study, with the option to complete anthropometric, haemodynamic and serum biochemistry through their general practitioner. Appointments were completed at the Clinical Trials Unit at the Lyell McEwin Hospital. Height of women and children was measured with a stadiometer to the nearest 0.1cm. Children's weight was measured with a standard balance beam scale to the nearest 100g. Body composition in women was assessed using the TANITA SC-330 bioimpedance scale (Tokyo, Japan) which measured fat mass to the nearest 0.1kg, fat percentage, fat mass, fat free mass and BMI. Body composition in children was assessed by standardized BMI score based on the Centre for Disease Control (CDC) growth charts for children and teenagers aged 2 to 19 years of age[476]. Waist circumference was measured in both women and children

to the nearest 0.5cm[477]. Peripheral systolic, diastolic and mean arterial blood pressure was assessed using the USCOM BP+ (USCOM, Sydney, Australia) using appropriately sized cuffs for arm circumference, while participants were rested for at least 20 minutes and seated. The USCOM BP+ was used to perform several non-invasive measures of cardiovascular function, including pulse rate, peripheral systolic and diastolic blood pressures, central systolic and diastolic blood pressures, which reflect blood pressure in the aorta and functionality of the heart, and augmentation index (AIx) which is an indicator of arterial stiffness and tone. The USCOM BP+ has been validated for use in adults, pregnant women, and children[478-480]. Recruited participants were excluded if the signal to noise ratio, a quality control measure of cuff reading quality was <6[479]. Women provided fasting blood samples to assess blood glucose, insulin, non-HDL lipids, HDL-cholesterol, and C-reactive protein. Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) using fasting blood glucose and fasting insulin values[481]. Metabolic syndrome status at 3 years postpartum was defined based on the International Diabetes Federation (IDF) definition[30], which requires presence of central adiposity (defined by waist circumference which are ethnicity specific (for women of all ethnicities, this is ≥80cm) and/or an obese BMI ≥30kg/m^2) and at least two of the following:

- Raised systolic blood pressure ≥130mmHg or diastolic blood pressure ≥80mmHg or treatment of previously diagnosed hypertension
- Raised serum triglycerides ≥1.7mmol/L or being on medication for increased triglycerides

- Raised fasting plasma glucose ≥5.6mmol/L or previously diagnosed type 2 diabetes mellitus
- Reduced HDL cholesterol ≤ 1.29mmol/L

10.4.2. Statistical analysis

Data was analysed using IBM SPSS Version 26. Women who were diagnosed with GDM in their index pregnancy were compared to those who were not (normoglycemic). Similarly, children who were born to mothers with GDM were compared for CVD risk factors with children who were born to mothers without GDM. Univariate analysis was used to compare anthropometric and baseline variables between GDM and normoglycemic pregnancies, with data presented as mean (SD) or n (%). Child variables were adjusted for child age, with the exception of BMI SDS as this has been adjusted for child age and sex already. As obesity is a significant predictor of both GDM and CVD[27, 482], secondary subgroup analysis was undertaken and both GDM and normoglycemic groups were stratified by obesity in early pregnancy (i.e. BMI ≥30kg/m^2) or non-obese (i.e. BMI ≤29.9kg/m^2). As the normoglycemic group includes women with other pregnancy complications that influence cardiovascular and metabolic health, to rule out any effect of these complications on the outcomes, exploratory analyses of cardiometabolic outcomes in pregnancy and 3 years postpartum were also performed in women with uncomplicated index pregnancies and their offspring.

For hemodynamic measures, blood pressure was measured in pregnant women who attended the study as per protocol. A proportion of women (n=22, 7.8%) were pregnant at the time of follow-up and these women were excluded from the descriptive analysis of hemodynamic outcomes at 3 years postpartum. Linear regression analysis was undertaken to assess the association between developing GDM in the index pregnancy, and exposure

to GDM *in utero*, and hemodynamic measurements compared to those with an uncomplicated pregnancy, with data presented as mean difference (95% CI). Adjustment was made for SEI and BMI in early pregnancy as both of these parameters influence both GDM and CVD development.

10.5. Results

10.5.1. Participant demographics

There were 1,363 women who participated in the STOP study. Figure 10.5.1.1. demonstrates the flow chart of participation in the follow-up study. There were 281 woman-child dyads who consented and participated in the follow-up study from January 2019 until June 2021. In the index pregnancy, 241 participants had a normoglycemic pregnancy and 40 participants experienced GDM. The participants who did not experience GDM (i.e. had a normoglycemic pregnancy) were comprised of women who had an uncomplicated pregnancy, or evidence of a maternal placental syndrome manifest as hypertensive disorder of pregnancy (i.e. preeclampsia or gestational hypertension), delivered preterm (<37 weeks' gestation) and/or delivered a small-for-gestational-age infant (below 10^{th} customised percentile).

There was no significant difference in BMI at 9-16 weeks' gestation nor in percentage GDM during the index pregnancy between women who participated in the follow-up study compared to those who did not. Socioeconomic index during index pregnancy was also not significantly different between all participants in the follow-up study compared to those who did not participate. However, those who attended the follow-up study who had GDM in their index pregnancy had significantly higher SEI than those with GDM who did not attend (37.1 ± 16.8 vs. 33.4 ± 12.5 p=0.001, on a scale of 10-90) (Supplementary Table 10.8.1).

Demographics of the participants who attended the 3 year follow-up are presented in Table 10.5.1.1. Of these women, those who had developed GDM had significantly higher SEI than those who did not have GDM in the index pregnancy (37.1 ± 16.8 vs. 33.3 ± 13.6 p=0.016). More women with a history of GDM had a bachelor's degree than those without GDM (p=0.001). BMI in early pregnancy was significantly higher

in the GDM participants than normoglycemic participants (30.8 ± 8.2 vs. 27.4 ± 6.8 p=0.013) (Table 10.5.1.1).

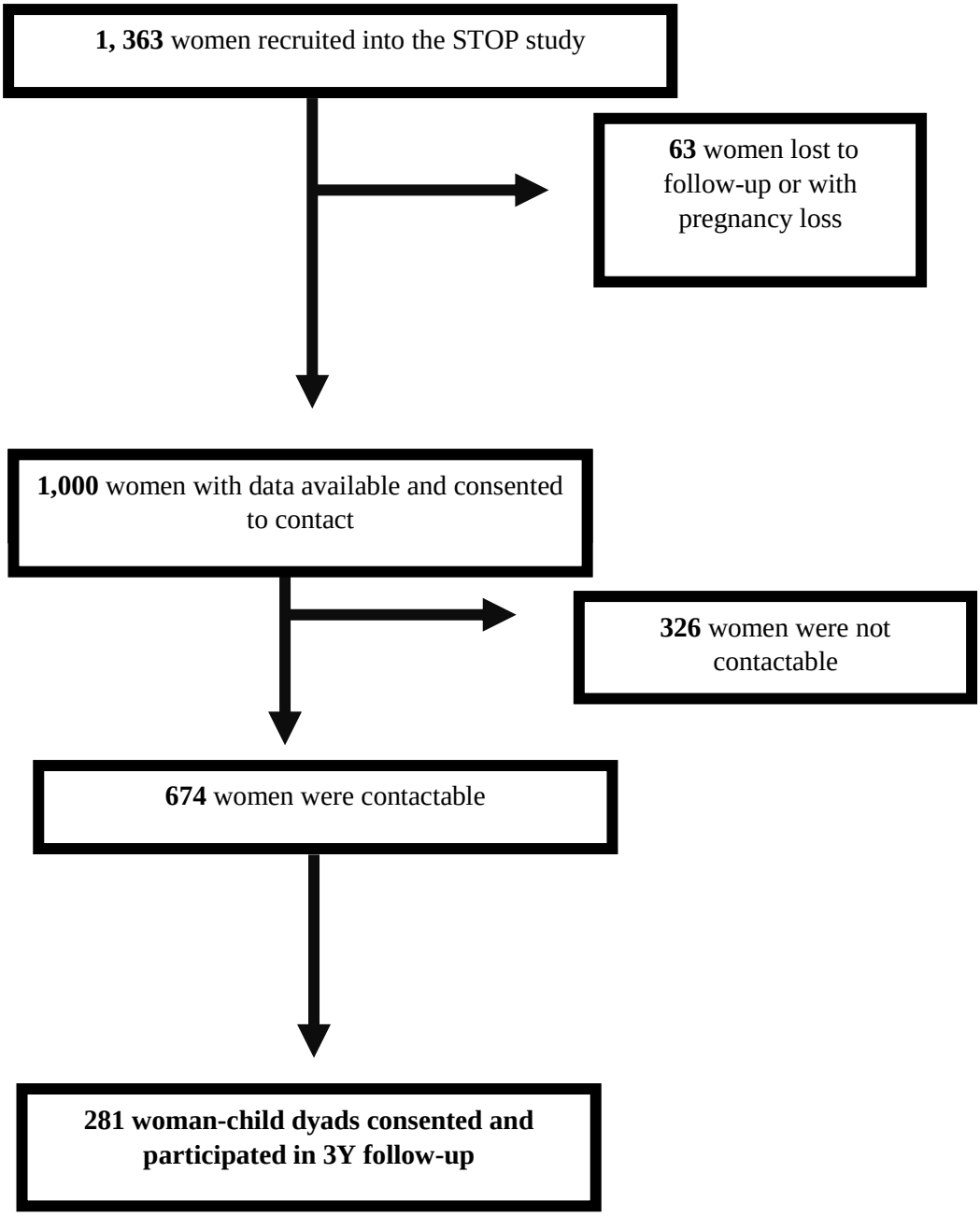


Figure 10.5.1.1 Flow chart of participant recruitment

Table 10.5.1-1 Participant Demographics at 3 year follow-up in women who participated in the STOP study and STOP 3 year Follow-Up Study

Characteristic*	**GDM (n=40)**	**Non-GDM (n=241)**	**p-value**
Index pregnancy			
Mean BMI (kg/m^2)	30.8 (8.2)	27.4 (6.8)	**0.013**
Gravidity	1.85 (0.8)	2.05 (1.0)	0.924
SEI**	37.1 (16.8)	33.3 (13.6)	**0.016**
Caucasian ethnicity (n=)	35 (87.5%)	217 (89.3%)	0.731
Education Status (n=)			**0.001**
Did not complete year 10	2 (5%)	3 (1.2%)	
Year 10	2 (5%)	17 (7%)	
Year 12	9 (22.5%)	31 (12.8%)	
Certificate	15 (37.5%)	92 (37.9%)	
Bachelor	10 (25%)	41 (16.9%)	
Higher degree	2 (5%)	7 (10%)	
Pregnancy complications experienced			
Uncomplicated	0	151 (62.1%)	**0.000**
Gestational hypertension	5 (12.5%)	13 (5.3%)	0.086
Preeclampsia	4 (10%)	25 (10.3%)	0.956
Preterm Birth	4 (10%)	10 (4.1%)	0.112
Small for gestational age	8 (20%)	29 (11.9%)	0.161
Child gestational age (weeks)	38.6 (2.1)	39.5 (1.7)	0.621
Child birthweight (g)	3202.8 (600)	3364.6 (501)	0.221
3 years postpartum			
Maternal age (years)	33 (5.6)	31 (4.9)	0.164
BMI (kg/m^2)	29.7 (7.4)	29.1 (8.5)	0.891
Waist circumference(cm)	95 (21.1)	90 (19.4)	0.463

*data are presented as Mean (SD) or *n*= (%)

**SEI is the New Zealand Socioeconomic Index on a scale of 10-90 with the lowest score indicating the person lives with the greatest disadvantage

^pregnancy complications are not mutually exclusive and participants may have experienced more than one pregnancy complication in index pregnancy

10.5.2. Cardiovascular risk factors during gestation and at 3 years postpartum:

10.5.2.1. Baseline (9-16 weeks' gestation)

Women with GDM during their pregnancy, had higher mean systolic blood pressure, diastolic blood pressure, mean arterial pressure, central systolic blood pressure and central diastolic blood pressure at 9-16 weeks' gestation compared to those who did not develop GDM in the index pregnancy (Table 10.5.2.3-1) (Supplementary Figure 10.8.1). Exploratory analysis of GDM vs. uncomplicated pregnancy showed that at 9-16 weeks' gestation, mean systolic blood pressure diastolic blood pressure mean arterial pressure central systolic blood pressure and central diastolic blood pressure were higher in those with GDM in index pregnancy compared to those with uncomplicated pregnancies (Table 10.5.2.3-1). As per protocol, fasting glucose at 28 weeks' gestation was significantly higher in women with GDM compared to those with a normoglycemic pregnancy and those with an uncomplicated pregnancy (Table 10.5.2.3-1). Metabolic syndrome was more common in women with an uncomplicated pregnancy in early pregnancy than those who developed GDM (Table 10.5.2.3-1).

10.5.2.2. 34 weeks' gestation

At 34 weeks' gestation, compared to women with uncomplicated pregnancies, women with GDM in their index pregnancy had significantly higher mean diastolic blood pressure, mean arterial pressure, central systolic blood pressure and central diastolic blood pressure (Table 10.5.2.3-1).

10.5.2.3. 3 years postpartum

Central systolic blood pressure was higher in women with a history of GDM than in those with a normoglycemic pregnancy. There were only 126 participants who completed blood collection in the follow-up study. Circulating insulin was significantly

higher in those with a history of GDM in pregnancy than those with an uncomplicated pregnancy (Table 10.5.2.3-1). There were more women with a history of GDM with elevated triglycerides (i.e. >=1.7mmol/L) compared to those without a history of GDM but this difference was not statistically significant. The percentage with metabolic syndrome was significantly higher in women with a history of GDM compared to those with an uncomplicated index pregnancy. Only one participant who had hypertension at the time of the follow-up was taking antihypertensive medication. A history of GDM was associated with a 0.3mmol/L increase in serum triglycerides at 3 years postpartum compared to history of uncomplicated pregnancy, after adjustment for covariates (Table 10.5.2.3-2).

Table 10.5.2.3-1 Cardiovascular risk factors in women at baseline (9-16 weeks'), 34 weeks' gestation and at 3 years postpartum.

Baseline visit (9-16 weeks' gestation)					
Variable	**GDM (n=40)**	**Normoglycemic pregnancy (n=241)**	**p-value**	**Uncomplicated pregnancy (n=149)**	
Peripheral systolic blood pressure (mmHg)	120.9 (14.8)	114.6 (12.2)	0.056	112.3 (11.3)	**0.013**
Peripheral diastolic blood pressure (mmHg)	72.4 (10.9)	67.7 (8.2)	**0.012**	66.3 (7.7)	**0.004**
Mean arterial pressure (mmHg)	85.9 (12.1)	80.7 (9.0)	**0.002**	79 (8.2)	**0.000**
Augmentation Index (%)	36.5 (20.2)	32.0 (14.5)	0.125	47.6 (18.1)	0.160
Central systolic blood pressure (mmHg)	111.2 (13.7)	105.5 (11.2)	0.051	103.9 (11)	**0.036**
Central diastolic blood pressure (mmHg)	76.4 (9.7)	70.7 (7.6)	**0.030**	69.1 (7.8)	**0.009**
	GDM (n= 38)	**Normoglycemic pregnancy (n= 219)**	**p-value**	**Uncomplicated pregnancy (n=142)**	**p-value**
Total cholesterol (mmol/L)	4.5 (0.7)	4.6 (0.7)	0.864	4.6 (0.7)	0.811
Triglycerides(mmol/L)	1.3 (0.5)	1.2 (0.4)	0.282	1.2 (0.5)	0.778
HDL-C(mmol/L)	1.6 (0.3)	1.6 (0.3)	0.890	1.6 (0.3)	0.784
CRP	4.8 (4.1)	5.2 (8.3)	0.383	4.3 (4.4)	0.895
Metabolic Syndrome rate	13 (35%)	48 (78.7%)	0.084	24 (64.9%)	**0.024**
Third trimester (34 weeks' gestation)					
	GDM (n=18)	**Normoglycemic pregnancy (n=130)**	**p-value**	**Uncomplicated pregnancy (n=77)**	**p-value**
Peripheral systolic blood pressure (mmHg)	125.9 (11.8)	117.8 (11.1)	0.519	114.3 (9.5)	0.117
Peripheral diastolic blood pressure (mmHg)	76.4 (9.7)	70.7 (7.6)	0.251	68.7 (6.1)	**0.030**
Mean arterial pressure (mmHg)	90.9 (10.1)	83.3 (8.3)	0.271	80.9 (6.7)	**0.032**
Augmentation Index (%)	49.6 (15.4)	48.0 (17.7)	0.065	30.5 (15.4)	0.091

Central systolic blood pressure (mmHg)	113.8 (13)	106.0 (10.2)	0.168	102.9 (8.9)	**0.028**
Central diastolic blood pressure (mmHg)	79.6 (9.8)	73.9 (7.8)	0.260	71.9 (6.4)	**0.045**
3 years postpartum					
	GDM (n=34)	**Normoglycemic pregnancy (n=202)**	**p-value**	**Uncomplicated pregnancy (n=138)**	**p-value**
Peripheral systolic blood pressure (mmHg)	121.2 (15.3)	120.6 (13.2)	0.270	119.4 (13.8)	0.487
Peripheral diastolic blood pressure (mmHg)	70.6 (12.3)	67.3 (11.2)	0.428	66.8 (12.3)	0.947
Mean arterial pressure (mmHg)	85 (14.4)	82.5 (11.7)	0.078	81.6 (12.3)	0.250
Augmentation Index (%)	52.5 (15.1)	55.3 (23.1)	0.076	53.5 (24.1)	0.078
Central systolic blood pressure (mmHg)	110.2 (16.6)	110.6 (12.4)	**0.046**	109.5 (13.2)	0.174
Central diastolic blood pressure (mmHg)	73.3 (12.7)	70.7 (10.6)	0.231	70 (11.5)	0.714
	GDM (n= 16)	**Normoglycemic pregnancy (n= 66)**	**p-value**	**Uncomplicated (n=44)**	**p-value**
Fasting glucose(mmol/L)	4.8 (0.4)	4.6 (0.4)	0.995	4.4 (0.9)	0.686
Insulin (mU/L)	13.2 (9.5)	9.4 (6.1)	0.660	8.6 (5.0)	**0.022**
HOMA-IR	2.80 (2.2)	1.97 (1.3)	0.065	2.7 (6.4)	0.692
Triglycerides(mmol/L)	1.2 (0.6)	1.1 (0.6)	0.851	0.89 (0.4)	0.055
HDL-C(mmol/L)	1.4 (0.4)	1.4 (0.4)	0.638	2.6 (0.5)	0.722
LDL-C(mmol/L)	2.7 (0.5)	2.7 (0.7)	0.141	2.6 (0.5)	0.085
Total Cholesterol/HDL ratio	3.6 (1.0)	4.0 (3.9)	0.400	3.2 (0.7)	0.115
Non-HDL Cholesterol	3.3 (0.5)	3.1 (0.8)	0.067	3.1 (0.9)	0.686
Total Cholesterol(mmol/L)	4.7 (0.6)	5.2 (0.5)	0.367	4.5 (0.9)	0.174
CRP (mmol/L)	4.02 (3.6)	6.52 (19.1)	0.311	6.7 (20.9)	0.323
Assessment of metabolic syndrome components in women at 3 years postpartum					
	GDM (n=16)	**Normoglycemic pregnancy (n=66)**	**p-value**	**Uncomplicated (n=44)**	**p-value**
Abdominal obesity**	25 (62.5%)	128 (54%)	0.270	75 (53.1%)	0.738
Hypertension***	13 (32.5%)	53 (22.3%)	0.147	32 (21.9%)	0.137
Dysglycaemia^	1 (2.5%)	2 (0.8%)	0.341	0	0.159
Triglycerides >= 1.7mmol/L	3 (7.5%)	6 (2.5%)	0.096	4 (2.7%)	0.721
Reduced HDL < 1.29mmol/L	6 (15%)	28 (11.8%)	0.487	16 (10.9%)	0.759

Metabolic syndrome rate	26 (61%)	130 (50.1%)	0.192	3 (6%)	**0.000**

NB: Postpartum numbers for blood results and metabolic syndrome cases are reduced due to non-compliance or being pregnant during follow-up.
*results are reported as mean (SD) unless stated otherwise
**Abdominal obesity was waist circumference >=80cm and/or obese BMI >=30kg/m^2)
***Hypertension was defined as raised systolic blood pressure >=130mmHg or diastolic blood pressure or treatment of previously diagnosed hypertension)
^Dysglycaemia was defined as raised fasting plasma glucose >=5.6mmol/L or previously diagnosed type 2 diabetes mellitus
Normoglycemic pregnancy includes those with other pregnancy complications including preeclampsia, gestational hypertension, spontaneous preterm birth and small for gestational age

Table 10.5.2.3-2 Linear regression to assess association between GDM in pregnancy compared to uncomplicated pregnancy and subsequent cardiometabolic risk factors in mothers and children at 3 years post-pregnancy

Outcomes	**Adjusted Mean Difference (95% CI)***
Child waist circumference at 3 years**	1.9 (0.41 to 3.3)
Maternal Serum triglycerides at 3 years postpartum	**0.3 (0.07 to 0.6)**
Maternal Serum insulin at 3 years postpartum	1.9 (-1.5 to 5.2)

*adjusted for maternal BMI at booking and SEI
**also adjusted for child age
Bold indicates statistical significance

10.5.3. **Cardiovascular risk factors in children aged 3 years**

Waist circumference was significantly greater in children exposed to GDM *in utero* compared to those who were born to mothers with a normoglycemic pregnancy and those born to mothers with an uncomplicated pregnancy. However, this was attenuated by maternal BMI and SEI at early pregnancy. Peripheral and central blood pressures and vascular stiffness were similar in all groups of children (Table 10.5.3.1).

Table 10.5.3-1 Cardiometabolic differences between children born to mothers with gestational diabetes mellitus compared to those who were not at 3 years postpartum

3 years follow-up					
	Children born to mothers with GDM (n=33)	**Children born to mothers with normoglycemic pregnancy (n=198)**	**p-value***	**Children born to mothers with uncomplicated pregnancies (n=144)**	**p-value***
BMI SDS^	67 (28.7)	56.5 (30.7)	0.192	50.8 (32.6)	0.097
Waist circumference (cm)	53.6 (5)	51 (3.7)	**0.001**	51.2 (3.5)	**0.02**
	(n=18)	**(n=107)**		**(n=94)**	
Systolic blood pressure (mmHg)	96.3 (18.6)	99.4 (14.0)	0.649	101.2 (13.1)	0.521
Diastolic blood pressure (mmHg)	56.1 (10.9)	57.7 (12)	0.905	57.0 (12.4)	0.826
Mean arterial pressure (mmHg)	69.0 (14.1)	71.3 (14.9)	0.842	72 (15.2)	0.889
Augmentation Index (AIx) (%)	89.6 (56.9)	82.5 (30.7)	0.979	89.1 (45)	0.914
Central systolic blood pressure (mmHg)	89.6 (15.3)	92.5 (15.2)	0.521	95.1 (15.6)	0.329
Central diastolic blood pressure (mmHg)	61.3 (10.4)	60.8 (11.1)	0.430	61.2 (12.0)	0.318

Reduced numbers for hemodynamic assessment due to non-compliance
Results are mean (SD) unless reported otherwise
*all outcomes except BMI SDS are corrected for child age
^BMI SDS is adjusted for child age and sex

10.5.4. Effect of obesity in early pregnancy on CVD risk factors in women and children

10.5.4.1. 9-16 weeks' gestation

Amongst those who had a normoglycemic pregnancy, obese women had higher systolic blood pressure and mean arterial pressure than those who were not obese (Supplementary Table 10.8.2).

10.5.4.2. 34 weeks' gestation

Augmentation Index was significantly higher at 34 weeks' gestation in the obese women in the GDM group than in non-obese women with GDM. For those with a normoglycemic pregnancy, women who were obese had significantly higher systolic blood pressure, diastolic blood pressure, and mean arterial pressure, than those who were non-obese (Supplementary Table 10.8.2).

10.5.4.3. 3 years postpartum

Augmentation index at 3 years postpartum in women with uncomplicated pregnancies was higher in those who were obese in early pregnancy compared to those who were not obese at the same timepoint. Those who were obese in the GDM group had significantly higher serum insulin, insulin resistance (HOMA-IR), LDL-C, and CRP, than those who were not obese. For those with a normoglycemic pregnancy, women who were obese in early pregnancy had significantly higher serum insulin, insulin resistance, total cholesterol/HDL ratio, and CRP than those who were not obese in early pregnancy. For women with an uncomplicated index pregnancy, those who were obese had significantly higher serum insulin, insulin resistance, and CRP levels at 3 years postpartum than women who were not obese in early pregnancy (Supplementary Table 10.8.2).

10.5.4.4. Children aged 3

Children born to obese mothers with a normoglycemic pregnancy had higher diastolic blood pressure than those who were born to non-obese mothers. Children born to obese mothers with a normoglycemic pregnancy had a significantly higher waist circumference than children born to non-obese mothers with a normoglycemic pregnancy. Children born to obese mothers with an uncomplicated pregnancy had significantly higher BMI-SDS and waist circumference than those children born to non-obese mothers with an uncomplicated pregnancy at 3 years of age (Supplementary Table 10.8.2).

10.6. Discussion

Our observational follow up study revealed that women with a history of GDM had higher serum insulin and triglycerides at 3 years postpartum compared to those with no history of GDM. However, the association between GDM and insulin was attenuated by maternal BMI and SEI in early pregnancy. Children exposed to GDM *in utero* had significantly higher waist circumference than children born to women with uncomplicated pregnancies but this was attenuated for the same covariates. There were more women with a history of GDM who had metabolic syndrome at 3 years postpartum than those with uncomplicated pregnancy. Our subgroup analysis showed differences in hemodynamic and serum values between participants who were and were not obese in pregnancy at 3 years postpartum in women with a history of GDM, a history of normoglycemic pregnancy and a history of uncomplicated pregnancy.

Obesity promotes development of insulin resistance and increases in free fatty acids and inflammatory markers [7, 483]. In mid to late pregnancy, placental inflammatory hormones together with inflammation due to obesity, increase oxidative stress in pancreatic beta cells which impairs compensatory insulin secretion that counteracts elevated insulin resistance leading to GDM [7, 483]. There is discrepancy between studies regarding whether serum insulin levels are higher in women with previous GDM [471, 484] or if it is similar to controls [485, 486 487]. A previous study assessed obese and non-obese women at 1 year postpartum and found that the relationship between GDM and serum insulin postpartum was mediated by obesity[484]. Our subgroup analysis showed that obese women in GDM, normoglycemic and uncomplicated groups had elevated CRP, an inflammatory marker and insulin resistance. Therefore, being obese, together with history of GDM, may actually worsen metabolic health at an earlier time postpartum.

The elevation of serum triglycerides at 3 years postpartum in women with a history of GDM supports that found in other studies. It has previously been shown that women at 3.5 years postpartum following GDM, had increased adjusted odds ratios for hypertriglyceridemia compared to those without a history of GDM[488]. Furthermore, our 2020 systematic review found that serum triglycerides were elevated as early as <1 year postpartum in women who had been diagnosed with GDM[36]. Elevated serum triglycerides can be apparent 10 years before diagnosis of T2DM[489] and therefore may identify women who will develop T2DM later as glucose intolerance is associated with altered uptake of fatty acids. Our data support the need for early follow-up of metabolic health including serum lipids and glucose tolerance in women with a history of GDM.

We found that 3 year old children who were exposed to GDM *in utero* exhibit higher waist circumference than those whose mothers had an uncomplicated pregnancy; however, this was mediated by maternal BMI and SEI during early pregnancy. Previous literature has shown an association between maternal GDM and childhood obesity. A recent report showed that maternal glucose levels and BMI during pregnancy were independently associated with BMI, body fat and waist circumference in their exposed children at 11 years of age [490]. However, combined exposure *in utero* increased the risk of obesity in the offspring further. If there is an effect of GDM on childhood adiposity at 3 years of age, it is likely that our study was underpowered to assess this and further studies are required to look at this association.

This observational follow-up study has some strengths. The inclusion and exclusion criteria of the original STOP study were quite strict. Including only nulliparous women in the cohort allowed us to assess the effect of pregnancy complications without confounding by greater parity. Furthermore, women with serious medical conditions or at high risk for pregnancy complications due to underlying conditions were also excluded. Therefore, the effect of pregnancy complications on maternal health could be assessed in young women. This cohort

of women is generally overlooked in cardiovascular risk assessment. Risk for heart attack statistical models are usually targeted to an older age group and based primarily on risk factors common in men. We were able to assess haemodynamic and metabolic risk factors non-invasively in women in both early and late pregnancy and at 3 years postpartum, allowing a complete assessment of cardio-metabolic health from conception to the early postpartum period. Furthermore, we were able to assess haemodynamics in their children at 3 years of age. These non-conventional vascular assessments have seldom been reported in the literature for women, and particularly in early childhood. Our data, despite coming from a small cohort, contribute to the growing evidence on vascular health, and how it can be perturbed by pregnancy complications, in young mothers and their children.

Cohort studies often include participants with moderate to high SES. Our study assessed women and children from a hospital servicing a disadvantaged population. As for all populations studied, elevated BMI reduces cardio-metabolic health. Our study has highlighted the impact of socioeconomic disadvantage on cardiovascular risk factors in young women and their children. The high incidence of obesity in early pregnancy in participants in the STOP Study makes it possible that many of these women may have entered pregnancy with undiagnosed insulin resistance and glucose intolerance making a diagnosis of GDM more likely. We recommend future larger studies in women and young children in disadvantaged communities to confirm or refute our findings. If socioeconomically disadvantaged women with GDM are shown to be at higher risk of cardio-metabolic disorders in the early postpartum period, non-invasive haemodynamic and simple biochemical screening could be a means to identify those who would benefit from early intervention.

Our study has some limitations. Approximately one quarter of participants from the original STOP study attended the 3-year follow-up. Majority of this loss is due to loss of contact. Indeed 42% of the women who were contactable agreed to participate. The difficulties associated with

living with disadvantage, reduce the likelihood that such a population will participate in clinical research[491]. Therefore, there may be risk of selection bias in our study. Although we have shown statistically significant differences in some parameters these are relatively small. This may simply reflect the fact that 3 years postpartum may be very early in the progression to CVD. Nevertheless, these small metabolic changes may amplify over time.

We were unable to assess any potential paternal effects on child development and metabolic health. It is well established that paternal obesity mediates epigenetic programming through transmission of epigenetic factors through sperm[492]. It has been shown that high fat diets in mice promoted hyperglycaemia in female pups, due to epigenetic changes in germ cells, specifically of methylation of insulin growth factor 2 (IGF-2)/H19 loci and imprinting. Therefore, future studies should assess both epigenetic and lifestyle factors from both parents to ascertain child metabolic health[493].

Furthermore, the observational nature of the study means that we cannot infer causality. Although we recruited 281 participants, there were only 82 women who completed a fasting blood test, and some data are missing for anthropometric and hemodynamic measures in the offspring due to non-compliance. Missing data for fasting serum parameters may mean that the rate of metabolic syndrome in the cohort could be underreported. Some women who attended the follow-up were pregnant (n=22, 7.8%) and therefore 3 years postpartum data were missing for these participants. We recommend further longitudinal assessments in a larger, better powered cohort to determine whether anthropometric, haemodynamic and metabolic changes exacerbate in the long term.

10.7. Conclusion

Cardiovascular risk factors in women with a history of GDM and their offspring are present at 3 years after delivery, with maternal BMI and SEI in early pregnancy either mediating or

attenuating these associations. Our data warrant larger, more highly powered and longitudinal studies of cardiometabolic health in women and children exposed to GDM. Our study suggests that early interventions for socioeconomically disadvantaged young women and children may be important to improving long term health in communities that are known to have high rates of chronic diseases.

10.8. Supplementary Data

Supplementary Table 10.8 1 Differences in attendees and non-attendees for STOP 3 year follow-up

All participants		
	Mean (SD)	P value
NZSEI	Attended: 33.8 (14.0) Did not attend: 32.7 (13.9)	0.172
Age (years)	Attended: 31.2 (5.0) Non attendee: 29.6 (6.7)	0.387
Booking BMI (kg/m2)	Attended: 27.8 (7.2) Did not attend: 28 (7.1)	0.648
GDM participants only		
NZSEI	Attended: 36.9 17.3 Non attendee: 33.4 12.5	0.002
Booking BMI (kg/m2)	Attended 31 8.3 Did not attend: 32.1 8.8	0.697

Supplementary Table 10.8 2 Subgroup analysis of obesity at index pregnancy on cardiovascular risk factors in women and children

Baseline visit (9-16 weeks' gestation)									
Variable	**GDM (n=40)**			**Normoglycemic pregnancy (n=241)**			**Uncomplicated (n=151)**		
	Obese (n=21)	**Non-obese (n=19)**	**p-value**	**Obese (n=62)**	**Non-obese (n=179)**	**p-value**	**Obese (n=27)**	**Non-obese (n=124)**	**p-value**
Peripheral systolic blood pressure (mmHg)	127.5 (13.8)	113.6 (12.6)	0.173	122.4 (12.8)	111.8 (10.8)	**0.034**	119.0 (11.7)	110.9 (10.6)	0.425
Peripheral diastolic blood pressure (mmHg)	77.5 (11.1)	66.9 (7.7)	0.124	72.5 (9.3)	66.1 (7.2)	0.052	71 (8.5)	65.3 (7.1)	0.512
Mean arterial pressure (mmHg)	91.6 (11.8)	79.5 (9.0)	0.214	86.6 (10.2)	78.6 (7.7)	**0.014**	85 (8.3)	77.7 (7.6)	0.463
Augmentation Index (%)	50.1 (16.7)	49.2 (14.3)	0.344	43.8 (16.1)	49.5 (18)	0.101	43.2 (18.1)	48.6 (17.9)	0.584
Central systolic blood pressure (mmHg)	117.2 (12.7)	104.5 (11.6)	0.610	111.6 (11.4)	103.4 (10.4)	0.161	109 (10.9)	102.2 (10.7)	0.696
Central diastolic blood pressure (mmHg)	80.4 (10.9)	69.8 (7.6)	0.148	75.7 (9.4)	69 (7.4)	0.106	73.4 (8.5)	67.8 (7.2)	0.557
	Obese (n=20)	**Non-obese (n=17)**	**p-value**	**Obese (n=25)**	**Non-Obese (n=117)**	**p-value**	**Obese (n=25)**	**Non-obese (n=117)**	**p-value**
Total cholesterol (mmol/L)	4.7 (0.8)	4.4 (0.6)	0.446	4.7 (0.5)	4.6 (0.8)	0.055	4.7 (0.5)	4.6 (0.8)	0.055
Triglycerides(mmol/L)	1.4 (0.6)	1.3 (0.4)	0.119	1.2 (0.4)	1.2 (0.5)	0.509	1.2 (0.4)	1.2 (0.5)	0.509
HDL-C(mmol/L)	1.5 (0.3)	1.7 (0.3)	0.671	1.5 (0.3)	1.6 (0.3)	0.537	1.5 (0.3)	1.6 (0.3)	0.537
Third trimester (34 weeks' gestation)									
	GDM (n=18)			**Normoglycemic pregnancy (n=130)**			**Uncomplicated (n=77)**		
	Obese (n=11)	**Non-obese (n=7)**	**p-value**	**Obese (n=35)**	**Non obese (n=95)**	**p-value**	**Obese (n=14)**	**Non-obese (n=63)**	**p-value**

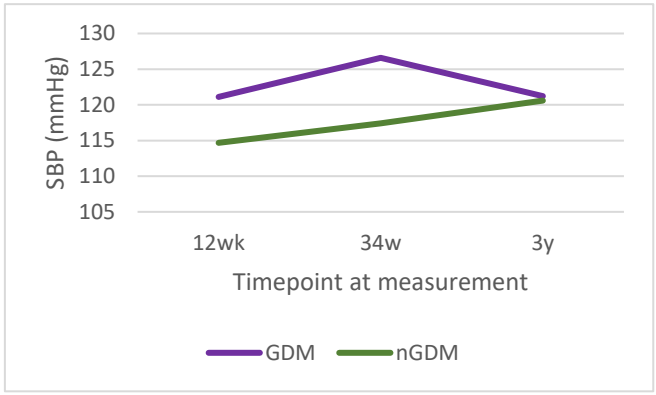
Peripheral systolic blood pressure (mmHg)	129.8 (9.6)	119.9 (13)	0.699	126.4 (11.1)	114.6 (9.3)	**0.042**	122.3 (9.3)	112.6 (8.7)	0.595
Peripheral diastolic blood pressure (mmHg)	77.6 (7.8)	74.6 (12.6)	0.350	74.5 (9.3)	69.3 (6.4)	**0.004**	71.6 (6.5)	68.1 (5.9)	0.483
Mean arterial pressure (mmHg)	92.4 (8.2)	88.7 (13)	0.589	88.5 (9.8)	81.4 (6.9)	**0.012**	84.9 (7.5)	80 (6.3)	0.322
Augmentation Index (%)	34.9 (14.2)	39 (28.5)	**0.049**	33.9 (16.1)	31.3 (14)	0.674	28.4 (14.5)	(31 (14.7)	0.844
Central systolic blood pressure (mmHg)	117.3 (10)	108.6 (15.9)	0.673	113.6 (10.3)	103.3 (8.8)	0.065	109.9 (8.7)	101.4 (8.2)	0.841
Central diastolic blood pressure (mmHg)	81.0 (8.1)	77.4 (12.3)	0.483	78.1 (9.3)	72.3 (6.6)	**0.006**	75.2 (6.8)	71.1 (6.2)	0.496
3 years postpartum (women)									
	GDM (n=38)			**Normoglycemic pregnancy (n=202)**			**Uncomplicated (n=137)**		
	Obese (n=20)	**Non-obese (n=14)**	**p-value**	**Obese (n=53)**	**Non-obese (n=149)**	**p-value**	**Obese (n=26)**	**Non-obese (n=111)**	**p-value**
Peripheral systolic blood pressure (mmHg)	127.0 (15.7)	113 (10.6)	0.251	125.9 (14.8)	118.7 (12.2)	0.268	125.8 (16.3)	117.3 (12.1)	0.127
Peripheral diastolic blood pressure (mmHg)	74.5 (13.1)	65.5 (8.9)	0.203	72 (12.1)	66.2 (10.5)	0.217	71.5 (12.8)	65.3 (11.4)	0.562
Mean arterial pressure (mmHg)	91.2 (14.6)	76.3 (8.9)	0.090	88 (12.8)	80.5 (10.6)	0.135	88.6 (12.1)	79.5 (11.3)	0.691
Augmentation Index (%)	56.1 (13.1)	47.2 (16.7)	0.511	58.9 (29.3)	54.0 (20.5)	0.150	59.4 (35.7)	52.1 (20.5)	**0.040**
Central systolic blood pressure (mmHg)	115.7 (18.2)	102.8 (10.7)	0.274	115.5 (13.5)	108.9 (11.6)	0.356	115.1 (15.3)	107 (11.9)	0.280
Central diastolic blood pressure (mmHg)	77.3 (14)	68.2 (8.8)	0.083	74.9 (12.1)	69.2 (9.6)	0.093	74.8 (13.4)	68.4 (10.5)	0.182

	GDM (n= 16)			Normoglycemic pregnancy n= 69)			Uncomplicated (n=41)		
Characteristic	**Obese (n=10)**	**Non-obese (n=6)**	**p-value**	**Obese (n=24)**	**Non-Obese (n=45)**	**p-value**	**Obese (n=9)**	**Non-obese (n=32)**	**p-value**
Insulin (mU/L)	16.7 (10.9)	7.9 (2.8)	**0.022**	13.5 (7.11)	7.4 (3.9)	**0.004**	14.3 (7.2)	7.1 [26]	**0.000**
HOMA-IR	3.6 (2.5)	1.7 (0.6)	**0.032**	4.7 (8.8)	1.5 (0.9)	**0.009**	7.4 (13.3)	1.4 (0.6)	**0.000**
Triglycerides(mmol/L)	1.4 (0.4)	1.3 (0.6)	0.385	1.4 (0.8)	0.87 (0.4)	**0.000**	1.2 (0.4)	0.8 (0.3)	0.815
HDL-C(mmol/L)	1.3 (0.4)	1.5 (0.4)	0.968	1.3 (0.8)	1.4 (0.3)	0.238	1.3 (0.3)	1.4 (0.3)	0.803
LDL-C(mmol/L)	2.7 (0.6)	2.7 (0.1)	**0.046**	2.9 (0.6)	2.6 (0.7)	0.476	3.1 (0.9)	2.5 (0.7)	0.640
Total Cholesterol/HDL ratio	3.8 (1.1)	3.3 (0.7)	0.437	5.1 (5.8)	3.3 (0.8)	**0.015**	3.6 (0.6)	3.1 (0.7)	0.631
Non-HDL Cholesterol	3.4 (0.7)	3.2 (0.2)	0.071	3.6 (0.9)	3.0 (0.8)	0.676	3.8 (1)	2.9 (0.8)	0.329
Total Cholesterol(mmol/L)	4.7 (0.6)	4.8 (0.4)	0.396	5.1 (5.8)	3.2 (0.9)	0.634	5.0 (1.2)	4.3 (0.8)	0.389
CRP (mmol/L)	5.4 (4)	1.9 (1.2)	**0.048**	11.7 (29.8)	3.4 (5.5)	**0.026**	19.5 (43)	2.5 (2.6)	**0.001**
3 years post pregnancy (children)									
	Children born to mothers with GDM (n=33)			**Children born to mothers with normoglycemic pregnancy (n=220)**			**Children born to mothers with uncomplicated pregnancy (n=121)**		
	Obese (n=18)	**Non-obese (n=18)**	**p-value***	**Obese (n=56)**	**Non-obese (n=164)**	**p-value***	**Obese (n=22)**	**Non-obese (n=99)**	**p-value***
BMI SDS ^	70.5 (32.4)	58.3 (27.4)	0.221	64.7 (30)	50.8 (31.3)	0.209	65.2 (32.3)	48 (32.1)	**0.005**
Waist circumference	55.4 (5.4)	52.1 (4.1)	0.079	52.5 (3.8)	50.6 (3.7)	**0.01**	53.4 (3.7)	50.7 (3.3)	**0.001**
	(n=8)	**(n=14)**		**(n=43)**	**(n=113)**		**(n=16)**	**(n=73)**	
Systolic blood pressure (mmHg)	100.3 hi(14.3)	98.2 (18.3)	0.929	101.6 (14.2)	100.1 (14.6)	0.666	102.50 (12.4)	100.7 (13.4)	0.579
Diastolic blood pressure (mmHg)	59 (7.6)	58 (14)	0.739	60.3 (13)	57.1 (16.2)	0.171	58.2 (10.5)	57.7 (12.8)	0.836
Mean arterial pressure (mmHg)	79.3 (19.1)	68.9 (15)	0.152	75.1 (15.6)	70.4 (15)	0.108	73.6 (12.8)	71.6 (15)	0.575
Augmentation Index (%)	86.4 (33.6)	89.7 (62.5)	0.934	84.4 (46.1)	90.1 (39.7)	0.540	91.9 (61.8)	59.4 (41.6)	0.756

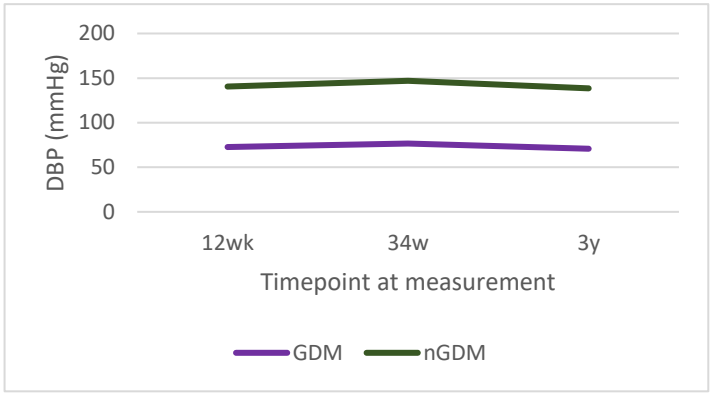
Central systolic blood pressure (mmHg)	91.2 (12.8)	92.1 (15.2)	0.894	95.3 (15.2)	93.3 (15.2)	0.512	98.8 (22.5)	94.3 (13.8)	0.294
Central diastolic blood pressure (mmHg)	65.8 (15.2)	63.3 (13.3)	0.986	66.2 (14.5)	60 (11.8)	**0.010**	63.2 (13.4)	60.7 (11.8)	0.482

Results are mean (SD) unless otherwise stated

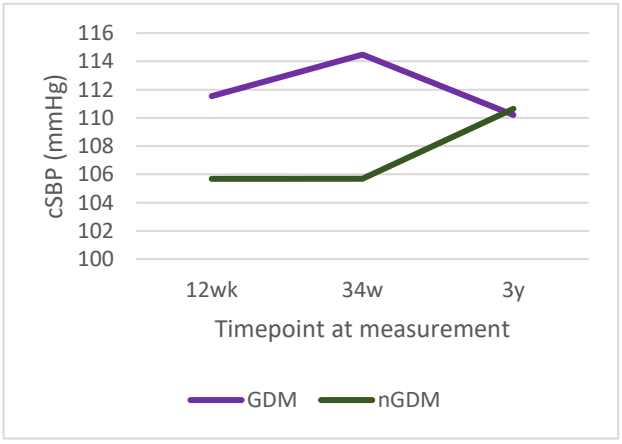
A



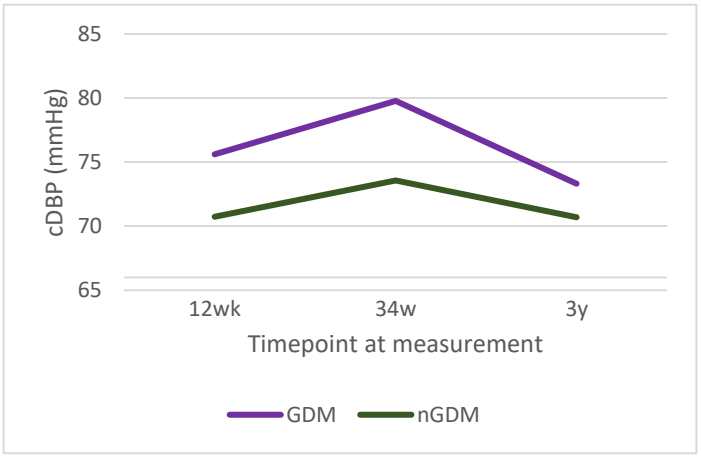
B



C



D



Supplementary Figure 10.8 1 Means of peripheral and central measures at 12 weeks' gestation, 34 weeks' gestation and 3 years postpartum for women with a history of gestational diabetes mellitus (GDM) and those without a history of gestational diabetes mellitus (nGDM)**.** SBP – systolic blood pressure, DBP – diastolic blood pressure, cSBP – central systolic blood pressure, cDBP – central diastolic blood pressure

Chapter 11

11. The influence of breast feeding for at least 6 months on haemodynamic and metabolic health of women and their children aged 3 years

Maleesa M Pathirana, Prabha H Andraweera, Emily Aldridge, Madeline Harrison, Jade Harrison, Shalem Leemaqz, Margaret A Arstall, Gustaaf Dekker, Claire T Roberts

11.1.Statement of Authorship

Title of Paper	The effect of breast feeding on haemodynamic and metabolic health of women who experience major pregnancy complications and their children
Publication Status	Submitted for consideration of publication in *International Breastfeeding Journal*
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Ethics submission, recruitment, site specific administration, undertaking assessments with participants, data collection, analysis of results, interpretation of results, writing of manuscript.
Overall Percentage (%)	80%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature	**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Prabha H Andraweera	
Contribution to the Paper	Designed protocol, ethics submission, contributed to manuscript and supervision	
Signature		**Date 28/02/2022**

Name of Co-Author	Emily Aldridge	
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, contributed to manuscript and technical advice.	
Signature		**Date 14/02/2022**

Name of Co-Author	Shalem Leemaqz	
Contribution to the Paper	Statistical analysis assistance, contributed to manuscript and technical advice.	
Signature		**Date 23/02/2022**

Name of Co-Author	Madeline Harrison	
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, reviewed manuscript	
Signature		**Date 15/02/2022**

Name of Co-Author	Jade Harrison
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, reviewed manuscript

Signature		**Date 15/02/2022**

Name of Co-Author	Margaret A Arstall	
Contribution to the Paper	Conceived and designed protocol, assisted with data interpretation, contribute to manuscript and technical advice. Provided clinical guidance from cardiology perspective	
Signature		**Date 28/02/2022**

Name of Co-Author	Gustaaf A Dekker.	
Contribution to the Paper	Conceived and designed protocol, recruited women into original STOP study, contributed to manuscript and provided clinical guidance from obstetrics perspective	
Signature		**Date 28/02/2022**

Name of Co-Author	Claire Roberts	
Contribution to the Paper	Conceived and designed protocol and original STOP study, contributed intellectually to manuscript and supervised.	
Signature		**Date 28/02/2022**

11.2. Abstract

Introduction: Breastfeeding has mutual benefits for both mother and child in reducing risk of future cardiovascular disease. Pregnancy complications, which affect nearly 1/3 of Australian pregnancies, increase the risk of type 2 diabetes mellitus and cardiovascular disease in both mothers and children. The aim of this study was to assess the influence of breastfeeding for at least 6 months on cardiovascular and metabolic risk among women and their children 3 years postpartum. A secondary aim was to assess whether there was a difference in these cardiometabolic outcomes in women who experienced at least one pregnancy complication in their index pregnancy.

Methods: Women were recruited to the Screening Tests to Predict Poor Outcomes of Pregnancy study from 2015 to 2017. These women and their children were invited to attend a health check-up at 3 years postpartum. Women's breastfeeding status for at least 6 months postpartum was ascertained through their child health record. Anthropometric measurements were taken from women and children. USCOM BP+ was used to assess haemodynamic parameters non-invasively in women and children. A fasting blood sample was taken from women to measure blood glucose and lipids.

Results: A total of 160 woman-child dyads were assessed in this study. Women in their index pregnancy experienced an uncomplicated pregnancy or a complicated pregnancy (comprised of complications including gestational diabetes mellitus, preeclampsia, and gestational hypertension, delivering preterm or delivery of a small for gestational age baby). Data from 160 women who had an adequate child health record were analysed for this study. Women who breastfed for at least 6 months had significantly lower serum insulin (8.1 mU/L ± 6.6 vs. 13.2mU/L ±7 p=0.001), insulin resistance (HOMA-IR 1.7 ± 0.6 vs. 2.8 ±02.1 p=0.000) compared to those who did not breastfeed for at least 6 months. However, this association was

attenuated for BMI and socioeconomic index in early pregnancy. There were no differences in child anthropometric or hemodynamic variables at 3 years of age between those children who had been breastfed for at least 6 months and those who had not been. Subgroup analysis on women who had one or more pregnancy complications during the index pregnancy demonstrated that women who breastfed for at least 6 months had significantly lower insulin (7.5mmol/L ± 2.1 vs. 16.5 ± 10.2 p=0.001), insulin resistance (1.6 ± 0.5 vs. 3.5 ± 2.2 p=0.001) and triglycerides (1.0mmol/L ± 0.5 vs. 1.6mmol/L ± 0.8 p=0.004) than those who did not. Among children exposed to at least one pregnancy complication *in utero*, those who were breastfed for at least 6 months had significantly lower standardized BMI score (BMI-SDS) than those who were not (58.8 ± 27.3 vs. 56.2 ± 32, p=0.046).

Conclusion: Breastfeeding for at least 6 months may reduce some cardiovascular risk factors in women at 3 years postpartum, in particular in those who have experienced a complication of pregnancy. Breastfeeding for at least 6 months may be beneficial for offspring of mothers who experienced a pregnancy complication.

11.3. Introduction

Pregnancy complications, such as gestational diabetes mellitus (GDM), preeclampsia, gestational hypertension, spontaneous preterm birth (sPTB), and small-for-gestational-age delivery, affect approximately 30% of all pregnancies in Australia. There is ample evidence suggesting that major pregnancy complications, including preeclampsia and gestational diabetes, confer increased risk for later life cardiovascular disease (CVD) [35, 227, 494]. Pregnancy complications also have long lasting implications for the offspring, likely through epigenetic changes in response to an adverse intrauterine environment [495-497]. These changes, which may be protective *in utero,* confer risk in the postnatal environment, and increase risk for development of components of the metabolic syndrome at an earlier age in offspring [48].

Breastfeeding is mutually beneficial for both mother and child, with human milk considered "the gold standard for infant feeding" [397]. The World Health Organisation recommends breastfeeding exclusively for up to 6 months [498]. It has been shown that breastfeeding for over 12 months promotes a significant reduction in both chronic hypertension and diabetes in women [59]. Breastfeeding also provides adequate nutrition to children and decreases the risk of developing obesity and T2DM compared to those who are not breastfed [429].

A recent systematic review and meta-analysis demonstrates that women with a history of GDM who breastfeed have reduced blood glucose and decreased risk of developing type 2 diabetes mellitus [499]. Despite the benefits shown for women with a history of GDM, there were not enough studies that directly assessed cardiovascular risk factors in offspring exposed to GDM *in utero* who were breastfed compared to those that were not breastfed. Furthermore, there is still minimal evidence on whether breastfeeding is beneficial for both women and children who have been exposed to other pregnancy complications such as hypertensive disorders of

pregnancy. One systematic review in 2019 found that breastfeeding was beneficial in reducing metabolic and cardiovascular risk in offspring born small for gestational age [500].

Therefore, the aim of this study is to assess the influence of breastfeeding for at least 6 months on cardiovascular and metabolic risk factors in mothers and their children at 3 years postpartum. Our secondary aim is to assess the same cardiometabolic outcomes and the influence of breastfeeding in a subgroup of women who experienced at least one pregnancy complication in their index pregnancy.

11.4. Methods

11.4.1. Study population

The study participants included women and their children from the Screening Tests to Predict Poor Outcomes of Pregnancy [1] study. The STOP study was a prospective cohort study that aimed to assess women's risk for pregnancy complications. A total of 1,383 nulliparous women, their partners and babies were originally recruited during the period 2015-2017. Majority of the participants were recruited from The Lyell McEwin Hospital in northern Adelaide, which services one of the most socioeconomically disadvantaged regions in metropolitan Australia. This area harbours some of the highest rates of chronic disease, diabetes, heart disease and mental illness in Australia/South Australia [72, 452]. For the STOP follow-up study, women were contacted using phone numbers provided during the STOP study, or from hospital records. If women could not physically attend an appointment, an external participation package was posted to their address and returned via paid postage. Ethics approval was granted by the Central Adelaide Local Health Network (STOP study: HREC/14/WCHN/90; STOP follow-up: HREC 18/CAHLN/318) (ACTRN12614000985684).

In the original STOP study, detailed information was collected at 9-16 weeks' (average 11 weeks'), and 34 weeks' gestation and after delivery of the baby. Gestational hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg on two or more measurements 6 hours apart after 20 weeks' gestation. Preeclampsia was defined using the revised International Society for the Study of Hypertension in Pregnancy definition of gestational hypertension or postpartum hypertension with proteinuria (24-hour urinary protein of 300 mg or spot urine protein/creatinine ratio of ≥ 30 mmol/L creatinine or urine dipstick protein ≥ ++)

or any multisystem complication of preeclampsia or utero-placental dysfunction as evidenced by intrauterine growth restriction (9). Small-for-gestational-age-delivery was defined as a birth weight below the 10th customized centile adjusted for maternal height, weight, parity and ethnicity, gestational age at delivery, and infant sex. sPTB was defined as spontaneous preterm labour or preterm premature rupture of membranes resulting in a preterm birth at < 37 weeks of gestation. Gestational diabetes mellitus is screened at 24-28 weeks' gestation in Australia. GDM was diagnosed at 24-28 weeks' gestation according to the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria (i.e. one or more values equal to or exceeding: fasting plasma glucose of 5.1mmol/L, and/or a 2h plasma glucose level of 8.5mmol/l following a 75g Oral Glucose Tolerance Test (OGTT)[400]. Women who were at high risk of GDM completed a 75g OGTT in their first trimester and, if normal, the OGTT was repeated at 24-28 weeks' gestation. Data collected after delivery included newborn weight, length, arm circumference, birthweight centile, and data on complications during the neonatal period and type of feeding at discharge from hospital.

Women were recruited into the STOP follow-up study within 3 months of when their first child reached 3 years of age. Appointments were completed at the Clinical Trials Unit at the Lyell McEwin Hospital or completed externally as a postage paid package. Heights of women and children were measured with a stadiometer to the nearest 0.1cm. Children's weights were measured with a standard balance beam scale to the nearest 100g. Body composition in women was assessed using the TANITA SC-330 bioimpedance scale (Tokyo, Japan), which measured fat to the nearest 0.1kg, fat percentage, fat mass, fat free mass and body mass index (BMI). Those who participated in the study externally, self-reported weight and height only. Body composition in children was assessed by standardized BMI score (BMI-SDS) based on the centre for

disease control (CDC) growth charts for children and teenagers aged 2 to 19 years of age [501]. Waist circumference was measured in both women and children to the nearest 0.1cm, based on the World Health Organisation guidelines [502]. Peripheral systolic and diastolic blood pressures were assessed using the USCOM BP+ (USCOM, Sydney, Australia) using appropriately sized cuffs for arm circumference while participants were seated. The USCOM BP+ was also used to perform a non-invasive measure of cardiovascular function, such as central systolic and diastolic blood pressure, peripheral blood pressure, arterial stiffness and tone [assessed as augmentation index (AIx)], pulse rate variability and ventricular contractility (assessed as dP/dt max) [480]. The USCOM BP+ has been validated for use in children [478]. Cases were excluded if the signal to noise ratio, an indicator of blood pressure recording quality, was < 6. Fasting blood samples were collected from women to assess glucose, HbA1C, insulin, non-HDL lipids, HDL-cholesterol, and C-reactive protein. Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) using fasting blood glucose and fasting insulin values [481]. Some fasting blood data are missing due to some participants being pregnant or due to non-compliance. These numbers are reported in the results. Some children's data are missing due to non-compliance and numbers are reported accordingly in the results.

11.4.2. **Breastfeeding status**

Duration of breastfeeding was ascertained by collecting information on breastfeeding at 1-4 weeks, 6-8 weeks, 6-9 months, and 18-24 months of age from the child's "blue book" (i.e. Child Health record) which is given to all parents of newborns in South Australia. This data is collected by a child health nurse or their GP who record the self-report of the mother at the time of assessment.

11.4.3. **Statistical analysis**

Data were analysed using IBM SPSS Version 26. Women who breastfed for at least 6 months were compared to those who did not. Similarly, children who had been breastfed for at least 6 months were compared to those who had not. The justification to select this time point for breastfeeding status is based on the World Health Organisation recommendation that children should be exclusively breastfed up until 6 months postpartum.

Subgroup analysis was undertaken assessing women who experienced a complicated index pregnancy (i.e. diagnosis of one or more of the following: preeclampsia, gestational hypertension, GDM, delivery of a small for gestational age infant, delivery of a preterm infant, sPTB). Univariate analysis was used to compare anthropometric and haemodynamic variables between the two groups with data presented as mean (SD), n (%) or median (IQR). Associations between breastfeeding/being breastfed for at least 6 months postpartum and maternal or child metabolic risk factors were analysed using linear regression, adjusted for BMI and socioeconomic index (SEI), which was defined by the New Zealand Socioeconomic Index (NZSEI) at index pregnancy. SEI is scored between a value of 10 to 90; with a lower score reflecting greater socioeconomic disadvantage.

11.5. Results

11.5.1. Participant demographics

A total of 1,373 women were recruited to the STOP pregnancy study. Figure 1 demonstrates the flow chart of participant selection. Of these women, 1,007 agreed to be contacted for future studies at the time of their index pregnancy. However, only 674 were contactable at the time of follow-up. Of these, 257 woman-child dyads consented and participated in the follow-up study from January 2019 until June 2021. Of these participants, 160 women had adequate child health data with information on breastfeeding, therefore data for these participants were analysed in this study (Figure 11.1). Seventy women (46.9%), reported breastfeeding at 1-4 weeks postpartum, 56 women (35%) reported breastfeeding at 6-9 weeks' postpartum, 38 women (23.8%) reported breastfeeding at 6-9 months postpartum and 13 women (8.1%) reported breastfeeding at 12-18 months postpartum. Educational status at baseline was significantly different between those who breastfed and those who did not (p=0.001). There was no significant difference in BMI in early pregnancy between women who participated in the follow-up study compared to those who did not. Socioeconomic status (SES) during index pregnancy was also not significantly different between the participants in the follow-up study compared to those who did not participate (data not shown).

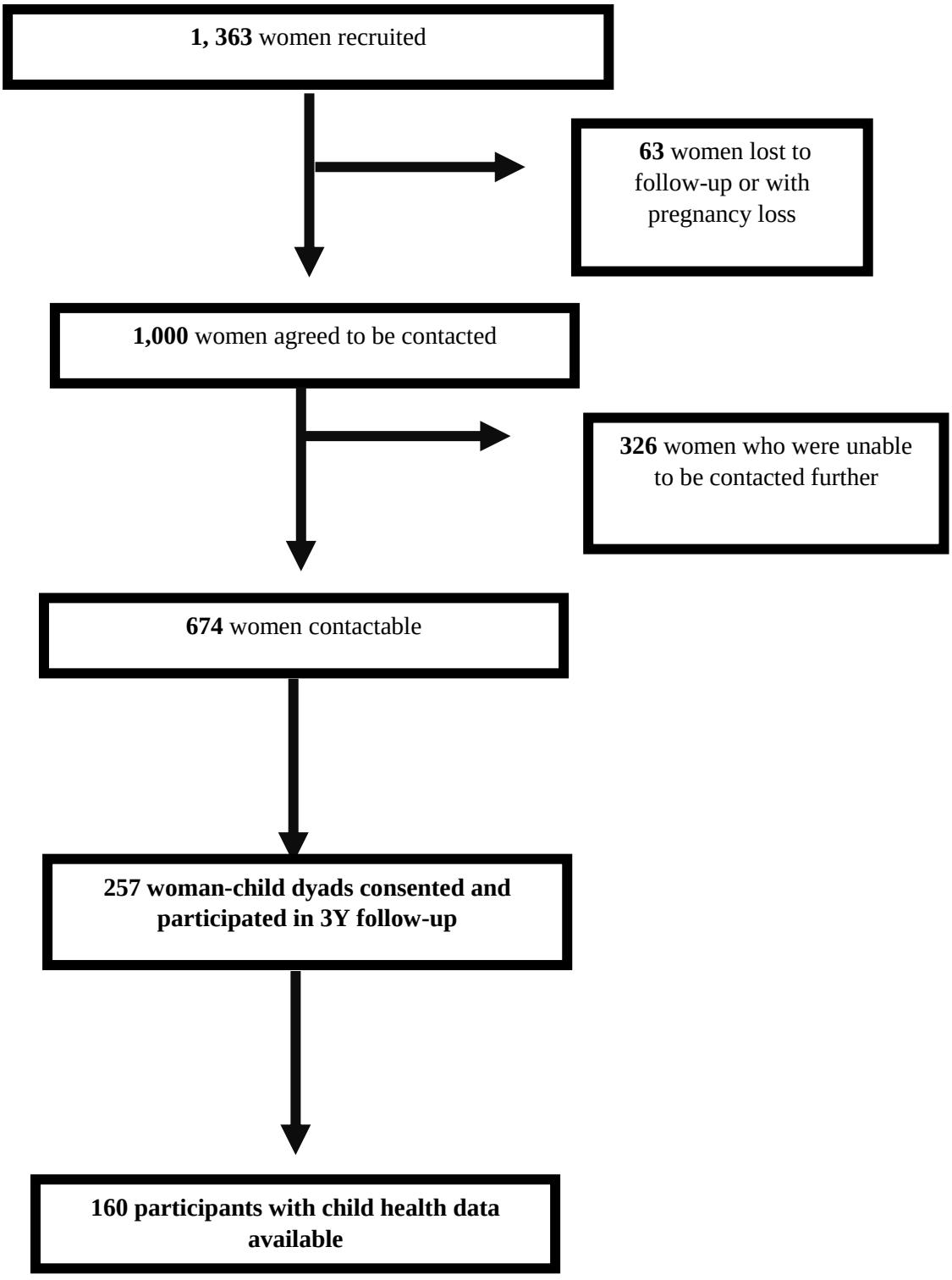


Figure 11.5.1.1 Flow chart of follow-up participant recruitment

Demographics of the participants who attended the 3-year follow-up are presented in Table 11.5.1.1. There were no differences in baseline parameters such as maternal age, SEI, BMI at booking, child birthweight, gestational age at delivery, nor waist circumference at 3 years postpartum between women who breastfed for at least 6 months and those who did not.

Table 11.5.1-1 Baseline data from the woman-child dyads who participated in the STOP 3Y follow-up study

Variable	**Breastfed for at least 6 months (n= 74)**	**Did not breastfeed for at least 6 months (n= 86)**	**p-value**
Socioeconomic Index (Mean (SD))	33.2 (13.7)	34.3 (15)	0.141
Caucasian ethnicity	61 (82.4%)	80 (93.0%)	0.144
Education Status			**0.001**
Did not complete year 10	0	1 (1.2%)	
Year 10	4 (5.4%)	12 (14.0%)	
Year 12	14 (18.9%)	25 (29.1%)	
Certificate	30 (40.5%)	33 (38.4%)	
Bachelor	23 (31.1%)	11 (12.8%)	
Higher Degree	3 (4.1%)	4 (4.7%)	
BMI at 9-16 weeks' gestation	27.4 (7.3)	29.1 (8.0)	0.332
Pregnancy Complications*			
Gestational Diabetes	14 (18.9%)	14 (16.3%)	0.077
Gestational Hypertension	5 (6.8%)	7 (8.1%)	0.741
Preeclampsia	6 (8.1%)	9 (10.5%)	0.610
Small for gestational age baby	12 (16.2%)	9 (10.5%)	0.283
Spontaneous preterm birth	4 (5.4%)	3 (3.5%)	0.554
Gestational age (weeks)	39.5 (1.7)	39.4 (1.7)	0.754
Child birthweight (g)	3265.3 (491.2)	3360 (531.9)	0.612
Current Maternal Age (Mean (SD))	31.8 (5.0)	31.4 (5.2)	0.655

*pregnancy complications are not mutually exclusive and one woman can have multiple pregnancy complications

11.5.2. **Women**

Data for fasting blood sample were available for 61 women (Table 11.5.2.1). At 3 years postpartum, women who breastfed for at least 6 months postpartum had significantly lower serum insulin and insulin resistance compared to those who did not breastfeed for at least 6 months. When adjusting for BMI and SEI in early pregnancy, the association between both serum insulin and insulin resistance at 3 years with breastfeeding for at least 6 months was attenuated (Table 11.5.2.2). At 3 years postpartum, there was no significant difference in BMI, fat mass and waist circumference in those who breastfed for at least 6 months vs those who did not. There were no differences in hemodynamic parameters including peripheral systolic and diastolic blood pressures, mean arterial pressure, augmentation index, pulse rate and central systolic and diastolic blood pressures between the two groups (Table 11.5.2.1).

Table 11.5.2-1 Cardiovascular risk factors at 3 years postpartum in women who breastfed for at least 6 months compared to those who did not with subgroup analysis of those who had at least one complication of pregnancy during index pregnancy

	Breastfed for at least 6 months (n=70)	**Did not breastfeed for at least 6 months (n=74)**	**p-value**	**Women with complicated pregnancies who breastfed for at least 6 months (n=34)**	**Women with complicated pregnancies who did not breastfeed for at least 6 months (n=35)**	**p-value**
BMI (kg/m2)	28.4 (8)	31.6 (10.2)	0.116	28.4 (7.8)	33.0 (8.9)	0.909
Fat mass (kg)	29.1 (17.3)	36.4 (19.3)	0.213	27.6 (16.3)	40.2 (20.3)	0.312
Waist circumference (cm)	88.6 (20.6)	95.9 (20.5)	0.175	89.2 (21.5)	102.8 (23.4)	0.484
Systolic blood pressure (mmHg)	119.0 (12.7)	122.5 (14.6)	0.336	121.2 (12.1)	124.5 (15.6)	0.141
Diastolic blood pressure (mmHg)	66.9 (9.3)	70.2 (11.3)	0.370	67.7 (9.5)	72.5 (11.1)	0.503
Mean arterial pressure (mmHg)	80.8 (9.8)	85.1 (14.1)	0.101	81.6 (9.8)	88.3 (14.5)	0.106
Augmentation Index (%)	53.1 (18)	56.7 (22.8)	0.118	52.2 (16.6)	61 (22.1)	0.205
Central systolic blood pressure (mmHg)	109.4 (11.9)	111.9 (13.9)	0.476	111.2 (12)	115.4 (14.7)	0.211
Central diastolic blood pressure (mmHg)	69.6 (9.4)	73.1 (11.8)	0.215	70.9 (9.5)	75.3 (11.4)	0.407
	(n=24)	**(n=30)**	**p-value**	**(n=13)**	**(n=19)**	**p-value**
Fasting glucose (mmol/L)	4.7 (0.5)	4.7 (0.5)	0.168	4.8 (0.5)	4.7 (0.5)	0.677
Insulin (mU/L)	8.1 (3.1)	13.2 (9.2)	**0.001**	7.5 (2.1)	16.5 (10.2)	**0.001**
HOMA-IR	1.7 (0.6)	2.8 (2.1)	**0.000**	1.6 (0.5)	3.5 (2.2)	**0.001**
Triglycerides(mmol/L)	0.9 (0.4)	1.3 (7.5)	**0.006**	1.0 (0.5)	1.6 (0.8)	**0.04**
HDL-C(mmol/L)	1.4 (0.8)	1.4 (0.4)	0.605	1.3 (0.3)	1.2 (0.3)	0.404
LDL-C(mmol/L)	1.2 (0.3)	2.6 (0.7)	0.974	2.7 (0.5)	2.7 (0.5)	0.870
Total Cholesterol/HDL ratio	3.2 (0.8)	4.8 (5.3)	0.100	3.4 (0.8)	6.2 (7.2)	0.091
Non-HDL Cholesterol	3.1 (0.8)	3.2 (0.8)	0.761	3.1 (0.6)	2.5 (0.6)	0.849
Total Cholesterol(mmol/L)	4.3 (0.9)	4.4 (0.8)	0.935	4.4 (0.5)	4.6 (0.6)	0.308
C-Reactive Protein	3.8 (4.8)	3.4 (2.5)	0.080	3.0 (4)	3.8 (2.5)	0.687

Data reported as mean (SD)

*reduction in serum blood results due to noncompliance

Table 11.5.2-2 Mean differences in maternal cardiovascular risk factors at 3 years postpartum in women who breastfed for at least 6 months compared to those who did not, assessed by linear regression.

	*Adjusted Mean Difference (95% CI)
Insulin (mg/dL)	-1.7 (-4.6 to 1.2)
HOMA-IR^	-1.4 (-7.7 to 4.8)

*adjusted for BMI at booking, SEI at booking.
^log transformed variable

11.5.3. **Children**

Of the 160 children who attended for follow-up, anthropometric data were available for 139 children at 3 years of age. Hemodynamic data were available for just 72 children due to poor USCOM BP+ readings or non-compliance of children. There was no difference in anthropometric or hemodynamic parameters between children who were breastfed for at least 6 months compared to those who were not (Table 11.5.3.1). Subgroup analysis demonstrated that children who were exposed to a pregnancy complication *in utero* had significantly higher BMI-SDS compared to those born to an uncomplicated pregnancy.

Table 11.5.3-1 Cardio metabolic outcomes for offspring who were breastfed for at least 6 months compared to those who were not with subgroup analysis for those exposed to at least one complication of pregnancy *in utero*.

3 years of age						
	Offspring who were breastfed for at least 6 months (n=68)	Those who were not breastfed for at least 6 months (n=71)	p-value	Offspring exposed to pregnancy complication(s) *in utero* that were breastfed for at least 6 months (n=34)	Offspring exposed to uncomplicated pregnancy *in utero* that were breastfed for at least 6 months (n=35)	p-value
BMI SDS*	55.6 (29.8)	58.4 (31.7)	0.314	58.8 (27.3)	56.2 (32)	**0.046**
Waist circumference*	51.1 (3.5)	51.8 (4.5)	0.378	52 (2.7)	50.9 (2.8)	0.918
^^	**(n=38)***	**(n=34)***		**(n=20)***	**(n-15)***	
Systolic blood pressure (mmHg)	101.9 (12.1)	96.1 (18.5)	0.097	99.6 (11.0)	91.9 (24.6)	0.169
Diastolic blood pressure (mmHg)	58.8 (10.5)	58.1 (15.8)	0.833	58.7 (11.8)	55.8 (17.5)	0.421
Mean arterial pressure (mmHg)	73.1 (13.3)	71.1 (18.3)	0.584	73.1 (14.9)	67.2 (18.8)	0.220
Augmentation Index (%)	87.2 (38.4)	98.3 (52.5)	0.643	97.8 (45.9)	81.9 (28.7)	0.179
Central systolic blood pressure (mmHg)	94.2 (12.4)	91.6 (20.3)	0.471	91.2 (13.1)	85.2 (21.2)	0.181
Central diastolic blood pressure (mmHg)	62.6 (10.1)	61.2 (13.0)	0.616	62.1 (11.8)	60 (17.8)	0.506

*BMI SDS is adjusted for age and sex[501], all other outcomes are adjusted for child age.

^^ The sample size for hemodynamic variables is smaller due to noncompliance with the USCOM BP+

11.6. Discussion

The primary aim of this observational study was to assess whether breastfeeding for at least 6 months promotes a reduction in cardiovascular risk factors in women and their children at 3 years postpartum. Women who breastfed for at least 6 months demonstrated a reduction in serum insulin and insulin resistance at 3 years postpartum compared to those who did not. This association was attenuated by maternal BMI and SEI early in the index pregnancy.

Subgroup analysis of women with at least one pregnancy complication during the index pregnancy revealed that serum insulin, insulin resistance and serum triglycerides were significantly higher in those who did not breastfeed for at least 6 months postpartum. There was no difference in cardio metabolic outcomes at 3 years of age between children who were breastfed for at least 6 months and those who were not. However, when stratifying by exposure *in utero* to at least one pregnancy complication, children who were breastfed for at least 6 months had significantly lower BMI-SDS than those who were not.

Our previous systematic review and meta-analysis on breastfeeding after a GDM pregnancy did not show a difference in serum insulin between women with a history of GDM who breastfed compared to those who did not but there was a reduction in the risk of developing T2DM later [503]. Women who are diagnosed with pregnancy complications such as preeclampsia and GDM are generally more likely to be insulin resistant in the postpartum period compared to those with an uncomplicated pregnancy [487, 504].

In our study, breastfeeding for at least 6 months reduced serum triglyceride levels in women who experienced at least one pregnancy complication. A study by Blair *et al.* (2021) found that among those with a history of GDM, breastfeeding for as little as 8 weeks had significantly lower triglycerides at 8 weeks than those who were not breastfeeding [505]. Yu and colleagues found the same association in a cohort of women with a history of pregnancy complications

who were breastfeeding at 6 months postpartum [506]. Both studies found that the risk of metabolic syndrome was also significantly reduced. Therefore, breastfeeding could be encouraged in women diagnosed with a pregnancy complication to reduce their risk of developing cardiovascular risk factors and metabolic syndrome.

Our study showed that there was no difference in anthropometric or hemodynamic parameters in children who were breastfed until at least 6 months of age compared to those who were not. However, when stratified by children who were or were not exposed to at least one pregnancy complication, BMI SDS score was significantly reduced in offspring who were breastfed for at least 6 months compared to those who were not. There is minimal evidence on the effect of breastfeeding on cardiovascular risk in children exposed to a pregnancy complication *in utero.* Hui *et al.* 2018 showed that breastfeeding did not attenuate the association between GDM exposure *in utero* and BMI in offspring during infancy and childhood [405]. Exclusive breastfeeding for a mean time of 180 days of children born small for gestational age promoted a healthy weight in these children at pre-school age [507]. Breastfeeding promotes good health outcomes in general populations of children. Breastfeeding for greater than 6 months was associated with increased intake in fruits and vegetables, specifically an increased frequency and variety of vegetables and higher frequency of fruit intake in offspring at age 7, including after adjustment for demographic variables [434]. Evidence shows pregnancy complications associate with increased cardiovascular risk factors in exposed offspring [74, 508]. Further studies are warranted to understand the mechanisms by which an adverse intrauterine environment confers cardiovascular risk for offspring and to define how breastfeeding may ameliorate risk.

There were many strengths in this observational study. We were able to assess non-conventional markers of cardiovascular risk in women and children such as augmentation index and mean arterial pressure. Our cohort was recruited from a hospital servicing a low SES population enabling our findings, if replicated in larger studies, to be generalizable to

disadvantaged communities. Due to the difficulties in recruiting disadvantaged participants in research, many studies report on participants in moderate to high SES communities who generally tend to have fewer cardio-metabolic risk factors and better health.

There are limitations to address in this study. Due to the low SES community, it was difficult to recruit and maintain engagement in the cohort with a high percentage unable to be contacted for follow-up. Just one quarter of participants from the original STOP study attended the 3 year follow-up, albeit 50% of those who consented to follow-up and were contactable. The women recruited into the STOP study are from an area of severe disadvantage, where engagement in exercise is much lower than the national average and the rate of diabetes is 22% higher than the national average [509]. Therefore, finding an association between breastfeeding and metabolic risk factors in this cohort may be confounded by the poorer health in the local population compared to state and national averages. It is known that low socioeconomic status has a significant impact on breastfeeding practices, which therefore may have also a significant effect on our results [491]. As the study is observational in nature, there are variables that we cannot fully control for. Some women were pregnant at the time of follow-up so they were excluded from these analyses as anthropometric and hemodynamic variables are not comparable between pregnant and non-pregnant states. The child health data recorded in the child's blue book (health record) were incomplete for a significant number of women. This is because blue book completion is not mandatory. Many women take their children for check-ups to their general practitioner rather than a child nurse who would normally enter data in the book. Other studies undertook detailed questionnaires on lactation via telephone or in person at the time of infant follow-up, which detailed frequency of lactation and addition of formula or solid foods [510]. These would provide a better profile of breastfeeding status. Although we recruited 257 participants, there were only blue book data available for 160, of whom only 54 women

presented for fasting blood sampling. Furthermore, there were adequate hemodynamic data for just 72 children. Therefore, future studies will require a larger sample size.

11.7. Conclusion

Women with previous GDM should be encouraged to breastfeed to reduce their risk of CVD later in life. More research in this area is required in order to integrate it fully for clinical use and disease mitigation strategies. Lactation specialists should promote breastfeeding in women with previous GDM through integrating what is known about the benefits of breastfeeding on cardiovascular disease risk factors. More research is needed to determine the effects of breastfeeding on cardiovascular risk factors in children exposed to GDM *in utero*, but the limited literature reports protective effects.

Chapter 12

12. Exposure to gestational diabetes mellitus *in utero* and neurodevelopment at 3 years of age

Maleesa M Pathirana, Prabha H Andraweera, Emily Aldridge, Madeline Harrison, Jade Harrison, Shalem Leemaqz, Margaret A Arstall, Gustaaf Dekker, Claire T Roberts

12.1. Statement of Authorship

Title of Paper	Exposure to gestational diabetes mellitus *in utero* and neurodevelopment at 3 years of age
Publication Status	Submitted to Paediatric Research
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Maleesa Pathirana
Contribution to the Paper	Ethics submission, recruitment, site specific administration, undertaking assessments with participants, data collection, analysis of results, interpretation of results, writing of manuscript.
Overall Percentage (%)	80%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	**Date**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Prabha H Andraweera	
Contribution to the Paper	Designed protocol, ethics submission, contributed to manuscript and supervision	
Signature		**Date 28/02/2022**

Name of Co-Author	Emily Aldridge	
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, contributed to manuscript and technical advice.	
Signature		**Date 14/02/2022**

Name of Co-Author	Shalem Leemaqz	
Contribution to the Paper	Statistical analysis assistance, contributed to manuscript and technical advice.	
Signature		**Date 23/02/2022**

Name of Co-Author	Madeline Harrison	
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, reviewed manuscript	
Signature		**Date 15/02/2022**

Name of Co-Author	Jade Harrison
Contribution to the Paper	Recruitment of participants, undertaking assessments with participants, data collection, reviewed manuscript

Signature		**Date 15/02/2022**

Name of Co-Author	Margaret A Arstall
Contribution to the Paper	Conceived and designed protocol, assisted with data interpretation, contribute to manuscript and technical advice.

Signature		**Date 28/02/2022**

Name of Co-Author	Gustaaf A Dekker.
Contribution to the Paper	Conceived and designed protocol, recruited women into original STOP study, contributed to manuscript.

Signature		**Date 28/02/2022**

Name of Co-Author	Claire Roberts
Contribution to the Paper	Conceived and designed protocol and original STOP study, contributed intellectually to manuscript and supervised.

Signature		**Date 28/02/2022**

12.2. Abstract

Introduction: Gestational diabetes mellitus affects 1 in 7 pregnancies globally. It is thought that there is an association between exposure to GDM *in utero* and poor neurodevelopment in the offspring. The aim of this study was to determine whether there is an association between exposure to GDM *in utero* with child neurodevelopment at three years of age in a community of women and children with socioeconomic disadvantage. Our secondary aim was to determine whether there are sex specific differences in neurodevelopment in offspring exposed to GDM *in utero.*

Methods: Of the 1,300 participants who participated in the pregnancy study between 2015 to 2017, there were 223 woman-child dyads who attended the 3 year follow-up and completed the ASQ-3. There were only two children who were diagnosed with ASD at time of the 3 year follow-up. Communication scores in the ASQ-3 were significantly lower in children exposed to GDM *in utero* compared to unexposed children [49.2 (12.3) vs. 53.4 (7.8) p=0.010]. This was also observed after adjustment for maternal history of depression, current child age and gestational age. There were more children exposed to GDM *in utero* who scored below the threshold indicating developmental delay and need for clinical assessment in the communication, problem solving and personal social domains than those not exposed to GDM *in utero.* There were more children who scored below the threshold for communication between those exposed to GDM *in utero* than those exposed to an uncomplicated pregnancy. Males exposed to GDM *in utero* had a lower mean problem solving score than females exposed to GDM *in utero* [42 (13) vs. 50 (16) p=0.026].

Conclusion: Children exposed to GDM *in utero* have reduced communication skills at 3 years of age compared to those not exposed to GDM *in utero* independent of covariates. Males exposed to GDM *in utero* have lower problem solving score than females. Children exposed to GDM *in utero* may benefit from neurodevelopmental screening by age 3 years.

12.3. Introduction

Early to mid-childhood is a critical period for neurodevelopment. It is established that children who have not achieved key neurodevelopmental milestones by the age of 5 years are more likely to have academic and socio-emotional problems by the time they commence primary school[511]. Impaired early childhood neurodevelopment is associated with poor social functioning, chronic disease, mental illness and reduced economic productivity later [511, 512]. It is thought that maternal stress during pregnancy plays a critical role in disrupting early brain development, through inflammatory processes [513-515]. In particular, exposure to inflammation *in utero* can perturb attainment of key neurodevelopmental milestones from birth to age 3 years [512]. Inflammation is also associated with oxidative stress that is thought to contribute to neurodevelopmental disorders like autism spectrum disorder (ASD) [516]. Maternal pre-pregnancy obesity is associated with an increased risk of developmental delay and emotional/behavioural problems in offspring due to increased inflammation [514, 515]. Therefore, it is necessary to understand what early life exposures influence childhood neurodevelopment.

Gestational diabetes mellitus (GDM) affected 15% of all pregnancies in Australia in 2016-2017, and is defined as diabetes that is first diagnosed in pregnancy[4]. Evidence suggests that exposure to GDM *in utero* increases the risk of developing cardiovascular risk factors in the offspring later in life[299]. However, there is also evidence to suggest that the same inflammatory processes that promote poor metabolic health also have a significant impact on brain development *in utero.* Higher circulating beta-hydroxybutyrate, which is involved in various metabolic processes during pregnancy, is associated with psychomotor development in offspring of diabetic mothers at age 2 [517]. In women with GDM, long-chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA), which are necessary for fetal neurodevelopment, cannot be effectively transferred to the placenta due to excess glucose levels, and this is thought to decrease cognitive function in the offspring [62]

Studies have shown an association between exposure to GDM *in utero* and poor neurodevelopment in the offspring during childhood[68, 518, 519]. Children of school age who are born to mothers with GDM have diminished attention span and motor skills compared to those whose mothers did not have GDM [520]. A recent study also reported that maternal GDM was associated with child developmental delay demonstrated in the communication domain of the Ages and Stages Questionnaire-3 (ASQ-3) at age 1. For every 1 SD increase in the glycaemic value, there was a higher risk of being below the threshold for the personal social domain of ASQ-3 at age 1[521].

Many of these studies have focused on cohorts in high or middle socioeconomic communities, and there has not been a specific focus on disadvantaged communities. This is particularly important as the latter are the populations that are more likely to have a higher prevalence of obesity, diabetes and higher rates of psychological distress[72]. Maternal wellbeing during pregnancy is important to consider for child health as it is thought that maternal perinatal depression is associated with child socioemotional problems[522].

It has been established in clinical and animal studies that fetal sex influences vulnerability to adverse pregnancy complications *in utero.* Women carrying male fetuses are more likely to experience early spontaneous preterm birth and potentially GDM, while women carrying female fetuses are more likely to experience early onset preeclampsia [523]Na. While the biological processes underlying these associations are still being understood, it is important to determine whether these sex differences are observed in the association between exposure to GDM *in utero* and neurodevelopment.

Therefore, the primary aim of our study is to determine whether there is an association between exposure to GDM *in utero* with child neurodevelopment at three years of age, assessed in five domains from the Ages and Stages Questionnaire-3 at 36 months. Our secondary aims are to

assess whether this association is influenced by maternal depression, and to determine if there are sex-specific differences in neurodevelopment among offspring exposed to GDM *in utero.*

12.4. Methods

12.4.1. Study population

The study participants included women and their children from the Screening Tests to Predict Poor Outcomes of Pregnancy [1] study from 2015 to 2017. The STOP study was a prospective cohort study of nulliparous pregnant women that aimed to predict the risk of pregnancy complications. A total of 1,363 nulliparous women, their partners and babies were originally recruited. The great majority of the participants were recruited from the Lyell McEwin Hospital in northern Adelaide, which serves one of the most socioeconomically disadvantaged regions in metropolitan Australia [524]. For the STOP follow-up study, women were contacted using phone numbers provided during the STOP study, or from hospital records. If women could not physically attend an appointment, an external participation package was posted to their address and returned via pre-paid postage. In the original STOP study, detailed information was collected at 9-16 weeks' gestation (average 12 weeks') and 34 weeks' gestation and at time of delivery of the baby. The maternal data included demography, medical history, fertility history, information on previous pregnancies, diet, exercise, employment, smoking, intake of alcohol and recreational drugs, measures of stress, anxiety and depression. Physical measurements including height, weight, waist and hip circumference, BMI and haemodynamic measurements were also obtained at 9-16 weeks' gestation during the first pregnancy. GDM was assessed at 24-28 weeks' gestation, and diagnosed according to the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria (i.e. one or more values equal to or exceeding: fasting plasma glucose of 5.1mmol/L, and/or a 2h plasma glucose level of

8.5mmol/l following a 75g Oral Glucose Tolerance Test (OGTT) [400]. Women who were considered at high risk for GDM were also asked to complete a 75g OGTT in first trimester and, if negative then, another at 24-28 weeks of gestation. Data collected following birth include newborn weight, length, arm circumference, birthweight centile, and complications during the neonatal period and type of feeding at discharge from hospital.

During early pregnancy, depression was assessed using the Edinburgh Postnatal Depression Score (EDPS), with a score of ≥13 indicating a need to follow-up for diagnosis of antenatal depression[455]. Likelihood of depression was assessed using the EPDS, where "low risk" of depression was scored 0-9, "moderate risk" of depression in the following year score 10-12, and "likely depressed" score 13-30. Anxiety in pregnancy was defined using the STAI-6 score, where a score below 30 was defined as "low to no anxiety", 31-49 "normal level of anxiety" and a score of 45-80 was defined as a participant having an "elevated state of anxiety". Socioeconomic index (SEI) was assessed using the New Zealand Socioeconomic Index (NZSEI) [475] with a scale of 10-90 where a lower score indicates more disadvantage.

Women were recruited into the STOP follow-up study within 3 months prior to and 3 months after their first child turned 3 years old. The appointment involved an update of demographic, obstetric and medical history. Anthropometric and hemodynamic measures were made for both mothers and children. Women were asked whether their child had a diagnosis of autism spectrum disorder (ASD) or attention deficit hyperactive disorder (ADHD). Assessment of depression and anxiety in mothers at 3 years postpartum was evaluated using the Patient Health Questionnaire-9 (PHQ9) and General Anxiety Disorder-7

(GAD7) tools, respectively. Neurodevelopment in the children was assessed using the Ages and Stages Questionnaire-3 at 36 months (ASQ-3-36) [525]. The ASQ-3 is a screening instrument devised to assess developmental delay in children, with various versions for different age groups targeting age-specific developmental milestones. The ASQ-3 assesses five areas of neurodevelopment: communication, gross motor, fine motor, problem solving and personal-social behaviour. Each area has six questions in which children are assessed on whether they are able to perform certain tasks reflecting each domain, scored from 0 (never), 5 (sometimes) and 10 (always). A total score of 60 can be achieved for each domain and cut-offs have been determined for each area as recommended in the ASQ-3 manual[526]. Scoring below the cut-off score is based on the threshold scores used for developmental delay in the ASQ-3 at 36 months. These were calculated according to the ASQ-3 manual, as 2 standard deviation scores below the mean score of the population sample of the ASQ-3[526]. This cohort is described in more detail in the ASQ-3 technical manual. Scoring equal to or below the cut off was transformed into a binary outcome (below cut off = yes or no). A score equal to or below the cut-off indicates a potential developmental delay and requires follow-up by a health professional for further assessment.

The ASQ-3 was assessed either at the appointment by a trained researcher, or mothers were able to complete the questionnaire at home, in a safe, comfortable environment for their child. The ASQ-3 has been designed for parents to complete in a home setting, with assistance of family members if required. Analysis was only performed for children who were aged between 2.9 years to 3.2 years old as per the ASQ-3 at 36 month age criteria for assessment.

12.4.2. **Statistical analysis**

Data were analysed using IBM SPSS Version 26. Children who were exposed to GDM *in utero* were compared to those who were not exposed to GDM *in utero*. Univariate analysis was used to compare developmental areas in the ASQ-3 and baseline variables between offspring exposed to GDM *in utero* and those not exposed to GDM *in utero*, with data presented as mean [527], or n (%). Linear regression analysis was used to assess the association between GDM exposure *in utero* and facets of the ASQ-3, with data presented as adjusted mean difference (95% CI). Associations between GDM and ASQ-3 scoring in children were adjusted for maternal history of depression ascertained in pregnancy, child age and gestational age. These were selected based on whether they were associated with both GDM and neurodevelopment in offspring.

12.5. Results

12.5.1. Participant demographics

There were 1,300 women who participated in the STOP study for whom pregnancy outcome data are available (Figure 12.5.1.1). Of these women, 1,000 agreed to be contacted for future studies at the time of their index pregnancy but only 674 were contactable. Of these participants, 257 woman-child dyads consented and participated in the follow-up study from January 2019 until March 2021. Of the women who attended the follow-up, 219 participants had not experienced GDM in the first pregnancy, and 38 had experienced a pregnancy complicated by GDM. However, there were 192 participants from the non-GDM group and 31 from the GDM group who completed the Ages and Stages questionnaire at the follow-up appointment. The participants who did not experience GDM were comprised of women who had an uncomplicated pregnancy, or hypertensive disorder of pregnancy (i.e. preeclampsia or gestational hypertension) or delivered preterm and/or birthed a small-for-gestational-age infant.

There was no significant difference in BMI in early pregnancy between women who participated in the follow-up study compared to those who did not, nor in the proportion of GDM participants in the follow-up study and of those with GDM who did not participate in the follow-up. SEI during index pregnancy was also not significantly different between all participants in the follow-up study compared to those who did not participate. However, those who attended the follow-up study who had GDM in their index pregnancy had significantly higher SEI than those who had GDM and did not participate (Mean 36.7 SD (17.3) vs 33.4 SD (12.5) p=0.003).

Demographics data for the participants who attended the 3-year follow-up are presented in Table 12.5.1.1. Of the women who attended the 3-year follow-up, those with GDM had significantly higher SEI than those who did not have GDM in the index pregnancy ((Mean 36 SD (17.4) vs 33 SD (13.9) p=0.019). BMI in early pregnancy was significantly higher in the GDM participants than in non-GDM participants (30.1 SD (8.4. vs. 27.4 SD (6.9) p=0.012). There was no difference in smoking status in first trimester or at 3 years postpartum, nor in waist circumference at 3 years postpartum between GDM participants and non-GDM participants (Table 12.5.1.1). There was no difference in anxiety and depression rates in women with GDM in the index pregnancy compared to those with a non-GDM pregnancy. Risk of mental health disorder in early pregnancy was similar between the groups who attended the 3-year visit. However, risk of depression was higher in those in the non-GDM group than in the GDM group in early pregnancy (5.64 (5.1) vs. 5.5 (3.7)) p=0.033).

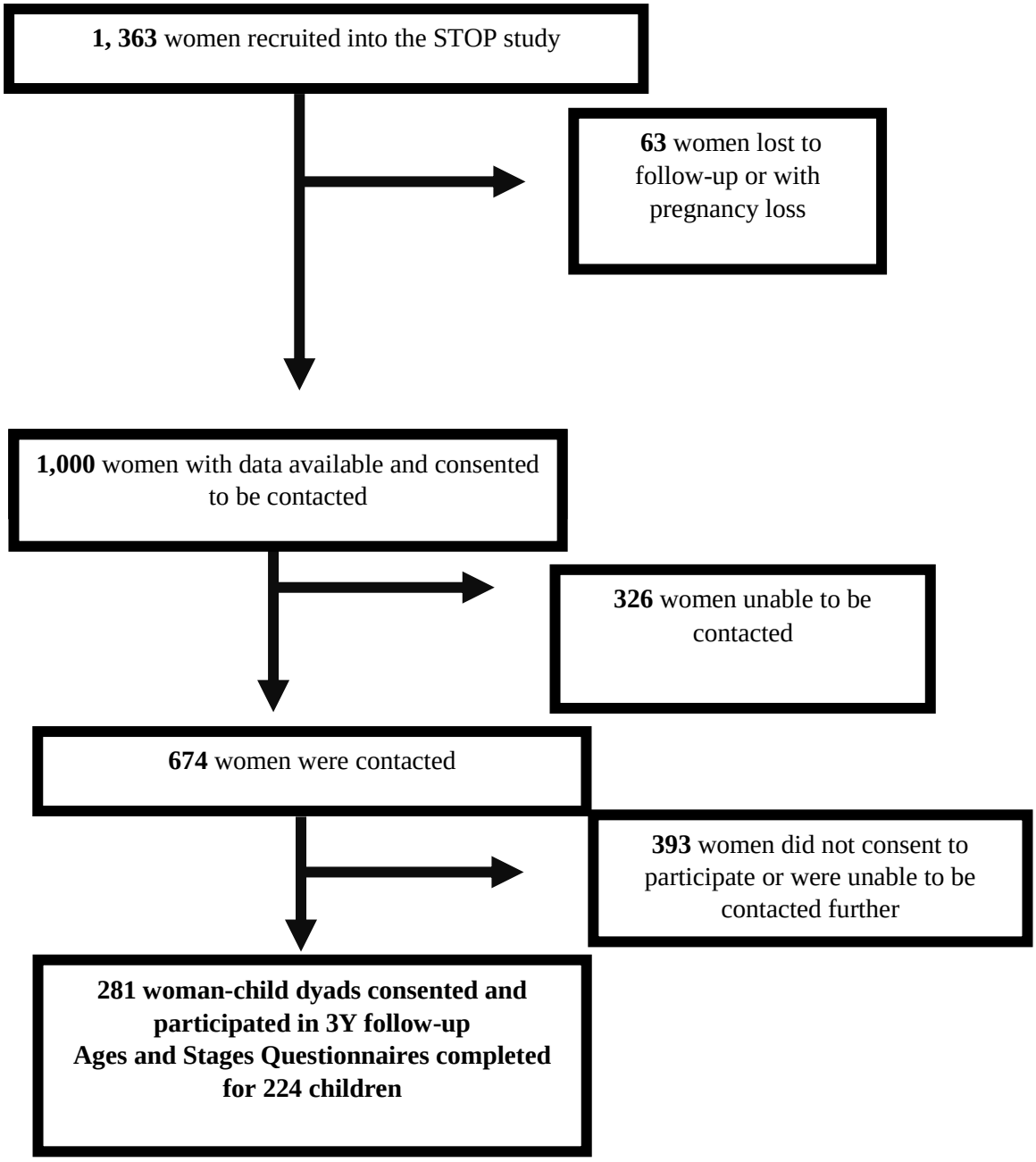


Figure 12.5.1.1 Flow chart of woman-child dyads who participated in the STOP follow-up study

Table 12.5.1-1 Demographics of mothers participating in the STOP follow up study collected at index pregnancy and at 3 years postpartum.

Variable	GDM (n= 38)	Non-GDM (n=219)	p-value
Index pregnancy			
BMI (m^2/kg)	30.1 (8.4)	27.4 (6.9)	**0.012**
SEI *	36 (17.4)	33 (13.9)	**0.019**
Caucasian ethnicity	34 (89.5%)	198 (89.6%)	
Education Status*			**0.001**
Did not complete year 10	2 (5.3%)	2 (0.9%)	
Year 10	2 (5.3%)	29 (13.1%)	
Year 12	8 (21.1%)	56 (25.3%)	
Certificate	14 (36.8%)	81 (36.7%)	
Bachelor	10 (26.3%)	39 (17.6%)	
Higher degree	2 (5.3%)	14 (6.3%)	
Early pregnancy EPDS	5.5 (3.7)	5.64 (5.1)	**0.033**
Smoking at 1st trimester	7 (18.4%)	36 (16.3%)	0.744
Smoking at 3Y	3 (7.9%)	26 (11.8%)	0.087
Uncomplicated pregnancy	-	133 (60.2%)	-
Preeclampsia**	4 (10.5%)	22 (10.0%)	-
Gestational hypertension**	4 (10.5%)	12 (5.4%)	-
Small for gestational age**	8 (21.1%)	28 (12.7%)	-
Spontaneous preterm birth**	4 (10.5%)	10 (4.5%)	-
Gestational Age (weeks)	38.5	39.4	0.334
Birthweight (g)	3173 (595)	3352 (511)	0.822
3 years postpartum			
Maternal Age	33.2 (5.4)	30.9 (4.87)	0.182
BMI (kg/m^2)	29.5 (7.5)	29 (8.7)	0.888
Waist circumference (cm)	94.8 (21.7)	89.1 (21.6)	0.673
GAD-7 Score	3.2 (3.7)	4.8 (4.4)	0.084
PHQ-9 Score	4.9 (5.4)	5.2 (4.5)	0.578

Data is reported as either mean (SD) or n= (%)

P-value was not obtained for these outcomes

*SEI is scored between 10-90 with a lower score indicating lower disadvantage

**pregnancy complications are not mutually exclusive and one woman can experience multiple pregnancy complications

12.5.2. Neurodevelopment in children at 3 years of age:

There were only two children who had been diagnosed with ASD by the 3-year follow-up, one in the GDM group and one in the non-GDM group (data not shown). Table 2 highlights the differences in developmental areas assessed in the ASQ-3. Children aged 3 years who were exposed to GDM *in utero* had significantly lower scores for communication skills than those who were not exposed to GDM *in utero* (Table 12.5.2.1). The adjusted mean difference for communication in these children remained the same after adjusting for maternal history of depression during early pregnancy, child age and gestational age at birth (Table 12.5.2.2). There was no difference in ASQ-3 communication scores between children born to a GDM pregnancy and those born to an uncomplicated pregnancy (Table 12.5.2.1). There was a higher percentage of children who scored below the threshold (indicating developmental delay) in communication, problem-solving and personal social domains of the ASQ-3 in the GDM group than the non-GDM group (Table 12.5.2.3). More children exposed to GDM *in utero* were below the threshold for communication and problem solving domains than children exposed to an uncomplicated pregnancy *in utero.*

Table 12.5.2-1 Differences in ASQ-3 domains between those exposed to GDM *in utero* and those who are not

ASQ-3 Variable	GDM (n=31)	Non-GDM (n=192)	p-value	Uncomplicated (n=131)	p-value
Communication	49.2 (12.3)	53.4 (7.8)	**0.010**	52.9 (8.7)	0.085
Gross Motor	52.3 (13.4)	55.7 (7.7)	0.075	55.8 (7.7)	0.106
Fine Motor	42.6 (16)	45.7 (14.2)	0.208	45.6 (13.9)	0.536
Problem Solving	50 (12.9)	53.9 (8.4)	0.060	53.7 (8.2)	0.309
Personal Social	49.4 (11.1)	51.8 (7.8)	0.179	52 (7.9)	0.284

Scores are Mean (SD)
**adjusted for child age and gestational age*

Table 12.5.2-2 Association between maternal GDM and communication score in children at age 3

ASQ-3 Variable	*Adjusted mean difference
Communication	-4.4 (-7.7 to -1.1)

*adjusted for maternal history of depression, child age and gestational age

Table 12.5.2-3 Differences in participants who scored below the threshold of the ASQ-3

ASQ-3 Variable	GDM (n=31)	Non-GDM (n=190)	p-value	Uncomplicated (n=131)	p-value
Communication	7 (18.4%)	9 (4.1%)	**0.000**	7 (5.2%)	**0.017**
Gross Motor	4 (10.5%)	9 (4.1%)	0.177	4 (9.5%)	0.221
Fine Motor	3 (7.9%)	8 (3.7%)	0.154	3 (7.1%)	0.265
Problem Solving	5 (13.2%)	5 (2.3%)	**0.001**	2 (1.5%)	**0.002**
Personal Social	5 (13.2%)	9 (4.1%)	**0.018**	6 (4.4%)	0.071

**adjusted for child age and gestational age*

12.5.3.Sex differences:

There were 6 males and 16 females who were exposed to GDM *in utero*. Males who were exposed to GDM *in utero* exhibited lower scores for problem solving skills compared to females after adjusting for child age and gestational age at birth (Table 12.5.3.1)

Table 12.5.3-1 Differences in ASQ-3 domains between male and females

ASQ-3 Variable	Male (n=6)	Female (n=16)	p-value*
Communication	43.3 (10.3)	47.5 (16.3)	0.187
Gross Motor	59 (2.2)	48.6 (15)	0.208
Fine Motor	35 (21.2)	43.7 (16.8)	0.340
Problem Solving	42 (13)	50 (16.0)	**0.026**
Personal Social	45 (15.2)	50.6 (10.1)	0.216

12.6. Discussion

Our study showed that offspring exposed to GDM *in utero* had lower scores for communication skills at 3 years of age compared to those who were not exposed to GDM *in utero.* Furthermore, the percentage of children who scored below the threshold indicating developmental delay for communication, problem solving and personal social skills was higher for those exposed to GDM *in utero* compared to those who were not so exposed. In addition, male children had a lower mean score for problem solving than female children. Importantly, our research has identified 3 year old children who would benefit from further clinical assessment of their neurodevelopment who would not otherwise have been identified in routine care.

Previous studies have shown an association between exposure to GDM *in utero* and a delay in achieving neurodevelopmental milestones. A similar recent study found greater externalising and internalising behaviours in 2 year old children exposed to GDM *in utero.* These were attenuated for covariates including maternal depression at 12 months postpartum and prenatal maternal diet [68].

GDM and socioeconomic disadvantage have been shown to have a synergistic effect that impairs neurodevelopment. Both exposure to GDM *in utero* and disadvantage are associated with a 2-fold increased risk of attention deficit hyperactive disorder (ADHD) at age 6 [518]. Communication scores in our study were lower in children exposed to GDM *in utero,* and reduced communication ability is often seen in offspring with ADHD. In our study there were no children who were clinically diagnosed with ADHD by age 3 years. However, it is not likely that we would have seen a child with a diagnosis of ADHD at age 3 because the median age of diagnosis for children with current ADHD is 6 years, and severe cases are seen as early as 4 years [528]. In the Northern Adelaide region, where this study was conducted, there are higher rates of mental illness, low income, accommodation insecurity and poor diet [452].

Socioeconomic disadvantaged children have shown reduced cognitive and behavioural function compared to those living with socioeconomic advantage [529].

The association between maternal GDM and reduced communication score in the ASQ-3 remained after adjusting for child age and maternal history of depression. There have been many studies that have shown that poor maternal mental health in pregnancy affects neurodevelopment in the infant, such as delayed cognition, behavioural and motor differences in childhood, brain development and connectivity [530]. Exposure to GDM *in utero* appears to add to this risk. As the ASQ-3 has a high specificity and sensitivity for detecting neurodevelopmental disorders [531], it may be important to assess neurodevelopment in this cohort at an early age to enable early intervention to reduce the risk of neurodevelopmental delay.

We found that female children exposed to GDM *in utero* had a reduced mean problem solving score than male children exposed to GDM *in utero.* This finding is particularly interesting as, despite the fact that our sample size is small, it agrees with the literature that suggests that males are affected more by intrauterine stress than females [523, 532]. It is thought that the gene encoding o-linked n-acetylglucosamine transferase (OGT) that occurs on the X chromosome, and plays a role in neurodevelopment and metabolism, escapes X inactivation. Therefore, males have reduced expression of this gene in the brain and thus may be more vulnerable to intrauterine stressors [533]. Hyperactivity is observed at a younger age in males and may only become apparent in females as they get older [534]. A recent study found that male offspring exposed to a higher level of maternal glucose *in utero* were more likely to have lower scores in the personal social domain of the ASQ-3 than females [521]. We saw a lower mean score for males but this was not significant.

The percentage of women with previous GDM who participated in this 3-year follow-up reflects the national average (approximately 15%) [4]. From conception to 3 years of age, there is a significant increase in neural synapses and myelination that can be affected by nutrition and inflammation [512]. Assessing offspring at a young age aids early intervention, which evidence shows reduces neurodevelopmental disorders in children [535]. The women and children recruited from this population are from a socioeconomically disadvantaged community, therefore our results are generalisable to similar cohorts.

We acknowledge the following limitations in this study. Only approximately one quarter of participants from the original STOP study attended the 3-year follow-up. Due to the disadvantage in this community, it is difficult to engage the population in clinical research. Approximately 58% of the original STOP Study participants who were contactable either declined to be part of the study, were noncompliant with attendance or were not contactable after first contact. As the study is observational in nature, there are variables for which we could not fully control. Our population was primarily Caucasian. Therefore, our results may not be generalizable to women and children of other ethnicities. Furthermore, we compared offspring exposed to GDM *in utero* to those without GDM *in utero,* but this group encompassed women with different pregnancy complications such as preeclampsia. As preeclampsia can severely impair placental perfusion and reduce nutrient flow to the fetus, it has been shown to also be associated with impaired neurodevelopment[536]. Therefore, it may be that in our non-GDM group other pregnancy complications may have contributed to reduced neurodevelopment masking the full magnitude of effects of GDM.

12.7. Conclusion

We found that exposure to GDM *in utero* was associated with reduced communication skills in 3-year-old children compared to unexposed children after adjustment for maternal history of

depression, child age and gestational age at birth. In addition, exposure to GDM was also associated with a higher percentage of children scoring below the threshold for communication, problem solving and personal social skills, indicating developmental delay. Furthermore, males exposed to GDM *in utero* have reduced problem solving skills compared to their female counterparts. Clinical neurodevelopmental assessment of young children exposed to GDM *in utero* may be beneficial to identify those who would benefit from early intervention. It may be important to investigate the association between GDM and sexual dimorphism in neurodevelopment further.

SECTION 4: Discussion

Final Discussion

Introduction to discussion

The overarching aim of this thesis was to investigate the association between gestational diabetes mellitus (GDM), and antenatal and postpartum health of women with a history of GDM, and the health of their children exposed to GDM *in utero*, three years following birth in a cohort of women and children with low socioeconomic status (SES).

Summary of thesis

In chapters 3, 4 and 6 we completed comprehensive reviews of the literature to elucidate the effect of GDM on subsequent maternal and child cardiovascular health and a detailed investigation of associated risk factors. Women with a history of GDM demonstrate an increase in systolic blood pressure, diastolic blood pressure, body mass index (BMI), total cholesterol, serum triglycerides, low density lipoprotein (LDL), fasting blood glucose, fasting insulin and a decrease in high density lipoprotein (HDL) cholesterol and risk of developing metabolic syndrome compared to those who do not have a history of GDM. These differences were seen as early as <1 year postpartum. Children exposed to GDM *in utero* had significantly higher systolic blood pressure, BMI z-score and serum glucose than those who were not exposed.

Based on the findings of the previous reviews, we sought to determine whether breastfeeding conferred a protective influence on cardiovascular risk factors in women with a history of GDM and children exposed to GDM *in utero.* Our systematic review and meta-analysis revealed that, among women with a history of GDM, breastfeeding was associated with lower serum glucose and lower risk of developing type 2 diabetes mellitus compared to women who did not breastfeed. However, there were not enough

studies to complete a meta-analysis on the effect of breastfeeding on cardiovascular risk factors in children exposed to GDM *in utero.*

We were interested in understanding the effect of antenatal maternal health on development of GDM. Chapter 8 is an observational cohort analysis of the STOP study participants to determine whether antenatal mental health was associated with development of GDM. Risk of developing a mental health disorder, history of depression, antenatal depression, high functioning anxiety and high perceived stress were not associated with development of GDM. Socioeconomic status of the participants may have contributed to the lack of difference between GDM and non-GDM participants.

To complement our systematic review and meta-analysis series and to understand the impact of GDM on cardiovascular disease in a cohort from a socioeconomically disadvantaged background, we completed an observational follow-up of women and their children from the Screening Tests to Predict Poor Outcomes of Pregnancy (STOP) study at 3 years postpartum. In chapter 8, we assessed whether women with a history of GDM and their children exposed to GDM *in utero* exhibited cardiovascular disease risk factors as early as 3 years postpartum. We found that fasting serum insulin was significantly higher in women with a history of GDM compared to those with an uncomplicated pregnancy but this association was mediated by BMI in early index pregnancy and socioeconomic index (SEI). A history of GDM was associated with elevated maternal fasting serum triglycerides at 3 years postpartum after adjustment for the same covariates. Children exposed to GDM *in utero* had greater waist circumference than those born after an uncomplicated pregnancy at 3 years of age. However, this was also attenuated by maternal early pregnancy BMI and SEI.

To determine whether breastfeeding was beneficial for women from a socioeconomically disadvantaged background and their children, we assessed whether breastfeeding for at least 6 months postpartum reduced cardiovascular risk factors in women and children from the STOP cohort at 3 years postpartum in chapter 10. Serum insulin and insulin resistance were significantly lower in women who breastfed for at least 6 months postpartum compared to those who did not but this was attenuated by BMI and SEI. There were no differences in child anthropometric or hemodynamic variables at 3 years of age among those who were breastfed for at least 6 months compared to those who were not. However, subgroup analysis of women who only experienced one or more pregnancy complications showed that women who breastfed for at least 6 months had reduced serum insulin, insulin resistance and serum triglycerides. Their children who were breastfed for at least 6 months had reduced BMI-SDS.

In chapter 11, we undertook an observational analysis of the children of the STOP 3 year follow-up cohort to determine whether children exposed to GDM *in utero* had impaired neurodevelopment compared to children who were not exposed to GDM *in utero,* based on the Ages and Stages Questionnaire at 36 months. There was a reduction in scores for communication, gross motor and problem-solving domains in children exposed to GDM *in utero* compared to children who were not. There were higher rates of failure for the communication, problem solving and personal social domains for children with exposure to GDM *in utero.* When stratified by GDM status and gender, girls exposed to GDM *in utero* had fewer problem solving skills than boys at 3 years of age.

Implications of findings

Hemodynamic profile of women who develop GDM

This study on cardiovascular risk factors in women with a history of GDM revealed that the women who attended the 3 year follow-up had significantly higher systolic and diastolic blood pressure, mean arterial pressure, central systolic and diastolic blood pressure in early gestation compared to those with a non-GDM pregnancy. There is some evidence to suggest that at the time of diagnosis of GDM, women have increased arterial stiffness and changes in hemodynamic function [537, 538]. Mecacci *et al.* 2021 found that women who developed GDM had lower cardiac output and systolic volume than controls at 26-30 weeks' gestation [539]. In this study, differences in diastolic blood pressure, mean arterial pressure, central systolic and diastolic blood pressure in women at 34 weeks' gestation were observed but only when women with GDM were compared with women who had an uncomplicated pregnancy.

There is limited evidence available on hemodynamic changes in early pregnancy preceding GDM. Khalil *et al.* (2012) found that at 11-13 weeks' gestation, women who went on to develop GDM had significantly higher systolic blood pressure and augmentation index (an indicator of arterial stiffness) compared to non-GDM pregnancies [540]. The association between arterial stiffness and development of diabetes is thought to be due to a few different mechanisms. Hyperglycaemia, hyperinsulinemia, oxidative stress and inflammation are thought to alter extracellular matrix and arterial remodelling, hence vascular tone [539, 540]. Women who develop GDM are likely to have poor preconception metabolic health and are more likely to be obese[541]. Therefore, while there may already be metabolic dysfunction pre-pregnancy, the hemodynamic changes that occur during pregnancy may place additional stress on maternal physiology, leading to accelerated vascular damage and β-cell dysfunction that promote

GDM. Hence, GDM status may be a sensitive indicator of poor cardiometabolic health in young women who would not conventionally be assessed for CVD at such an early stage in life.

Obesity and SEI as mediators

Obesity

We found that the associations between GDM in pregnancy and cardiovascular risk factors in women and their children were mediated by obesity. This is an important mediator of developing GDM in women who are young without history of familial diabetes. GDM has been associated with an increased risk of CVD in overweight women (BMI 25-29) but not in women with healthy weight [542]. Women who develop GDM are likely to have entered pregnancy obese/overweight and these women are more likely to exhibit components of metabolic syndrome [543]. In the SCOPE international study which included 5,530 low risk nulliparous women recruited in early pregnancy, women who had MetS in early pregnancy were at increased risk of developing preeclampsia and GDM even with adjustment for lifestyle factors[544].

It has been shown that offspring exposed to GDM *in utero* had higher rates of abnormal glucose tolerance, overweight or obesity, higher blood pressure compared to those who were not exposed to GDM *in utero,* measured at 7 and 11 years' of age, even when adjusted for maternal obesity [226]. At 15 years old, they were more likely to develop metabolic syndrome regardless of maternal obesity [545]. Furthermore, offspring who were born large for gestational age and exposed to either GDM or maternal obesity *in utero* were at higher risk of developing metabolic syndrome in childhood [546]. Children as young as two years old born to mothers who did not have GDM but were obese were more likely to be overweight or obese themselves [547].

Therefore, the association between maternal GDM and child cardio-metabolic outcomes may, at least in part, be attributed to maternal obesity, as well as dietary and exercise habits of the mother which would be similar in the children.

Tam *et al.* showed that offspring exposed to GDM *in utero* had higher rates of abnormal glucose tolerance, overweight or obesity, higher blood pressure compared to those who were not exposed to GDM *in utero,* measured at 7 and 11 years' of age, even when adjusted for maternal obesity [226]. At 15 years old, they were more likely to develop metabolic syndrome regardless of maternal obesity [545]. Boney *et al.* (2005) found that offspring who were born large for gestational age and exposed to either GDM or maternal obesity *in utero* were are a higher risk of developing metabolic syndrome in childhood [546]. Zou *et al.* found that children as young as two years old born to mothers who did not have GDM but were obese were more likely to be overweight or obese themselves [547]. Therefore, the association between maternal GDM and child cardio-metabolic outcomes may be attributed by maternal obesity, as well as dietary and exercise habits of the mother which would be similar in the children.

SEI

Our cohort resides in one of the lowest socioeconomic local government areas in metropolitan Australia, with the mean SEI score 29 (SEI is calculated between 10 and 90 with 10 being the lowest). This cohort reports 10% higher rates of smoking, 21.2% higher rates of mental health and behavioural problems and 6.3% higher rates of diabetes than the Australia average [72]. Therefore, it may be difficult to detect differences between groups due to their low SEI. The association between SEI and CVD is likely influenced by a combination of biological, behavioural and psychosocial risk factors. It has been shown that low to middle SES groups have a higher rate of CVD mortality even after adjustment for medications and CVD risk factors. Cullinan *et al.* (2012)

found that there was a high prevalence of GDM in women from the lowest socioeconomic group compared to the highest [548]. Alvarez-Galvez *et al.* found that poverty influences the effect of BMI on depression in European cohorts and suggested that the relationship between obesity and depression is worsened by SES [549]. Therefore, while it is difficult to engage low socioeconomic cohorts in clinical research, it is valuable to investigate the effect of GDM on maternal and child health in our STOP cohort and similarly disadvantaged communities as they will likely benefit from early screening and targeted preventive measures.

Breastfeeding and reduced cardiovascular risk factors in those exposed to GDM

The findings of this thesis reveal that breastfeeding may be beneficial for women with history of a pregnancy complication, including women with a history of GDM. Development of pregnancy complications may be mediated by genetic and lifestyle factors, including poor lifestyle and diet which contributes to poor metabolic health before pregnancy. When women with poor metabolic health become pregnant, this acts as a 'second hit' for CVD in these women even prior to phenotypic expression of symptoms [227]. However, it is thought that breastfeeding could promote a reduction in the metabolic changes that occur during pregnancy, including a reduction in triglycerides, serum insulin and glucose, which are all precursors for T2DM [550]. Lactation is known to improve insulin sensitivity and glucose tolerance. Women from the SWIFT cohort who experienced GDM but breastfed for at least 6 months had decreased triglycerides and reduced lipogenesis and an improvement in glycolysis at 1-2 years postpartum even with adjustment for maternal BMI and other covariates[551]. The increased energy expenditure during lactation facilitates weight loss and healthy weight retention, therefore benefiting both women with GDM and those who are

overweight/obese [551-553]. Therefore, it will be beneficial to promote breastfeeding in these women to reduce risk of CVD later in life.

Strengths and limitations

The fact that this thesis includes both a series of systematic reviews and meta -analyses and original research is an important strength. The systematic review and meta-analyses series is the first to observe all conventional CVD risk factors in women who experienced GDM and their children exposed to GDM *in utero,* rather than focusing on a few risk factors. The analysis on cardiovascular risk factors in women with a history of GDM is robust, based on evidence from 139 studies. Furthermore, subgroup analysis demonstrated that blood pressure, fasting glucose, triglycerides and risk of metabolic syndrome are already elevated as early as <1 year postpartum, thereby highlighting the importance of early screening for CVD risk factors after a pregnancy complicated by GDM. This timeline of risk factor stratification may be beneficial in preventative treatment for cardiovascular disease, especially in young women. Our analysis of BMI z-score in children with a history of GDM *in utero* includes 31,485 participants. Furthermore, it also included an analysis of cord blood metabolites such as cholesterol, LDL, HDL and glucose, which provide an understanding of the intrauterine environment to which the fetus is exposed.

However, there are limitations. Both GDM and CVD are multifactorial diseases which are influenced by genetic and environmental factors. Therefore, it was not possible to adjust for such important variables due to the limitations in the data that were available. In particular, for the analyses on children exposed to GDM *in utero,* subgroup analyses for sex and age were not possible due to limited data. Substantial heterogeneity was seen for some outcomes throughout all meta-analyses, based on I^2 and Chi^2 values. Heterogeneity was explored through subgroup analyses where practical. However, we attribute any heterogeneity in analyses due to differences in study design such as definition of GDM, time of postpartum screening and methodology.

Our observational follow-up study had some strengths. The original STOP cohort comprised only nulliparous women without serious medical conditions or high-risk pregnancy due to underlying conditions. The socioeconomic profile of the community and study participants render the findings valuable and generalizable to other communities with low socioeconomic status. Importantly, as the STOP study is longitudinal, spanning back to early in the index pregnancy, we were able to assess conventional and non-conventional cardiovascular risk factors in both women in early gestation, late gestation and at 3 years postpartum to allow for a more complete assessment of cardiovascular health from conception to 3 years. We were able to assess hemodynamic and anthropometric markers in STOP children at a young age, including hemodynamic variables that are seldom reported in the literature for this cohort.

A weakness of the STOP follow-up study is the participant loss to attrition. Only approximately ¼ of participants from the original STOP study attended the 3 year follow-up. Majority of this loss was due to loss of contact (primarily due to the low SES community). Hence, there may be risk of selection bias, particularly as those who attended the 3 year follow-up had significantly higher SEI, albeit still relatively low, than those who did not. The small sample size likely attributes to the relatively small, but statistically significant, differences seen in the analyses. As argued earlier this may also be attributable to the SES of the cohort. However, it may be that 3 years postpartum may be very early in the progression to cardiovascular disease making it more difficult to detect differences between pregnancy outcome groups. However, the data provide a baseline from which to assess these women in future to ascertain whether these small differences increase in magnitude over time. Furthermore, as pregnancy complications are not mutually exclusive, both GDM and non-GDM groups consisted of women who experienced other pregnancy complications, such as preeclampsia, gestational hypertension, small for gestational age delivery, and preterm delivery. These pregnancy complications confer their own individual risk of developing cardiovascular disease and

metabolic syndrome [74, 227, 494]. We were unable to control for any variance in this, other than conducting an exploratory analysis assessing women with a history of GDM and their children exposed to GDM *in utero* compared to those who were exposed to an uncomplicated pregnancy at index pregnancy.

Future direction and recommendations

To validate the findings of this thesis, a larger cohort is required. We were able to find small, albeit significant differences, throughout our analyses. The study needs replication in a larger population, ideally across socioeconomic strata, to identify a true association between maternal GDM and subsequent cardiovascular outcomes.

Future research should focus on risk factors that are apparent in young women who are planning pregnancy, such as obesity, in order to mitigate risk of developing GDM. There are no guidelines in Australia for CVD risk factor assessment in individuals younger than 30 years. Therefore, implementing guidelines for CVD risk in young women which incorporate risk mitigation and management of pregnancy complications should be considered. These guidelines should also educate on child health after being exposed to a pregnancy complication *in utero.*

It has previously been shown that postpartum diabetes screening in Australian women with a history of GDM was undertaken in just 66% which was even lower for women who were indigenous (approximately 30%)[554]. Evidence suggests that postpartum lifestyle interventions (i.e. diet and exercise) for women with a history of GDM within 3 years postpartum can reduce the development of diabetes by 43%[555]. Therefore, it is necessary to educate women on the importance of regular oral glucose tolerance testing every 2-3 years after a GDM pregnancy and maintaining a healthy lifestyle to significantly reduce their risk of CVD. A nurse practitioner led postpartum outpatient clinic for women after severe pregnancy complications

(including women who developed GDM in pregnancy who were on insulin or metformin therapy) is now provided through the Lyell McEwin Hospital for women who are referred for counselling at 6 months, 1 year and 5 years postpartum. This service provides a comprehensive assessment of maternal demographics, medical history and biochemical testing to ascertain cardiovascular risk status and provide advice on how to reduce this risk through healthy lifestyle change and further referral to GP and nutritional planning[556].

Final remarks

Pregnancy complications, including GDM, signal risk for future cardio-metabolic disease in both women and children. Preconception planning and assessing metabolic health, particularly mitigation of obesity and poor lifestyle factors, may reduce risk of developing GDM. Postpartum intervention for women with pregnancy complications is necessary to reduce the risk of cardio-metabolic disease later in life. This should be offered through postpartum interventions such as women's heart health clinics and regular monitoring provided by the GP, including educating women on the importance of a healthy lifestyle for a happy, fulfilling life for both mother and child.

References:

1. CHU SY, CALLAGHAN WM, KIM SY, et al. Maternal Obesity and Risk of Gestational Diabetes Mellitus. Diabetes Care 2007;30:2070-76.
2. WELFARE AIOHA. Incidence of gestational diabetes in Australia. Canberra: AIHW, 2019.
3. NANKERVIS A MH, MOSES R, ROSS G, CALLAWAY L, PORTER C ET AL. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes mellitus in Australia. . In: Society. ADiP, ed. Sydney, 2014.
4. AIHW. Incidence of gestational diabetes in Australia. Canberra: AIHW, 2019 (vol CVD 85

).
5. BUCHANAN TA, XIANG AH, PAGE KA. Gestational diabetes mellitus: risks and management during and after pregnancy. Nature reviews Endocrinology 2012;8:639-49.
6. GROUP HSCR. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes 2009;58:453-59.
7. ABELL SK, DE COURTEN B, BOYLE JA, TEEDE HJ. Inflammatory and Other Biomarkers: Role in Pathophysiology and Prediction of Gestational Diabetes Mellitus. Int J Mol Sci 2015;16:13442-73.
8. NAPSO T, YONG HEJ, LOPEZ-TELLO J, SFERRUZZI-PERRI AN. The Role of Placental Hormones in Mediating Maternal Adaptations to Support Pregnancy and Lactation. Front Physiol 2018;9:1091.
9. FASSHAUER M, BLÜHER M, STUMVOLL M. Adipokines in gestational diabetes. Lancet Diabetes Endocrinol 2014;2:488-99.
10. BUTLER AE, CAO-MINH L, GALASSO R, et al. Adaptive changes in pancreatic beta cell fractional area and beta cell turnover in human pregnancy. Diabetologia 2010;53:2167-76.
11. CATALANO PM, DRAGO NM, AMINI SB. Longitudinal changes in pancreatic beta-cell function and metabolic clearance rate of insulin in pregnant women with normal and abnormal glucose tolerance. Diabetes Care 1998;21:403-8.
12. DA ROCHA AF, LIBONI TF, KURAUTI MA, et al. Tumor necrosis factor alpha abolished the suppressive effect of insulin on hepatic glucose production and glycogenolysis stimulated by cAMP. Pharmacol Rep 2014;66:380-5.
13. OLSON AL. Regulation of GLUT4 and Insulin-Dependent Glucose Flux. ISRN Mol Biol 2012;2012:856987.
14. RUAN H, LODISH HF. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. Cytokine Growth Factor Rev 2003;14:447-55.
15. SOLOMON SS, ODUNUSI O, CARRIGAN D, et al. TNF-alpha inhibits insulin action in liver and adipose tissue: A model of metabolic syndrome. Horm Metab Res 2010;42:115-21.
16. REHMAN K, AKASH MS. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J Biomed Sci 2016;23:87.
17. IQBAL J, MASCARENO E, CHUA S, HUSSAIN MM. Leptin-mediated differential regulation of microsomal triglyceride transfer protein in the intestine and liver affects plasma lipids. J Biol Chem 2020;295:4101-13.
18. KARPICHEV IV, CORNIVELLI L, SMALL GM. Multiple regulatory roles of a novel Saccharomyces cerevisiae protein, encoded by YOL002c, in lipid and phosphate metabolism. J Biol Chem 2002;277:19609-17.
19. CONSIDINE RV, SINHA MK, HEIMAN ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292-5.
20. YAMAUCHI T, KAMON J, WAKI H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-6.
21. YAMAUCHI T, KAMON J, MINOKOSHI Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288-95.
22. NAYAK M, EEKHOFF ME, PEINHAUPT M, HEINEMANN A, DESOYE G, VAN POPPEL MN. Cytokines and their association with insulin resistance in obese pregnant women with different levels of physical activity. Cytokine 2016;77:72-8.
23. KORKMAZER E, SOLAK N. Correlation between inflammatory markers and insulin resistance in pregnancy. J Obstet Gynaecol 2015;35:142-5.
24. GEORGIOU HM, LAPPAS M, GEORGIOU GM, et al. Screening for biomarkers predictive of gestational diabetes mellitus. Acta Diabetol 2008;45:157-65.

25. LOWE LP, METZGER BE, LOWE WL, JR., DYER AR, MCDADE TW, MCINTYRE HD. Inflammatory mediators and glucose in pregnancy: results from a subset of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. J Clin Endocrinol Metab 2010;95:5427-34.
26. CHALLIS JR, LOCKWOOD CJ, MYATT L, NORMAN JE, STRAUSS JF, 3RD, PETRAGLIA F. Inflammation and pregnancy. Reprod Sci 2009;16:206-15.
27. KIM C. Maternal outcomes and follow-up after gestational diabetes mellitus. Diabet Med 2014;31:292-301.
28. AIHW. Cardiovascular diseases. Canberra, 2020 (vol CVD 83).
29. HAJAR R. Risk Factors for Coronary Artery Disease: Historical Perspectives. Heart views : the official journal of the Gulf Heart Association 2017;18:109-14.
30. FORD ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care 2005;28:2745-9.
31. MCLAUGHLIN T, LAMENDOLA C, LIU A, ABBASI F. Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. J Clin Endocrinol Metab 2011;96:E1756-60.
32. JUNG UJ, CHOI MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci 2014;15:6184-223.
33. TAN HW, LIU X, BI XP, et al. IL-18 overexpression promotes vascular inflammation and remodeling in a rat model of metabolic syndrome. Atherosclerosis 2010;208:350-7.
34. BELLAMY L, CASAS JP, HINGORANI AD, WILLIAMS D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373:1773-9.
35. KRAMER CK, CAMPBELL S, RETNAKARAN R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia 2019;62:905-14.
36. PATHIRANA MM, LASSI Z, ALI A, ARSTALL M, ROBERTS CT, ANDRAWEERA PH. Cardiovascular risk factors in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. Rev Endocr Metab Disord 2020.
37. *Diagnostic and statistical manual of mental disorders : DSM-5.* Washington, DC: American Psychiatric Association; Number of pages.
38. HUANG T, WANG T, ZHENG Y, et al. Association of Birth Weight With Type 2 Diabetes and Glycemic Traits: A Mendelian Randomization Study. JAMA Netw Open 2019;2:e1910915.
39. AIHW. Perinatal depression: data from the 2010 Australian National Infant Feeding Survey. Canberra: AIHW, 2012 (vol PHE 161).
40. OGBO FA, EASTWOOD J, HENDRY A, et al. Determinants of antenatal depression and postnatal depression in Australia. BMC Psychiatry 2018;18:49.
41. MÍGUEZ MC, VÁZQUEZ MB. Risk factors for antenatal depression: A review. World J Psychiatry 2021;11:325-36.
42. ISAACS AN, ENTICOTT J, MEADOWS G, INDER B. Lower Income Levels in Australia Are Strongly Associated With Elevated Psychological Distress: Implications for Healthcare and Other Policy Areas. Frontiers in psychiatry 2018;9:536-36.
43. MOULTON CD, PICKUP JC, ISMAIL K. The link between depression and diabetes: the search for shared mechanisms. Lancet Diabetes Endocrinol 2015;3:461-71.
44. OSMOND C, BARKER DJ. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000;108 Suppl 3:545-53.
45. BARKER DJ. Fetal origins of coronary heart disease. BMJ 1995;311:171-4.
46. LANDON MB, RICE MM, VARNER MW, et al. Mild gestational diabetes mellitus and long-term child health. Diabetes care 2015;38:445-52.
47. FANG J, MADHAVAN S, ALDERMAN MH. The influence of maternal hypertension on low birth weight: differences among ethnic populations. Ethn Dis 1999;9:369-76.
48. BARKER DJ. The origins of the developmental origins theory. J Intern Med 2007;261:412-7.
49. MITANCHEZ D, YZYDORCZYK C, SIDDEEK B, BOUBRED F, BENAHMED M, SIMEONI U. The offspring of the diabetic mother – Short- and long-term implications. Best Practice & Research Clinical Obstetrics & Gynaecology 2015;29:256-69.
50. PETTITT DJ, NELSON RG, SAAD MF, BENNETT PH, KNOWLER WC. Diabetes and Obesity in the Offspring of Pima Indian Women With Diabetes During Pregnancy. Diabetes Care 1993;16:310-14.

51. COLES N, PATEL BP, BIRKEN C, HANLEY AJ, RETNAKARAN R, J KH. Determinants of insulin resistance in children exposed to gestational diabetes in utero. Pediatr Diabetes 2020;21:1150-58.
52. ACETI A, SANTHAKUMARAN S, LOGAN KM, et al. The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. Diabetologia 2012;55:3114-27.
53. AGBAJE AO, BARKER AR, TUOMAINEN TP. Arterial stiffness in adolescence predicts elevated blood pressure in young adulthood: the ALSPAC study. European Heart Journal 2021;42.
54. BLOTSKY AL, RAHME E, DAHHOU M, NAKHLA M, DASGUPTA K. Gestational diabetes associated with incident diabetes in childhood and youth: a retrospective cohort study. Canadian Medical Association Journal 2019;191:E410-E17.
55. BIDER-CANFIELD Z, MARTINEZ MP, WANG X, et al. Maternal obesity, gestational diabetes, breastfeeding and childhood overweight at age 2 years. Pediatr Obes 2017;12:171-78.
56. SHOKRY E, MARCHIORO L, UHL O, et al. Impact of maternal BMI and gestational diabetes mellitus on maternal and cord blood metabolome: results from the PREOBE cohort study. Acta Diabetol 2019;56:421-30.
57. ORGANISATION WH. Exclusive breastfeeding for six months best for babies everywhere. Geneva: WHO, 2011.
58. MARTIN CR, LING PR, BLACKBURN GL. Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. Nutrients 2016;8.
59. RAMEEZ RM, SADANA D, KAUR S, et al. Association of Maternal Lactation With Diabetes and Hypertension: A Systematic Review and Meta-analysis. JAMA Netw Open 2019;2:e1913401.
60. YAN J, LIU L, ZHU Y, HUANG G, WANG PP. The association between breastfeeding and childhood obesity: a meta-analysis. BMC Public Health 2014;14:1267.
61. LAURITZEN L, BRAMBILLA P, MAZZOCCHI A, HARSLØF LB, CIAPPOLINO V, AGOSTONI C. DHA Effects in Brain Development and Function. Nutrients 2016;8.
62. ZORNOZA-MORENO M, FUENTES-HERNÁNDEZ S, CARRIÓN V, et al. Is low docosahexaenoic acid associated with disturbed rhythms and neurodevelopment in offsprings of diabetic mothers? Eur J Clin Nutr 2014;68:931-7.
63. THOMAS BA, GHEBREMESKEL K, LOWY C, OFFLEY-SHORE B, CRAWFORD MA. Plasma fatty acids of neonates born to mothers with and without gestational diabetes. Prostaglandins Leukot Essent Fatty Acids 2005;72:335-41.
64. DEVARSHI PP, GRANT RW, IKONTE CJ, HAZELS MITMESSER S. Maternal Omega-3 Nutrition, Placental Transfer and Fetal Brain Development in Gestational Diabetes and Preeclampsia. Nutrients 2019;11:1107.
65. DEVARSHI PP, GRANT RW, IKONTE CJ, HAZELS MITMESSER S. Maternal Omega-3 Nutrition, Placental Transfer and Fetal Brain Development in Gestational Diabetes and Preeclampsia. Nutrients 2019;11.
66. TALGE NM, NEAL C, GLOVER V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry 2007;48:245-61.
67. WANG T, LIU K, LI Z, et al. Prevalence of attention deficit/hyperactivity disorder among children and adolescents in China: a systematic review and meta-analysis. BMC Psychiatry 2017;17:32.
68. KRZECZKOWSKI JE, LAU A, FITZPATRICK J, et al. Maternal Metabolic Complications in Pregnancy and Offspring Behavior Problems at 2 Years of Age. Matern Child Health J 2019;23:746-55.
69. ALVES JM, LUO S, CHOW T, HERTING M, XIANG AH, PAGE KA. Sex differences in the association between prenatal exposure to maternal obesity and hippocampal volume in children. Brain Behav 2020;10:e01522.
70. LYNCH KM, ALVES JM, CHOW T, et al. Selective morphological and volumetric alterations in the hippocampus of children exposed in utero to gestational diabetes mellitus. Human brain mapping 2021;42:2583-92.
71. PHIDU. Social Health Atlas: 2021 Census data by Socioeconomic Disadvantage of Area. . In: PHIDU, ed. Adelaide: Torrens University, 2021.
72. PHN. Northern Adelaide:Undesrtanding the Health of the Adelaide Reigion *Undesrtanding the Health of the Adelaide Reigion* Adelaide: Primary Health Network, 2018.
73. ANDRAWEERA PH, DEKKER G, LEEMAQZ S, et al. Effect of Birth Weight and Early Pregnancy BMI on Risk for Pregnancy Complications. Obesity (Silver Spring) 2019;27:237-44.
74. PLUMMER MD, ANDRAWEERA PH, GARRETT A, et al. Hypertensive disorders of pregnancy and later cardiovascular disease risk in mothers and children. J Dev Orig Health Dis 2020:1-6.
75. GARRETT A. The impact of intrauterine exposures on neurodevelopmental outcomes in 8–10 year old children within a disadvantaged population: The University of Adelaide, 2019.
76. ORGANIZATION WH. Cardiovascular diseases (CVD)*Cardiovascular diseases*. Geneva: World Health Organization, 2017.
77. Cardiovascular disease in women—a snapshot of national statistics. In: AIHW, ed. Canberra: AIHW, 2019.

78. ANDRAWEERA PH, DEKKER GA, ARSTALL M, BIANCO-MIOTTO T, ROBERTS CT. Complications of Pregnancy and Future Cardiovascular Risk. *Encylopedia of Cardiovascular Research and Medicine*. Netherlands: Oxford, 2018 (vol 1).
79. FEDERATION ID. IDF Diabetes Atlas. Belgium, Brussels: International Diabetes Federation, 2017 (vol 8th Edition).
80. COUSTAN DR, LOWE LP, METZGER BE, DYER AR, INTERNATIONAL ASSOCIATION OF D, PREGNANCY STUDY G. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. American journal of obstetrics and gynecology 2010;202:654.e1-54.e6546.
81. ZIMMET PZ, ALBERTI KG, SHAW JE. Mainstreaming the metabolic syndrome: a definitive definition. Med J Aust 2005;183:175-6.
82. CHEN Z, IONA A, PARISH S, et al. Adiposity and risk of ischaemic and haemorrhagic stroke in 0·5 million Chinese men and women: a prospective cohort study. Lancet Glob Health 2018;6:e630-e40.
83. LACEY B, LEWINGTON S, CLARKE R, et al. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0·5 million adults in China: a prospective cohort study. Lancet Glob Health 2018;6:e641-e49.
84. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
85. METZGER BE, GABBE SG, PERSSON B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care 2010;33:676.
86. WELLS G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. http://www ohri ca/programs/clinical_epidemiology/oxford asp 2001.
87. HAKKARAINEN H, HUOPIO H, CEDERBERG H, PAAKKONEN M, VOUTILAINEN R, HEINONEN S. Post-challenge glycemia during pregnancy as a marker of future risk of type 2 diabetes: a prospective cohort study. Gynecol Endocrinol 2015;31:573-7.
88. HAKKARAINEN H, HUOPIO H, CEDERBERG H, PAAKKONEN M, VOUTILAINEN R, HEINONEN S. The risk of metabolic syndrome in women with previous GDM in a long-term follow-up. Gynecol Endocrinol 2016;32:920-25.
89. HEIDA KY, FRANX A, VAN RIJN BB, et al. Earlier Age of Onset of Chronic Hypertension and Type 2 Diabetes Mellitus After a Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus. Hypertension (0194911X) 2015;66:1116-22.
90. THOMANN R, ROSSINELLI N, KELLER U, et al. Differences in low-grade chronic inflammation and insulin resistance in women with previous gestational diabetes mellitus and women with polycystic ovary syndrome. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2008;24:199-206.
91. ANASTASIOU E, LEKAKIS JP, ALEVIZAKI M, et al. Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. Diabetes Care 1998;21:2111-15.
92. AKINCI B, CELTIK A, YENER S, YESIL S. Is fasting glucose level during oral glucose tolerance test an indicator of the insulin need in gestational diabetes? Diabetes Res Clin Pract 2008;82:219-25.
93. BANERJEE M, ANDERSON SG, MALIK RA, AUSTIN CE, CRUICKSHANK JK. Small artery function 2 years postpartum in women with altered glycaemic distributions in their preceding pregnancy. Clin Sci (Lond) 2012;122:53-61.
94. BENTLEY-LEWIS R, CLAGGETT B, LIU J, et al. Baseline characteristics and cardiovascular outcomes in women with a history of gestational diabetes in the evaluation of lixisenatide in acute coronary syndrome trial. Diabetes 2016;65:A356.
95. BO S, VALPREDA S, MENATO G, et al. Should we consider gestational diabetes a vascular risk factor? Atherosclerosis 2007;194:e72-9.
96. CALISKAN M, CAKLILI OT, CALISKAN Z, et al. Does gestational diabetes history increase epicardial fat and carotid intima media thickness? Echocardiography (Mount Kisco, NY) 2014;31:1182-7.
97. CARR DB, UTZSCHNEIDER KM, HULL RL, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care 2006;29:2078-83.
98. CELLINA G, LO CICERO G, BRINA A, ZANCHETTI A. Reversible alteration of myocardial function in gestational diabetes. Eur Heart J 1983;4:59-63.
99. CHARWAT-RESL S, YARRAGUDI R, HEIMBACH M, et al. Microvascular function in women with former gestational diabetes: A cohort study. Diabetes and Vascular Disease Research 2017;14:214-20.

100. DAVENPORT MH, GOSWAMI R, SHOEMAKER JK, MOTTOLA MF. Influence of hyperglycemia during and after pregnancy on postpartum vascular function. Am J Physiol Regul Integr Comp Physiol 2012;302:R768-75.
101. DAVIS CL, GUTT M, LLABRE MM, et al. History of gestational diabetes, insulin resistance and coronary risk. J Diabetes Complications 1999;13:216-23.
102. FAKHRZADEH H, ALATAB S, SHARIFI F, et al. Carotid intima media thickness, brachial flow mediated dilation and previous history of gestational diabetes mellitus. J Obstet Gynaecol Res 2012;38:1057-63.
103. FERRADA C, MOLINA M, CID L, RIEDEL G, FERRADA C, AREVALO R. [Relationship between gestational diabetes and metabolic syndrome]. Rev Med Chil 2007;135:1539-45.
104. FREIRE CM, NUNES MDO C, BARBOSA MM, et al. Gestational diabetes: a condition of early diastolic abnormalities in young women. J Am Soc Echocardiogr 2006;19:1251-6.
105. GUNDERSON EP, CHIANG V, PLETCHER MJ, et al. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the Coronary Artery Risk Development in Young Adults study. Journal of the American Heart Association 2014;3:e000490.
106. GUNDERSON EP, JACOBS DR, JR., CHIANG V, et al. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-Year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). Diabetes 2010;59:495-504.
107. HUNGER-DATHE W, MOSEBACH N, SAMANN A, WOLF G, MULLER UA. Prevalence of impaired glucose tolerance 6 years after gestational diabetes. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2006;114:11-7.
108. KO GTC, CHAN JCN, TSANG LWW, LI CY, COCKRAM CS. Glucose intolerance and other cardiovascular risk factors in Chinese women with a history of gestational diabetes mellitus. Australian and New Zealand Journal of Obstetrics and Gynaecology 1999;39:478-83.
109. KRISHNAVENI GV, HILL JC, VEENA SR, et al. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. Diabetes Research & Clinical Practice 2007;78:398-404.
110. LEE H, JANG HC, PARK HK, METZGER BE, CHO NH. Prevalence of type 2 diabetes among women with a previous history of gestational diabetes mellitus. Diabetes Research & Clinical Practice 2008;81:124-29.
111. LEE V, BURWICK R, PILLIOD R, SHAFFER B, CHENG Y, CAUGHEY A. Outcomes of late preterm pregnancies complicated by gestational diabetes mellitus and polyhydramnios. American Journal of Obstetrics and Gynecology 2015;212:S352.
112. MADARÁSZ E, TAMÁS G, TABÁK AG, KERÉNYI Z. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. Diabetes Research & Clinical Practice 2009;85:197-202.
113. MAI C, WANG B, WEN J, LIN X, NIU J. Lipoprotein-associated phospholipase A2 and AGEs are associated with cardiovascular risk factors in women with history of gestational diabetes mellitus. Gynecological Endocrinology 2014;30:241-44.
114. MEIER JJ, GALLWITZ B, ASKENAS M, et al. Secretion of incretin hormones and the insulinotropic effect of gastric inhibitory polypeptide in women with a history of gestational diabetes. Diabetologia 2005;48:1872-81.
115. MINOOEE S, RAMEZANI TEHRANI F, RAHMATI M, MANSOURNIA MA, AZIZI F. Diabetes incidence and influencing factors in women with and without gestational diabetes mellitus: A 15year population-based follow-up cohort study. Diabetes Research & Clinical Practice 2017;128:24-31.
116. MOLEDA P, FRONCZYK A, SAFRANOW K, MAJKOWSKA L. Is Uric Acid a Missing Link between Previous Gestational Diabetes Mellitus and the Development of Type 2 Diabetes at a Later Time of Life? PLoS One 2016;11:e0154921.
117. NOCTOR E, CROWE C, CARMODY LA, et al. Abnormal glucose tolerance post-gestational diabetes mellitus as defined by the International Association of diabetes and Pregnancy Study Groups criteria. European Journal of Endocrinology 2016;175:287-97.
118. NOUHJAH S, SHAHBAZIAN H, SHAHBAZIAN N, et al. Early postpartum metabolic syndrome in women with or without gestational diabetes: Results from Life after Gestational Diabetes Ahvaz cohort study. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2018;12:317-23.
119. RAUTIO N, JOKELAINEN J, KORPI-HYOVALTI E, et al. Lifestyle intervention in prevention of type 2 diabetes in women with a history of gestational diabetes mellitus: one-year results of the FIN-D2D project. J Womens Health (Larchmt) 2014;23:506-12.

120. ROCA-RODRIGUEZ MM, LOPEZ-TINOCO C, MURRI M, et al. Postpartum development of endothelial dysfunction and oxidative stress markers in women with previous gestational diabetes mellitus. J Endocrinol Invest 2014;37:503-9.
121. RYAN AS, MCLENITHAN JC, ZIETOWSKI GM. Accelerated metabolic susceptibility to type 2 diabetes in older women with a history of gestational diabetes. Endocrine Connections 2013;2:79-86.
122. SIMMONS D, KUMAR S, CROOK N, RUSH E. Diabetes among Māori women with self-reported past gestational diabetes mellitus in a New Zealand Māori community. Australian & New Zealand Journal of Obstetrics & Gynaecology 2017;57:599-603.
123. SRIHARAN M, REICHELT AJ, OPPERMAN MLR, et al. Total sialic acid and associated elements of the metabolic syndrome in women with and without previous gestational diabetes. Diabetes Care 2002;25:1331-35.
124. SUNG HC, SOO HK, YOUN BS, et al. High plasma retinol binding protein-4 and low plasma adiponectin concentrations are associated with severity of glucose intolerance in women with previous gestational diabetes mellitus. Journal of Clinical Endocrinology and Metabolism 2008;93:3142-48.
125. RAMEZANI TEHRANI F, HASHEMI S, HASHEMINIA M, AZIZI F. Follow-up of women with gestational diabetes in the Tehran Lipid and Glucose Study (TLGS): A population-based cohort study. Journal of Obstetrics & Gynaecology Research 2012;38:698-704.
126. VERMA A, BONEY CM, TUCKER R, VOHR BR. Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. Journal of Clinical Endocrinology and Metabolism 2002;87:3227-35.
127. VILMI-KERALA T, PALOMAKI O, KANKKUNEN P, JUURINEN L, UOTILA J, PALOMAKI A. Oxidized LDL, insulin resistance and central blood pressure after gestational diabetes mellitus. Acta Obstet Gynecol Scand 2016;95:1425-32.
128. WINHOFER Y, KRSSAK M, WOLF P, et al. Hepatic rather than cardiac steatosis relates to glucose intolerance in women with prior gestational diabetes. PLoS One 2014;9:e91607.
129. ZAJDENVERG L, RODACKI M, FARIA JP, PIRES MLE, OLIVEIRA JEP, HALFOUN VLC. Precocious markers of cardiovascular risk and vascular damage in apparently healthy women with previous gestational diabetes. Diabetology and Metabolic Syndrome 2014;6.
130. LIM S, CHOI SH, PARK YJ, et al. Visceral fatness and insulin sensitivity in women with a previous history of gestational diabetes mellitus. Diabetes Care 2007;30:348-53.
131. ALBAREDA M, DE LEIVA A, CORCOY R. Reproducibility of diabetes mellitus diagnosis (WHO 1999 criteria) in women. Acta Diabetol 2004;41:14-7.
132. BENTLEY-LEWIS R, HUYNH J, XIONG G, et al. Metabolomic profiling in the prediction of gestational diabetes mellitus. Diabetologia 2015;58:1329-32.
133. HANNEMANN MM, LIDDELL WG, SHORE AC, CLARK PM, TOOKE JE. Vascular function in women with previous gestational diabetes mellitus. Journal of Vascular Research 2002;39:311-19.
134. HU J, BJÖRKLUND A, NYMAN M, GENNSER G. Mechanical properties of large arteries in mother and fetus during normal and diabetic pregnancy. Journal of Maternal-Fetal Investigation 1998;8:185-93.
135. LAUENBORG J, MATHIESEN E, HANSEN T, et al. The prevalence of the metabolic syndrome in a Danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. Journal of Clinical Endocrinology and Metabolism 2005;90:4004-10.
136. LEKVA T, BOLLERSLEV J, GODANG K, et al. β-cell dysfunction in women with previous gestational diabetes is associated with visceral adipose tissue distribution. European Journal of Endocrinology 2015;173:63-70.
137. RETNAKARAN R, QI Y, CONNELLY PW, SERMER M, HANLEY AJ, ZINMAN B. The graded relationship between glucose tolerance status in pregnancy and postpartum levels of low-density-lipoprotein cholesterol and apolipoprotein B in young women: implications for future cardiovascular risk. J Clin Endocrinol Metab 2010;95:4345-53.
138. RUKSASAKUL R, THARAVANIJ T, SRITIPSUKHO P. Metabolic syndrome in Thai women previously diagnosed with gestational diabetes. Journal of the Medical Association of Thailand 2016;99:S195-S202.
139. TODORIC J, HANDISURYA A, PERKMANN T, et al. Circulating progranulin levels in women with gestational diabetes mellitus and healthy controls during and after pregnancy. European Journal of Endocrinology 2012;167:561-67.
140. WANG Y, CHEN L, HORSWELL R, et al. Racial differences in the association between gestational diabetes mellitus and risk of type 2 diabetes. J Womens Health (Larchmt) 2012;21:628-33.

141. UELAND T, MICHELSEN AE, AUKRUST P, HENRIKSEN T, BOLLERSLEV J, LEKVA T. Adipokines and macrophage markers during pregnancy-Possible role for sCD163 in prediction and progression of gestational diabetes mellitus. Diabetes Metab Res Rev 2019;35:e3114.
142. AJALA O, JENSEN LA, RYAN E, CHIK C. Women with a history of gestational diabetes on long-term follow up have normal vascular function despite more dysglycemia, dyslipidemia and adiposity. Diabetes Research & Clinical Practice 2015;110:309-14.
143. AKINCI B, CELTIK A, GENC S, et al. Evaluation of postpartum carbohydrate intolerance and cardiovascular risk factors in women with gestational diabetes. Gynecological Endocrinology 2011;27:361-67.
144. AKINCI B, CELTIK A, TUNALI S, et al. Circulating apelin levels are associated with cardiometabolic risk factors in women with previous gestational diabetes. Archives of Gynecology & Obstetrics 2014;289:787-93.
145. BOWES SB, HENNESSY TR, UMPLEBY AM, et al. Measurement of glucose metabolism and insulin secretion during normal pregnancy and pregnancy complicated by gestational diabetes. Diabetologia 1996;39:976-83.
146. BOZKURT L, GOBL CS, TURA A, et al. Fatty liver index predicts further metabolic deteriorations in women with previous gestational diabetes. PLoS One 2012;7:e32710.
147. COCILOVO G, TOMASI F, GUERRA S, ZAMPINI A, COCURULLO A. Risk factors associated with persistence of glucose intolerance one year after gestational diabetes. Diabete Metab 1990;16:187-91.
148. COUCH SC, PHILIPSON EH, BENDEL RB, WIJENDRAN V, LAMMI-KEEFE CJ. Maternal and cord plasma lipid and lipoprotein concentrations in women with and without gestational diabetes mellitus: Predictors of birth weight? Journal of Reproductive Medicine for the Obstetrician and Gynecologist 1998;43:816-22.
149. DEMIR T, AKINCI B, YENER S, ARGUN L, ÖZCAN M, ERASLAN S. Endothelium-Dependent Hemostatic Factors in Women with Previous Gestational. Turkish Journal of Endocrinology and Metabolism 2016;20.
150. DORNHORST A, BAILEY PC, ANYAOKU V, ELKELES RS, JOHNSTON DG, BEARD RW. Abnormalities of glucose tolerance following gestational diabetes. The Quarterly journal of medicine 1990;77:1219-28.
151. EROGLU D, ZEYNELOGLU HB. Metabolic disorders in patients with recent gestational diabetes mellitus. J Obstet Gynaecol Res 2006;32:408-15.
152. GADGIL MD, OZA-FRANK R, KANDULA NR, KANAYA AM. Type 2 diabetes after gestational diabetes mellitus in South Asian women in the United States. Diabetes/Metabolism Research and Reviews 2017;33.
153. KOUSTA E, LAWRENCE NJ, GODSLAND IF, et al. Insulin resistance and β-cell dysfunction in normoglycaemic European women with a history of gestational diabetes. Clinical Endocrinology 2003;59:289-97.
154. LEE AJ, HISCOCK RJ, WEIN P, WALKER SP, PERMEZEL M. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. Diabetes Care 2007;30:878-83.
155. LINNE Y, BARKELING B, ROSSNER S. Natural course of gestational diabetes mellitus: long term follow up of women in the SPAWN study. BJOG : an international journal of obstetrics and gynaecology 2002;109:1227-31.
156. MAGENHEIM R, EL HADJ OTHMANE T, SCHÄFER-GRAF UM, et al. Arterial stiffness of young women with previous gestational diabetes. Archives of Gynecology and Obstetrics 2010;282:S146-S47.
157. MCLACHLAN KA, ALFORD FP. The impact of acute elevation of non-esterified fatty acids on insulin sensitivity and secretion in women with former gestational diabetes. Clinical Endocrinology 2005;62:79-84.
158. MORBIDUCCI U, DI BENEDETTO G, KAUTZKY-WILLER A, DERIU MA, PACINI G, TURA A. Identification of a model of non-esterified fatty acids dynamics through genetic algorithms: The case of women with a history of gestational diabetes. Computers in Biology and Medicine 2011;41:146-53.
159. OSEI K, GAILLARD TR, SCHUSTER DP. History of gestational diabetes leads to distinct metabolic alterations in nondiabetic African-American women with a parental history of type 2 diabetes. Diabetes Care 1998;21:1250-57.
160. PIMENTA WP, CALDERON IMP, CRUZ NS, SANTOS ML, ARAGON FF, PADOVANI CR. Subclinical abnormalities of glucose metabolism in Brazilian women with a history of gestational diabetes mellitus. Acta Obstetricia et Gynecologica Scandinavica 2004;83:1152-58.
161. PRIKOSZOVICH T, WINZER C, SCHMID AI, et al. Body and liver fat mass rather than muscle mitochondrial function determine glucose metabolism in women with a history of gestational diabetes mellitus. Diabetes Care 2011;34:430-36.
162. RAWAL S, TSAI MY, HINKLE SN, et al. A longitudinal study of thyroid markers across pregnancy and the risk of gestational diabetes. Journal of Clinical Endocrinology and Metabolism 2018;103:2447-56.

163. RIVAS A, LANDON M, GAILLARD T, SCHUSTER D, OSEI K. Awareness of risk factors for type 2 diabetes in women with current and former gestational diabetes mellitus (GDM): Implications for future primary diabetes prevention. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2010;4:89-94.
164. RYAN EA, IMES S, LIU D, et al. Defects in insulin secretion and action in women with a history of gestational diabetes. Diabetes 1995;44:506-12.
165. SEGHIERI G, TESI F, BIANCHI L, et al. Taurine in women with a history of gestational diabetes. Diabetes Research & Clinical Practice 2007;76:187-92.
166. SHEN Y, WANG P, WANG L, et al. Gestational diabetes with diabetes and prediabetes risks: a large observational study. Eur J Endocrinol 2018;179:51-58.
167. SIMMONS D, KUMAR S, CROOK N, RUSH E. Diabetes among Maori women with self-reported past gestational diabetes mellitus in a New Zealand Maori community. Aust N Z J Obstet Gynaecol 2017;57:599-603.
168. TOBIAS DK, STUART JJ, SHANSHAN L, et al. Association of History of Gestational Diabetes With Long-term Cardiovascular Disease Risk in a Large Prospective Cohort of US Women. JAMA Internal Medicine 2017;177:1735-42.
169. VIGNEAULT J, LEMIEUX S, GARNEAU V, WEISNAGEL SJ, TCHERNOF A, ROBITAILLE J. Association between metabolic deteriorations and prior gestational diabetes according to weight status. Obesity (Silver Spring) 2015;23:345-50.
170. VITORATOS N, SALAMALEKIS E, KASSANOS D, et al. Maternal plasma leptin levels and their relationship to insulin and glucose in gestational-onset diabetes. Gynecol Obstet Invest 2001;51:17-21.
171. WANG YM, ZHAO LH, SU JB, et al. Glycemic variability in normal glucose tolerance women with the previous gestational diabetes mellitus. Diabetology and Metabolic Syndrome 2015;7.
172. WENDER-OZEGOWSKA E, SPORNA M, ZAWIEJSKA A, SPORNA A, BRAZERT J. Components of metabolic syndrome in women after gestational diabetes. Polskie Archiwum Medycyny Wewnetrznej 2007;117:457-62.
173. WINZER C, WAGNER O, FESTA A, et al. Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus. Diabetes Care 2004;27:1721-27.
174. KJOS SL, BUCHANAN TA, MONTORO M, COULSON A, MESTMAN JH. Serum lipids within 36 mo of delivery in women with recent gestational diabetes. Diabetes 1991;40:142-46.
175. FERRAZ TB, MOTTA RS, FERRAZ CL, CAPIBARIBE DM, FORTI AC, CHACRA AR. C-reactive protein and features of metabolic syndrome in Brazilian women with previous gestational diabetes. Diabetes Research & Clinical Practice 2007;78:23-29.
176. SECK A, HICHAMI A, DOUCOURE S, et al. Th1/Th2 Dichotomy in Obese Women with Gestational Diabetes and Their Macrosomic Babies. J Diabetes Res 2018;2018:8474617.
177. BEHBOUDI-GANDEVANI S, RAMEZANI TEHRANI F, RAHMATI M, AMIRI M, AZIZI F. Trend of various adiposity indices in women with and without history of gestational diabetes: a population-based cohort study. BMC Endocr Disord 2019;19:24.
178. HAN KT, CHO GJ, KIM EH. Evaluation of the Association between Gestational Diabetes Mellitus at First Pregnancy and Cancer within 10 Years Postpartum Using National Health Insurance Data in South Korea. Int J Environ Res Public Health 2018;15.
179. BENTLEY-LEWIS R, POWE C, ANKERS E, WENGER J, ECKER J, THADHANI R. Effect of race/ethnicity on hypertension risk subsequent to gestational diabetes mellitus. The American journal of cardiology 2014;113:1364-70.
180. RETNAKARAN R, QI Y, SERMER M, CONNELLY PW, HANLEY AJ, ZINMAN B. Beta-cell function declines within the first year postpartum in women with recent glucose intolerance in pregnancy. Diabetes Care 2010;33:1798-804.
181. BENJAMIN E, WINTERS D, MAYFIELD J, GOHDES D. Diabetes in pregnancy in Zuni Indian women: Prevalence and subsequent development of clinical diabetes after gestational diabetes. Diabetes Care 1993;16:1231-35.
182. CHEUNG NW, LIH A, LAU SM, PARK K, PADMANABHAN S, MCELDUFF A. Gestational diabetes: a red flag for future Type 2 diabetes in pregnancy? A retrospective analysis. Diabetic Medicine 2015;32:1167-71.
183. DALY B, TOULIS KA, THOMAS N, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study. PLoS Medicine 2018;15.
184. PERSSON M, WINKVIST A, MOGREN I. Lifestyle and health status in a sample of Swedish women four years after pregnancy: A comparison of women with a history of normal pregnancy and women with a history of gestational diabetes mellitus. BMC Pregnancy and Childbirth 2015;15.

185. PIRKOLA J, POUTA A, BLOIGU A, et al. Prepregnancy overweight and gestational diabetes as determinants of subsequent diabetes and hypertension after 20-year follow-up. The Journal of clinical endocrinology and metabolism 2010;95:772-8.
186. TURA A, BENEDETTO GD, MORBIDUCCI U, et al. Non-esterified fatty acids dynamics during an oral glucose tolerance test in women with a history of gestational diabetes. Diabetologia 2009;52:S32-S33.
187. STUEBE AM, MANTZOROS C, KLEINMAN K, et al. Gestational glucose tolerance and maternal metabolic profile at 3 years postpartum. Obstet Gynecol 2011;118:1065-73.
188. SHOSTROM DCV, SUN Y, OLESON JJ, SNETSELAAR LG, BAO W. History of gestational diabetes mellitus in relation to cardiovascular disease and cardiovascular risk factors in US women. Frontiers in Endocrinology 2017;8.
189. SOKUP A, GÓRALCZYK B, GÓRALCZYK K, ROSC D. Triglycerides as an early pathophysiological marker of endothelial dysfunction in nondiabetic women with a previous history of gestational diabetes. Acta Obstetricia et Gynecologica Scandinavica 2012;91:182-88.
190. SOKUP A, RUSZKOWSKA B, GÓRALCZYK B, et al. Elevation of sE-selectin levels 2-24 months following gestational diabetes is associated with early cardiometabolic risk in nondiabetic women. International Journal of Endocrinology 2012;2012.
191. WANG H, SHE G, ZHOU W, LIU K, MIAO J, YU B. Expression profile of circular RNAs in placentas of women with gestational diabetes mellitus. Endocr J 2019;66:431-41.
192. OZUGUZ U, ISIK S, BERKER D, et al. Gestational diabetes and subclinical inflammation: evaluation of first year postpartum outcomes. Diabetes Res Clin Pract 2011;94:426-33.
193. POKROPEK C, SOBOLEWSKI P, GETACHEW R, PAUL A, BOURA J, OGUNYEMI D. Dietary intake patterns and insulin resistance in women with a history of gestational diabetes in the National Health and Nutrition Examination Survey (NHANES) 2000-2010. American Journal of Obstetrics and Gynecology 2015;212:S308.
194. SARTORE G, DALFRÀ M, BARISON A, et al. Plasma phospholipid fatty acid composition and desaturases indices in women with gestational diabetes mellitus before and after delivery. Diabetologia 2011;54:S481-S82.
195. TEHRANI FR, HASHEMI S, HASHEMINIA M, AZIZI F. Follow-up of women with gestational diabetes in the Tehran Lipid and Glucose Study (TLGS): A population-based cohort study. Journal of Obstetrics and Gynaecology Research 2012;38:698-704.
196. TAM WH, MA RC, YANG X, et al. Prediction of women's long-term cardiometabolic risks using glycemic indices during pregnancy. J Obstet Gynaecol Res 2013;39:484-91.
197. RETNAKARAN R, QI Y, SERMER M, CONNELLY PW, HANLEY AJ, ZINMAN B. The postpartum cardiovascular risk factor profile of women with isolated hyperglycemia at 1-hour on the oral glucose tolerance test in pregnancy. Nutr Metab Cardiovasc Dis 2011;21:706-12.
198. KING KB, GERICH JE, GUZICK DS, KING KU, MCDERMOTT MP. Is a history of gestational diabetes related to risk factors for coronary heart disease? Research in nursing & health 2009;32:298-306.
199. TAM WH, MA RC, YANG X, et al. Cardiometabolic risk in Chinese women with prior gestational diabetes: a 15-year follow-up study. Gynecol Obstet Invest 2012;73:168-76.
200. PACINI G, TURA A, WINHOFER Y, KAUTZKY-WILLER A. Incretin effect in women with former gestational diabetes within a short period after delivery. International Journal of Endocrinology 2012;2012.
201. TURA A, MARI A, WINZER C, KAUTZKY-WILLER A, PACINI G. Impaired beta-cell function in lean normotolerant former gestational diabetic women. Eur J Clin Invest 2006;36:22-8.
202. XIANG AH, TAKAYANAGI M, BLACK MH, et al. Longitudinal changes in insulin sensitivity and beta cell function between women with and without a history of gestational diabetes mellitus. Diabetologia 2013;56:2753-60.
203. XIONG X, ELKIND-HIRSCH KE, XIE Y, et al. Periodontal disease as a potential risk factor for the development of diabetes in women with a prior history of gestational diabetes mellitus. Journal of Public Health Dentistry 2013;73:41-49.
204. AKINCI B, CELTIK A, YUKSEL F, et al. Increased osteoprotegerin levels in women with previous gestational diabetes developing metabolic syndrome. Diabetes Research & Clinical Practice 2011;91:26-31.
205. TUTINO GE, TAM WH, YANG X, CHAN JC, LAO TT, MA RC. Diabetes and pregnancy: perspectives from Asia. Diabet Med 2014;31:302-18.
206. ORGANIZATION WH. Noncommunicable diseases. Geneva World Health Organization 2018 (vol 2018).
207. PATHIRANA MM, LASSI ZS, ROBERTS CT, ANDRAWEERA PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. J Dev Orig Health Dis 2020:1-18.

208. KAUL P, SAVU A, NERENBERG KA, et al. Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. Diabet Med 2015;32:164-73.
209. PACE R, BRAZEAU A-S, MELTZER S, RAHME E, DASGUPTA K. Conjoint Associations of Gestational Diabetes and Hypertension With Diabetes, Hypertension, and Cardiovascular Disease in Parents: A Retrospective Cohort Study. American journal of epidemiology 2017;186:1115-24.
210. CHU SY, CALLAGHAN WM, KIM SY, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 2007;30:2070-6.
211. RYCKMAN KK, SPRACKLEN CN, SMITH CJ, ROBINSON JG, SAFTLAS AF. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. BJOG : an international journal of obstetrics and gynaecology 2015;122:643-51.
212. KJOS SL, PETERS RK, XIANG A, HENRY OA, MONTORO M, BUCHANAN TA. Predicting future diabetes in Latino women with gestational diabetes. Utility of early postpartum glucose tolerance testing. Diabetes 1995;44:586-91.
213. CHEUNG NW, BYTH K. Population health significance of gestational diabetes. Diabetes Care 2003;26:2005-9.
214. PLOWS JF, STANLEY JL, BAKER PN, REYNOLDS CM, VICKERS MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci 2018;19.
215. PONS RS, ROCKETT FC, DE ALMEIDA RUBIN B, OPPERMANN MLR, BOSA VL. Risk factors for gestational diabetes mellitus in a sample of pregnant women diagnosed with the disease. Diabetology & Metabolic Syndrome 2015;7:A80-A80.
216. WU L, CUI L, TAM WH, MA RC, WANG CC. Genetic variants associated with gestational diabetes mellitus: a meta-analysis and subgroup analysis. Sci Rep 2016;6:30539.
217. ALAGEEL S, WRIGHT AJ, GULLIFORD MC. Changes in cardiovascular disease risk and behavioural risk factors before the introduction of a health check programme in England. Preventive medicine 2016;91:158-63.
218. BAPTISTE-ROBERTS K, BARONE BB, GARY TL, et al. Risk factors for type 2 diabetes among women with gestational diabetes: a systematic review. The American journal of medicine 2009;122:207-14 e4.
219. RATNER RE, CHRISTOPHI CA, METZGER BE, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008;93:4774-9.
220. SEMENKOVICH CF. Insulin resistance and atherosclerosis. The Journal of clinical investigation 2006;116:1813-22.
221. RAFIEIAN-KOPAEI M, SETORKI M, DOUDI M, BARADARAN A, NASRI H. Atherosclerosis: process, indicators, risk factors and new hopes. International journal of preventive medicine 2014;5:927-46.
222. DI ANGELANTONIO E, SARWAR N, PERRY P, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009;302:1993-2000.
223. MØRKEDAL B, ROMUNDSTAD PR, VATTEN LJ. Informativeness of indices of blood pressure, obesity and serum lipids in relation to ischaemic heart disease mortality: the HUNT-II study. Eur J Epidemiol 2011;26:457-61.
224. ANDRAWEERA PH, DEKKER GA, ARSTALL M, BIANCO-MIOTTO T, ROBERTS CT. Complications of Pregnancy and Future Cardiovascular Risk. *Encyclopedia of Cardiovascular Research and Medicine*, 2018.
225. METZGER BE, LOWE LP, DYER AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
226. TAM WH, MA RCW, OZAKI R, et al. In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardiometabolic Risk in Offspring. Diabetes Care 2017;40:679-86.
227. ANDRAWEERA P, DEKKER, G., ARSTALL, M., BIANCO-MIOTTO, T., & ROBERTS, C. Complications of pregnancy and future cardiovascular risk. In: Sawyer IRVD, ed. *Encyclopedia of Cardiovascular Research and Medicine*. Netherlands: Oxford:Elsevier Inc., 2018.
228. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009;6:e1000097.
229. DRAHOTA ABE. RevMan Calculator: Cochrane.
230. WELLS GA SB, O'CONNELL D, PETERSON J, WELCH V, LOSOS M. Newcastle-Ottawa quality assessment scale. Ottawa Hospital Research Institute 2013.
231. BUZINARO EF, BERCHIERI CB, HADDAD AL, PADOVANI CR, PIMENTA WDE P. [Overweight in adolescent offspring of women with hyperglycemia during pregnancy]. Arq Bras Endocrinol Metabol 2008;52:85-92.
232. CATALANO PM, FARRELL K, THOMAS A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. Am J Clin Nutr 2009;90:1303-13.

233. CHANG Y, CHEN X, ZHANG ZK. Intrauterine Exposure to Maternal Diabetes is Associated with Adiposity in Children at 6 Years of Age in China. Biomed Environ Sci 2015;28:140-2.
234. KRISHNAVENI GV, VEENA SR, JONES A, et al. Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress in adolescent indians. J Clin Endocrinol Metab 2015;100:986-93.
235. PATEL S, FRASER A, SMITH GD, et al. Associations of gestational diabetes, existing diabetes, and glycosuria with offspring obesity and cardiometabolic outcomes. Diabetes care 2012;35:63-71.
236. TAM WH, MA RCW, YANG X, et al. Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: A 15-year follow-up study. Diabetes care 2010;33:1382-84.
237. WRIGHT CS, RIFAS-SHIMAN SL, RICH-EDWARDS JW, TAVERAS EM, GILLMAN MW, OKEN E. Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure. Am J Hypertens 2009;22:215-20.
238. PIRKOLA J, VAARASMAKI M, LEINONEN E, et al. Maternal type 1 and gestational diabetes: postnatal differences in insulin secretion in offspring at preschool age. Pediatr Diabetes 2008;9:583-9.
239. KRISHNAVENI GV, VEENA SR, HILL JC, KEHOE S, KARAT SC, FALL CH. Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. Diabetes care 2010;33:402-4.
240. LEE H, JANG HC, PARK HK, CHO NH. Early manifestation of cardiovascular disease risk factors in offspring of mothers with previous history of gestational diabetes mellitus. Diabetes Res Clin Pract 2007;78:238-45.
241. PAGE KA, ROMERO A, ENRIQUEZ F, XIANG AH, BUCHANAN TA. Increased fasting glucose levels in children exposed to gestational diabetes in utero. Diabetes 2013;62:A364.
242. TAM WH, MA RCW, YANG X, et al. Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus in utero. Pediatrics 2008;122:1229-34.
243. TSADOK MA, FRIEDLANDER Y, PALTIEL O, et al. Obesity and blood pressure in 17-year-old offspring of mothers with gestational diabetes: insights from the Jerusalem Perinatal Study. Exp Diabetes Res 2011;2011:906154.
244. VÄÄRÄSMÄKI M, POUTA A, ELLIOT P, et al. Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. American Journal of Epidemiology 2009;169:1209-15.
245. DAVIS JN, GUNDERSON EP, GYLLENHAMMER LE, GORAN MI. Impact of gestational diabetes mellitus on pubertal changes in adiposity and metabolic profiles in Latino offspring. J Pediatr 2013;162:741-5.
246. HOLDER T, GIANNINI C, SANTORO N, et al. A low disposition index in adolescent offspring of mothers with gestational diabetes: a risk marker for the development of impaired glucose tolerance in youth. Diabetologia 2014;57:2413-20.
247. KEARNEY M, PERRON J, MARC I, WEISNAGEL JS, TCHERNOF A, ROBITAILLE J. Association of prenatal exposure to gestational diabetes with offspring body composition and regional body-fat distribution. Diabetes 2017;66:A368.
248. PAGE KA, ROMERO A, BUCHANAN TA, XIANG AH. Gestational diabetes mellitus, maternal obesity, and adiposity in offspring. J Pediatr 2014;164:807-10.
249. WHITAKER RC, PEPE MS, SEIDEL KD, WRIGHT JA, KNOPP RH. Gestational diabetes and the risk of offspring obesity. Pediatrics 1998;101:E9.
250. BAPTISTE-ROBERTS K, NICHOLSON W, WANG N-Y, BRANCATI F. Gestational Diabetes and Subsequent Growth Patterns of Offspring: The National Collaborative Perinatal Project...[corrected] [published erratum appears in MATERN CHILD HEALTH J 2012; 16(1):266]. Maternal & Child Health Journal 2012;16:125-32.
251. LAWLOR DA, FRASER A, LINDSAY RS, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia 2010;53:89-97.
252. PAGE KA, ROMERO A, ENRIQUEZ I, CHIRIKIAN V, BUCHANAN TA, XIANG A. Increased central adiposity in hispanic children exposed to gestational diabetes in utero. Diabetes 2012;61:A517.
253. RETNAKARAN R, YE C, HANLEY A, et al. Effect of maternal gestational diabetes on the cardiovascular risk factor profile of infants at 1 year of age. Nutr Metab Cardiovasc Dis 2013;23:1175-81.
254. ESLAMIAN L, AKBARI S, MARSOOSI V, JAMAL A. Association between fetal overgrowth and metabolic parameters in cord blood of newborns of women with GDM. Minerva Med 2013;104:317-24.
255. JABER SM. Metabolic hormones profile in 2 weeks old healthy infants of diabetic mothers. Saudi Med J 2006;27:1338-45.

256. KÖNIG AB, JUNGINGER S, REUSCH J, LOUWEN F, BADENHOOP K. Gestational diabetes outcome in a single center study: Higher BMI in children after six months. Hormone and Metabolic Research 2014;46:804-09.
257. ZHAO P, LIU E, QIAO Y, et al. Maternal gestational diabetes and childhood obesity at age 9-11: results of a multinational study. Diabetologia 2016;59:2339-48.
258. LI S, ZHU Y, YEUNG E, et al. Offspring risk of obesity in childhood, adolescence and adulthood in relation to gestational diabetes mellitus: a sex-specific association. International journal of epidemiology 2017;46:1533-41.
259. KRISHNAVENI GV, HILL JC, LEARY SD, et al. Anthropometry, glucose tolerance, and insulin concentrations in Indian children: relationships to maternal glucose and insulin concentrations during pregnancy. Diabetes care 2005;28:2919-25.
260. NEHRING I, CHMITORZ A, REULEN H, VON KRIES R, ENSENAUER R. Gestational diabetes predicts the risk of childhood overweight and abdominal circumference independent of maternal obesity. Diabet Med 2013;30:1449-56.
261. NIELSEN GL, DETHLEFSEN C, LUNDBYE-CHRISTENSEN S, PEDERSEN JF, MOLSTED-PEDERSEN L, GILLMAN MW. Adiposity in 277 young adult male offspring of women with diabetes compared with controls: a Danish population-based cohort study. Acta Obstet Gynecol Scand 2012;91:838-43.
262. PIRKOLA J, POUTA A, BLOIGU A, et al. Risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal prepregnancy overweight and gestational diabetes mellitus. Diabetes care 2010;33:1115-21.
263. SILVERMAN BL, RIZZO TA, CHO NH, METZGER BE. Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. Diabetes care 1998;21 Suppl 2:B142-9.
264. VOHR BR, MCGARVEY ST, GARCIA COLL C. Effects of maternal gestational diabetes and adiposity on neonatal adiposity and blood pressure. Diabetes care 1995;18:467-75.
265. VOHR BR, MCGARVEY ST, TUCKER R. Effects of maternal gestational diabetes on offspring adiposity at 4-7 years of age. Diabetes care 1999;22:1284-91.
266. FARFEL A, RABINOVITZ R, KAMPINO G, et al. Children of mothers with pre-gestational and gestational diabetes tend to be overweight at age 17. Hormone Research in Paediatrics 2013;80:414.
267. RUTKOWSKA J, BANDURSKA-STANKIEWICZ E, WIATR-BYKOWSKA D, MYSZKA-PODGÓRSKA K, KUGLARZ E, MATUSZEWSKI W. The growth patterns in children born to mothers with gestational diabetes mellitus. Diabetologia 2015;58:S488.
268. LE MOULLEC N, FIANU A, MAILLARD O, et al. Sexual dimorphism in the association between gestational diabetes mellitus and overweight in offspring at 5-7 years: The OBEGEST cohort study. PLoS ONE 2018;13:e0195531.
269. TENG ZJ, XIA MJ, QU CH, YU HX. Long-term risk of metabolic disorders in gestational diabetes mellitus mothers and offspring. Biomedical Research (India) 2017;28:4466-70.
270. LÓPEZ MORALES CM, BRITO ZURITA OR, GONZÁLEZ HEREDIA R, CRUZ LÓPEZ M, MÉNDEZ PADRÓN A, MATUTE BRISEÑO JA. Placental atherosclerosis and markers of endothelial dysfunction in infants born to mothers with gestational diabetes. Medicina Clinica 2016;147:95-100.
271. MIETTINEN HE, RONO K, KOIVUSALO SB, ERIKSSON JG, GYLLING H. Effect of gestational diabetes mellitus on newborn cholesterol metabolism. Atherosclerosis 2018;275:346-51.
272. CHANDLER-LANEY PC, BUSH NC, GRANGER WM, ROUSE DJ, MANCUSO MS, GOWER BA. Overweight status and intrauterine exposure to gestational diabetes are associated with children's metabolic health. Pediatr Obes 2012;7:44-52.
273. BORGOÑO CA, HAMILTON JK, YE C, et al. Determinants of insulin resistance in infants at age 1 year: impact of gestational diabetes mellitus. Diabetes care 2012;35:1795-97.
274. BOZKURT L, GÖBL CS, RAMI-MERHAR B, et al. The Cross-Link between Adipokines, Insulin Resistance and Obesity in Offspring of Diabetic Pregnancies. Hormone Research in Paediatrics 2016;86:300-08.
275. PLAGEMANN A, HARDER T, KOHLHOFF R, ROHDE W, DORNER G. Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. Int J Obes Relat Metab Disord 1997;21:451-6.
276. PLAGEMANN A, HARDER T, KOHLHOFF R, ROHDE W, DORNER G. Glucose tolerance and insulin secretion in children of mothers with pregestational IDDM or gestational diabetes. Diabetologia 1997;40:1094-100.
277. CLAUSEN TD, MATHIESEN ER, HANSEN T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. Diabetes care 2008;31:340-6.

278. WILK M, HORODNICKA-JOZWA A, MOLEDA P, et al. Assessment of selected carbohydrate parameters in children exposed to gestational diabetes in utero. Neuro Endocrinol Lett 2015;36:504-10.
279. VISENTIN S, LONDERO AP, BELLAMIO B, et al. Fetal Endothelial Remodeling in Late-Onset Gestational Hypertension. Am J Hypertens 2016;29:273-9.
280. VISENTIN S, LAPOLLA A, LONDERO AP, et al. Adiponectin levels are reduced while markers of systemic inflammation and aortic remodelling are increased in intrauterine growth restricted mother-child couple. Biomed Res Int 2014;2014:401595.
281. CHEN X, WANG Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008;117:3171-80.
282. RAITAKARI OT, JUONALA M, KÄHÖNEN M, et al. Cardiovascular Risk Factors in Childhood and Carotid Artery Intima-Media Thickness in AdulthoodThe Cardiovascular Risk in Young Finns Study. JAMA 2003;290:2277-83.
283. OIKONEN M, NUOTIO J, MAGNUSSEN CG, et al. Repeated Blood Pressure Measurements in Childhood in Prediction of Hypertension in Adulthood. Hypertension 2016;67:41-7.
284. LEWINGTON S, CLARKE R, QIZILBASH N, PETO R, COLLINS R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
285. KIZIRIAN NV, KONG Y, MUIRHEAD R, et al. Effects of a low-glycemic index diet during pregnancy on offspring growth, body composition, and vascular health: a pilot randomized controlled trial. Am J Clin Nutr 2016;103:1073-82.
286. FREEDMAN DS, SHERRY B. The validity of BMI as an indicator of body fatness and risk among children. Pediatrics 2009;124 Suppl 1:S23-34.
287. KAWASAKI M, ARATA N, MIYAZAKI C, et al. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. PLoS One 2018;13:e0190676.
288. JAGO R, MENDOZA JA, CHEN T, BARANOWSKI T. Longitudinal associations between BMI, waist circumference, and cardiometabolic risk in US youth: monitoring implications. Obesity (Silver Spring, Md) 2013;21:E271-E79.
289. DISSANAYAKE HU, ANDERSON L, MCMULLAN RL, et al. Influence of maternal and placental factors on newborn body composition. J Paediatr Child Health 2019.
290. ENZI G, INELMEN EM, CARETTA F, VILLANI F, ZANARDO V, DEBIASI F. Development of adipose tissue in newborns of gestational-diabetic and insulin-dependent diabetic mothers. Diabetes 1980;29:100-4.
291. SKILTON MR, SIITONEN N, WÜRTZ P, et al. High birth weight is associated with obesity and increased carotid wall thickness in young adults: the cardiovascular risk in young Finns study. Arterioscler Thromb Vasc Biol 2014;34:1064-8.
292. D'ADAMO E, CAPRIO S. Type 2 diabetes in youth: epidemiology and pathophysiology. Diabetes care 2011;34 Suppl 2:S161-5.
293. RHODES ET, PROSSER LA, HOERGER TJ, LIEU T, LUDWIG DS, LAFFEL LM. Estimated morbidity and mortality in adolescents and young adults diagnosed with Type 2 diabetes mellitus.(Report)(Clinical report). Diabetic Medicine 2012;29:453.
294. LI L, PETERS H, GAMA A, et al. Maternal smoking in pregnancy association with childhood adiposity and blood pressure. Pediatr Obes 2016;11:202-9.
295. RIEDEL C, FENSKE N, MULLER MJ, et al. Differences in BMI z-scores between offspring of smoking and nonsmoking mothers: a longitudinal study of German children from birth through 14 years of age. Environ Health Perspect 2014;122:761-7.
296. GADEMAN MG, VAN EIJSDEN M, ROSEBOOM TJ, VAN DER POST JA, STRONKS K, VRIJKOTTE TG. Maternal prepregnancy body mass index and their children's blood pressure and resting cardiac autonomic balance at age 5 to 6 years. Hypertension 2013;62:641-7.
297. SHAAT N, GROOP L. Genetics of gestational diabetes mellitus. Curr Med Chem 2007;14:569-83.
298. WEST NA, CRUME TL, MALIGIE MA, DABELEA D. Cardiovascular risk factors in children exposed to maternal diabetes in utero. Diabetologia 2011;54:504-7.
299. PATHIRANA MM, LASSI ZS, ROBERTS CT, ANDRAWEERA PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. J Dev Orig Health Dis 2020;11:599-616.

300. PATHIRANA MM, LASSI ZS, ALI A, ARSTALL MA, ROBERTS CT, ANDRAWEERA PH. Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis. Endocrine 2021;71:310-20.
301. PATHIRANA MM, LASSI ZS, ROBERTS CT, ANDRAWEERA PH. Author response: cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. J Dev Orig Health Dis 2020;11:244-45.
302. LORENZO-ALMORÓS A, HANG T, PEIRÓ C, et al. Predictive and diagnostic biomarkers for gestational diabetes and its associated metabolic and cardiovascular diseases. Cardiovasc Diabetol 2019;18:140.
303. ALBERTI KG, ZIMMET PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
304. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama 2001;285:2486-97.
305. FAN J, SONG Y, CHEN Y, HUI R, ZHANG W. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies. Int J Cardiol 2013;168:4761-8.
306. WILSON PW, KANNEL WB, SILBERSHATZ H, D'AGOSTINO RB. Clustering of metabolic factors and coronary heart disease. Arch Intern Med 1999;159:1104-9.
307. ANDRAWEERA P, DEKKER, G., ARSTALL, M., BIANCO-MIOTTO, T., ROBERTS, C. . *Complications of pregnancy and future cardiovascular risk.* Netherlands: Oxford:Elsevier Inc.; Number of pages.
308. WELTY FK, ALFADDAGH A, ELAJAMI TK. Targeting inflammation in metabolic syndrome. Transl Res 2016;167:257-80.
309. GRIEGER JA, BIANCO-MIOTTO T, GRZESKOWIAK LE, et al. Metabolic syndrome in pregnancy and risk for adverse pregnancy outcomes: A prospective cohort of nulliparous women. PLoS Med 2018;15:e1002710-e10.
310. XU Y, SHEN S, SUN L, YANG H, JIN B, CAO X. Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. PLoS One 2014;9:e87863.
311. YANO Y, STAMLER J, GARSIDE DB, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. J Am Coll Cardiol 2015;65:327-35.
312. SON JS, CHOI S, KIM K, et al. Association of Blood Pressure Classification in Korean Young Adults According to the 2017 American College of Cardiology/American Heart Association Guidelines With Subsequent Cardiovascular Disease Events. JAMA 2018;320:1783-92.
313. UMER A, KELLEY GA, COTTRELL LE, GIACOBBI P, JR., INNES KE, LILLY CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health 2017;17:683.
314. DEEROCHANAWONG C, PUTIYANUN C, WONGSURYRAT M, SERIRAT S, JINAYON P. Comparison of National Diabetes Data Group and World Health Organization criteria for detecting gestational diabetes mellitus. Diabetologia 1996;39:1070-73.
315. CARPENTER MW, COUSTAN DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982;144:768-73.
316. ADA. 2. Classification and Diagnosis of Diabetes. Diabetes Care 2014;38:S8-S16.
317. RANI PR, BEGUM J. Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand. J Clin Diagn Res 2016;10:QE01-4.
318. O'SULLIVAN JB, MAHAN CM. CRITERIA FOR THE ORAL GLUCOSE TOLERANCE TEST IN PREGNANCY. Diabetes 1964;13:278-85.
319. FMS. Current Care Guideline. Gestational Diabetes. . In: Association FMSaMABoFD, ed. Helsinki, 2008.
320. WENDER-OZEGOWSKA E, SPORNA M, SPORNA A, BRAZERT J, ZAWIEJSKA A. Components of metabolic syndrome (MS) in women after gestational diabetes (GDM). Journal of Diabetes 2009;1:A286-A87.
321. HANSEN T, VESTERGAARD H. Increasing Incidence of Diabetes After Gestational Diabetes. Diabetes Care 2004;27:1194-9.
322. MAGHBOOLI Z, HOSSEIN-NEZHAD A, MIRZAEI K, et al. Association between retinol-binding protein 4 concentrations and gestational diabetes mellitus and risk of developing metabolic syndrome after pregnancy. Reproductive Sciences 2010;17:196-201.

323. ALBERTI KGMM, ZIMMET P, SHAW J. The metabolic syndrome—a new worldwide definition. The Lancet 2005;366:1059-62.
324. GRUNDY SM, CLEEMAN JI, DANIELS SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
325. HEALTH NIO. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies., 2014 (vol 2020).
326. BO S, MENATO G, GALLO ML, et al. Mild gestational hyperglycemia, the metabolic syndrome and adverse neonatal outcomes. Acta Obstet Gynecol Scand 2004;83:335-40.
327. DANE B, USTAOĞLU F, YILDIRIM Y, et al. Are the criteria of metabolic syndrome associated with pregnancy complications? Turk Jinekoloji ve Obstetrik Dernegi Dergisi 2011;8:100-06.
328. NEGRATO CA, JOVANOVIC L, RAFACHO A, et al. Association between different levels of dysglycemia and metabolic syndrome in pregnancy. Diabetol Metab Syndr 2009;1:3-3.
329. ZAMAN F, NOUHJAH S, SHAHBAZIAN H, SHAHBAZIAN N, LATIFI SM, JAHANSHAHI A. Risk factors of gestational diabetes mellitus using results of a prospective population-based study in Iranian pregnant women. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2018;12:721-25.
330. CHATZI L, PLANA E, PAPPAS A, et al. Metabolic syndrome in early pregnancy and risk of gestational diabetes mellitus. Diabetologia 2009;52:S457.
331. MIGDA M, MIGDA MS, MIGDA B, KRZYŻANOWSKA P, WENDER-OŻEGOWSKA E. Components of metabolic syndrome in the first trimester of pregnancy as predictors of adverse perinatal outcome. Ginekol Pol 2016;87:644-50.
332. RETNAKARAN R, WEN SW, TAN H, et al. Pregravid metabolic syndrome and risk of adverse outcomes in pregnancy: A preconception cohort study. Diabetes 2019;68.
333. COSTACOU T, BOSNYAK Z, HARGER GF, MARKOVIC N, SILVERS N, ORCHARD TJ. Postpartum adiponectin concentration, insulin resistance and metabolic abnormalities among women with pregnancy-induced disturbances. Prev Cardiol 2008;11:106-15.
334. SOMA-PILLAY P, NELSON-PIERCY C, TOLPPANEN H, MEBAZAA A. Physiological changes in pregnancy. Cardiovasc J Afr 2016;27:89-94.
335. AKINCI B, CELTIK A, GENC S, et al. Evaluation of postpartum carbohydrate intolerance and cardiovascular risk factors in women with gestational diabetes. Gynecol Endocrinol 2011;27:361-67.
336. ALBAREDA M, CABALLERO A, BADELL G, et al. Metabolic syndrome at follow-up in women with and without gestational diabetes mellitus in index pregnancy. Metabolism 2005;54:1115-21.
337. EDALAT B, SHARIFI F, BADAMCHIZADEH Z, et al. Association of metabolic syndrome with inflammatory mediators in women with previous gestational diabetes mellitus. J Diabetes Metab Disord 2013;12:8-8.
338. BO S, MENATO G, BOTTO C, et al. Mild gestational hyperglycemia and the metabolic syndrome in later life. Metab Syndr Relat Disord 2006;4:113-21.
339. DERBENT A, KARGILI A, KOCA C, et al. Serum platelet-activating factor acetylhydrolase activity: Relationship with metabolic syndrome in women with history of gestational diabetes mellitus. Gynecological Endocrinology 2011;27:128-33.
340. DI CIANNI G, LENCIONI C, VOLPE L, et al. C-reactive protein and metabolic syndrome in women with previous gestational diabetes. Diabetes Metab Res Rev 2007;23:135-40.
341. GUNDERSON EP, JACOBS JR DR, CHIANG V, et al. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: A 20-year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). Diabetes 2010;59:495-504.
342. HAKKARAINEN H, HUOPIO H, CEDERBERG H, VOUTILAINEN R, HEINONEN S. Future risk of metabolic syndrome in women with a previous LGA delivery stratified by gestational glucose tolerance: a prospective cohort study. BMC Pregnancy & Childbirth 2018;18:N.PAG-N.PAG.
343. IJÄS H, MORIN-PAPUNEN L, KERÄNEN AK, et al. Pre-pregnancy overweight overtakes gestational diabetes as a risk factor for subsequent metabolic syndrome. Eur J Endocrinol 2013;169:605-11.
344. KOUSTA E, EFSTATHIADOU Z, LAWRENCE NJ, et al. The impact of ethnicity on glucose regulation and the metabolic syndrome following gestational diabetes. Diabetologia 2006;49:36-40.
345. KRISHNAVENI GV, HILL JC, VEENA SR, et al. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. Diabetes Res Clin Pract 2007;78:398-404.
346. LI LJ, ARIS IM, SU LL, et al. Effect of gestational diabetes and hypertensive disorders of pregnancy on postpartum cardiometabolic risk. Endocr Connect 2018;7:433-42.

347. MADARÁSZ E, TAMÁS G, TABÁK AG, KERÉNYI Z. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. Diabetes Res Clin Pract 2009;85:197-202.
348. MAI C, HOU M, CHEN R, et al. Cardiovascular risk factors in Chinese women with a history of gestational diabetes mellitus. Int J Clin Exp Med 2015;8:21694-98.
349. NOCTOR E, CROWE C, CARMODY LA, et al. ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. Acta Diabetol 2014.
350. RETNAKARAN R, QI Y, CONNELLY PW, SERMER M, ZINMAN B, HANLEY AJG. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. Journal of Clinical Endocrinology and Metabolism 2010;95:670-77.
351. ROCA-RODRÍGUEZ MM, LÓPEZ-TINOCO C, FERNÁNDEZ-DEUDERO A, et al. Adipokines and metabolic syndrome risk factors in women with previous gestational diabetes mellitus. Diabetes/Metabolism Research & Reviews 2012;28:542-48.
352. RUKSASAKUL R, THARAVANIJ T, SRITIPSUKHO P. Metabolic Syndrome in Thai Women Previously Diagnosed with Gestational Diabetes. J Med Assoc Thai 2016;99 Suppl 4:S195-202.
353. SHEN Y, LI W, LENG J, et al. High risk of metabolic syndrome after delivery in pregnancies complicated by gestational diabetes. Diabetes Res Clin Pract 2019;150:219-26.
354. TAM WH, YANG XL, CHAN JC, et al. Progression to impaired glucose regulation, diabetes and metabolic syndrome in Chinese women with a past history of gestational diabetes. Diabetes/Metabolism Research & Reviews 2007;23:485-89.
355. VERMA A, BONEY CM, TUCKER R, VOHR BR. Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. J Clin Endocrinol Metab 2002;87:3227-35.
356. VILMI-KERÄLÄ T, PALOMÄKI O, VAINIO M, UOTILA J, PALOMÄKI A. The risk of metabolic syndrome after gestational diabetes mellitus - a hospital-based cohort study. Diabetol Metab Syndr 2015;7:43-43.
357. ZAWIEJSKA A, WENDER-OZEGOWSKA E, BRAZERT J, SODOWSKI K. Components of metabolic syndrome and their impact on fetal growth in women with gestational diabetes mellitus. J Physiol Pharmacol 2008;59 Suppl 4:5-18.
358. WIJEYARATNE CN, WADUGE R, ARANDARA D, et al. Metabolic and polycystic ovary syndromes in indigenous South Asian women with previous gestational diabetes mellitus. BJOG: An International Journal of Obstetrics and Gynaecology 2006;113:1182-87.
359. AKINCI B, CELTIK A, YENER S, YESIL S. Prediction of developing metabolic syndrome after gestational diabetes mellitus. Fertil Steril 2010;93:1248-54.
360. AKINCI B, CELTIK A, YUKSEL F, et al. Increased osteoprotegerin levels in women with previous gestational diabetes developing metabolic syndrome. Diabetes Res Clin Pract 2011;91:26-31.
361. DEHMER EW, PHADNIS MA, GUNDERSON EP, et al. Association Between Gestational Diabetes and Incident Maternal CKD: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Kidney Dis 2018;71:112-22.
362. FERRAZ TB, MOTTA RS, FERRAZ CL, CAPIBARIBE DM, FORTI AC, CHACRA AR. C-reactive protein and features of metabolic syndrome in Brazilian women with previous gestational diabetes. Diabetes Res Clin Pract 2007;78:23-29.
363. GUNDERSON EP, JACOBS DR, CHIANG V, et al. Lactation and lower incidence of the metabolic syndrome in women of reproductive age by gestational diabetes mellitus: A 20-year prospective study of CARDIA women. Diabetes 2009;58.
364. MAI C, WANG B, WEN J, LIN X, NIU J. Lipoprotein-associated phospholipase A2 and AGEs are associated with cardiovascular risk factors in women with history of gestational diabetes mellitus. Gynecol Endocrinol 2014;30:241-44.
365. TAM WH, MA RCW, YANG X, et al. Cardiometabolic risk in Chinese women with prior gestational diabetes: A 15-year follow-up study. Gynecol Obstet Invest 2012;73:168-76.
366. BONEY CM, VERMA A, TUCKER R, VOHR BR. Metabolic syndrome in childhood: Association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115:e290-e96.
367. CLAUSEN TD, MATHIESEN ER, HANSEN T, et al. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. J Clin Endocrinol Metab 2009;94:2464-70.

368. VÄÄRÄSMÄKI M, POUTA A, ELLIOT P, et al. Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. Am J Epidemiol 2009;169:1209-15.
369. MASLOVA E, HANSEN S, GRUNNET LG, et al. Maternal glycemic index and glycemic load in pregnancy and offspring metabolic health in childhood and adolescence—a cohort study of 68,471 mother–offspring dyads from the Danish National Birth Cohort. Eur J Clin Nutr 2019;73:1049-62.
370. PLOWS JF, STANLEY JL, BAKER PN, REYNOLDS CM, VICKERS MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci 2018;19:3342.
371. PONS RS, ROCKETT FC, DE ALMEIDA RUBIN B, OPPERMANN MLR, BOSA VL. Risk factors for gestational diabetes mellitus in a sample of pregnant women diagnosed with the disease. Diabetol Metab Syndr 2015;7:A80.
372. JAROSZ E. Lifestyle behaviours or socioeconomic characteristics? Gender differences in covariates of BMI in Hungary. Obes Sci Pract 2018;4:591-99.
373. MITANCHEZ D, YZYDORCZYK C, SIDDEEK B, BOUBRED F, BENAHMED M, SIMEONI U. The offspring of the diabetic mother--short- and long-term implications. Best Pract Res Clin Obstet Gynaecol 2015;29:256-69.
374. BUCHANAN TA, XIANG AH, PETERS RK, et al. Response of pancreatic beta-cells to improved insulin sensitivity in women at high risk for type 2 diabetes. Diabetes 2000;49:782-8.
375. SHEK NW, NGAI CS, LEE CP, CHAN JY, LAO TT. Lifestyle modifications in the development of diabetes mellitus and metabolic syndrome in Chinese women who had gestational diabetes mellitus: a randomized interventional trial. Arch Gynecol Obstet 2014;289:319-27.
376. FERRARA A, HEDDERSON MM, ALBRIGHT CL, et al. A pregnancy and postpartum lifestyle intervention in women with gestational diabetes mellitus reduces diabetes risk factors: a feasibility randomized control trial. Diabetes Care 2011;34:1519-25.
377. SONG C, LI J, LENG J, MA RC, YANG X. Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials. Obes Rev 2016;17:960-9.
378. AIHW. A picture of overweight and obesity in Australia. Canberrra: Australian Institute of Health and Welbeing, 2017.
379. BARKER DJ. The developmental origins of adult disease. J Am Coll Nutr 2004;23:588S-95S.
380. BLOTSKY AL, RAHME E, DAHHOU M, NAKHLA M, DASGUPTA K. Gestational diabetes associated with incident diabetes in childhood and youth: a retrospective cohort study. CMAJ 2019;191:E410-E17.
381. HALIPCHUK J, TEMPLE B, DART A, MARTIN D, SELLERS EAC. Prenatal, Obstetric and Perinatal Factors Associated With the Development of Childhood-Onset Type 2 Diabetes. Can J Diabetes 2018;42:71-77.
382. FEDERATION ID. The IDF consensus definition of the metabolic syndrome in children and adolescents International Diabetes Federation 2007.
383. HAN ES, KRAUSS RM, XU F, et al. Prepregnancy Adverse Lipid Profile and Subsequent Risk of Gestational Diabetes. J Clin Endocrinol Metab 2016;101:2721-7.
384. WEI YM, YANG HX, ZHU WW, et al. Risk of adverse pregnancy outcomes stratified for pre-pregnancy body mass index. J Matern Fetal Neonatal Med 2016;29:2205-9.
385. GUNDERSON EP, QUESENBERRY CP, JR., JACOBS DR, JR., FENG J, LEWIS CE, SIDNEY S. Longitudinal study of prepregnancy cardiometabolic risk factors and subsequent risk of gestational diabetes mellitus: The CARDIA study. Am J Epidemiol 2010;172:1131-43.
386. BUTTE NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr 2000;71:1256S-61S.
387. SMITH DE, LEWIS CE, CAVENY JL, PERKINS LL, BURKE GL, BILD DE. Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. JAMA 1994;271:1747-51.
388. CHATZI L, PLANA E, PAPPAS A, et al. The metabolic syndrome in early pregnancy and risk of gestational diabetes mellitus. Diabetes Metab 2009;35:490-94.
389. GUNDERSON EP, CHIANG V, PLETCHER MJ, et al. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the Coronary Artery Risk Development in Young Adults study. J Am Heart Assoc 2014;3:e000490-e90.
390. HAKKARAINEN H, HUOPIO H, CEDERBERG H, PÄÄKKÖNEN M, VOUTILAINEN R, HEINONEN S. The risk of metabolic syndrome in women with previous GDM in a long-term follow-up. Gynecol Endocrinol 2016;32:920-25.

391. NEGRATO CA, JOVANOVIC L, TAMBASCIA MA, et al. Mild gestational hyperglycaemia as a risk factor for metabolic syndrome in pregnancy and adverse perinatal outcomes. Diabetes/Metabolism Research & Reviews 2008;24:324-30.
392. WENDER-OZEGOWSKA E, SPORNA M, ZAWIEJSKA A, SPORNA A, BRAZERT J. Carbohydrate disturbances among women after gestational diabetes mellitus. Ginekol Pol 2007;78:223-28.
393. IDF. The IDF consensus definition of the metabolic syndrome in children and adolescents International Diabetes Federation 2007.
394. RANASINGHE P, MATHANGASINGHE Y, JAYAWARDENA R, HILLS AP, MISRA A. Prevalence and trends of metabolic syndrome among adults in the asia-pacific region: a systematic review. BMC Public Health 2017;17:101.
395. PATHIRANA MM, LASSI ZS, ALI A, ARSTALL MA, ROBERTS CT, ANDRAWEERA PH. Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis. Endocrine 2020.
396. ANDRAWEERA P, DEKKER, G., ARSTALL, M., BIANCO-MIOTTO, T., ROBERTS, C. . Complications of pregnancy and future cardiovascular risk. In: In R. Vasan DS, ed. *Encyclopedia of Cardiovascular Research and Medicine*. Netherlands: Oxford:Elsevier Inc., 2018 (vol 1).
397. LESSEN R, KAVANAGH K. Position of the academy of nutrition and dietetics: promoting and supporting breastfeeding. J Acad Nutr Diet 2015;115:444-9.
398. MA S, HU S, LIANG H, XIAO Y, TAN H. Metabolic effects of breastfeed in women with prior gestational diabetes mellitus: A systematic review and meta-analysis. Diabetes Metab Res Rev 2019;35:e3108.
399. FENG L, XU Q, HU Z, PAN H. Lactation and progression to type 2 diabetes in patients with gestational diabetes mellitus: A systematic review and meta-analysis of cohort studies. J Diabetes Investig 2018;9:1360-69.
400. METZGER BE, GABBE SG, PERSSON B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676-82.
401. ORMESHER L, JOHNSTONE ED, SHAWKAT E, et al. A clinical evaluation of placental growth factor in routine practice in high-risk women presenting with suspected pre-eclampsia and/or fetal growth restriction. Pregnancy Hypertens 2018;14:234-39.
402. NHLBI. Study Quality Assessment Tools. In: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, ed. *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies*, 2020 (vol 2020).
403. HAMMOUD NM, VISSER GHA, VAN ROSSEM L, BIESMA DH, WIT JM, DE VALK HW. Long-term BMI and growth profiles in offspring of women with gestational diabetes. Diabetologia 2018;61:1037-45.
404. LINGWOOD BE, HENRY AM, D'EMDEN MC, et al. Determinants of body fat in infants of women with gestational diabetes mellitus differ with fetal sex. Diabetes care 2011;34:2581-5.
405. HUI LL, LI AM, NELSON EAS, LEUNG GM, LEE SL, SCHOOLING CM. In utero exposure to gestational diabetes and adiposity: does breastfeeding make a difference? Int J Obes (Lond) 2018;42:1317-25.
406. MARTENS PJ, SHAFER LA, DEAN HJ, et al. Breastfeeding Initiation Associated With Reduced Incidence of Diabetes in Mothers and Offspring. Obstet Gynecol 2016;128:1095-104.
407. CHAMBERLAIN CR, OLDENBURG B, WILSON AN, et al. Type 2 diabetes after gestational diabetes: greater than fourfold risk among Indigenous compared with non-Indigenous Australian women. Diabetes Metab Res Rev 2016;32:217-27.
408. CORRADO F, GIUNTA L, GRANESE R, et al. Metabolic effects of breastfeeding in women with previous gestational diabetes diagnosed according to the IADPSG criteria. J Matern Fetal Neonatal Med 2019;32:225-28.
409. CHOUINARD-CASTONGUAY S, WEISNAGEL SJ, TCHERNOF A, ROBITAILLE J. Relationship between lactation duration and insulin and glucose response among women with prior gestational diabetes. Eur J Endocrinol 2013;168:515-23.
410. DIJIGOW FB, PAGANOTI CDE F, COSTA RA, FRANCISCO RP, ZUGAIB M. [The influence of breastfeeding in postpartum oral glucose tolerance test in women with recent gestational diabetes mellitus]. Rev Bras Ginecol Obstet 2015;37:565-70.
411. GUNDERSON EP, HEDDERSON MM, CHIANG V, et al. Lactation intensity and postpartum maternal glucose tolerance and insulin resistance in women with recent GDM: the SWIFT cohort. Diabetes Care 2012;35:50-6.
412. GUNDERSON EP, HURSTON SR, NING X, et al. Lactation and progression to type 2 diabetes mellitus after gestational diabetes mellitus a prospective cohort study. Annals of Internal Medicine 2015;163:889-98.

413. KIM SH, KIM MY, YANG JH, et al. Nutritional risk factors of early development of postpartum prediabetes and diabetes in women with gestational diabetes mellitus. Nutrition 2011;27:782-8.
414. KJOS SL, HENRY O, LEE RM, BUCHANAN TA, MISHELL DR, JR. The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. Obstet Gynecol 1993;82:451-5.
415. MCMANUS RM, CUNNINGHAM I, WATSON A, HARKER L, FINEGOOD DT. Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. Metabolism 2001;50:715-9.
416. NELSON AL, LE MH, MUSHERRAF Z, VANBERCKELAER A. Intermediate-term glucose tolerance in women with a history of gestational diabetes: natural history and potential associations with breastfeeding and contraception. Am J Obstet Gynecol 2008;198:699 e1-7; discussion 99 e7-8.
417. SAUCEDO R BL, GALVAN R, SANCHEZ J, HERNADEZ M, PUELLO E, ZARATE A. Duration of lactation is associated with lower leptin levels in patients with gestational diabetes mellitus. Instituto Mexican del Suguro Social 2014;06720.
418. SHUB A, MIRANDA M, GEORGIOU HM, MCCARTHY EA, LAPPAS M. The effect of breastfeeding on postpartum glucose tolerance and lipid profiles in women with gestational diabetes mellitus. Int Breastfeed J 2019;14:46.
419. YASUHI I, SODA T, YAMASHITA H, et al. The effect of high-intensity breastfeeding on postpartum glucose tolerance in women with recent gestational diabetes. Int Breastfeed J 2017;12:32.
420. ZIEGLER AG, WALLNER M, KAISER I, et al. Long-term protective effect of lactation on the development of type 2 diabetes in women with recent gestational diabetes mellitus. Diabetes 2012;61:3167-71.
421. MATTEI L, COLATRELLA A, BITTERMAN O, et al. Long Lasting Effects of Breastfeeding on Metabolism in Women with Prior Gestational Diabetes. Journal of Diabetes Mellitus 2014;4:257-63.
422. HALES CN, BARKER DJ. The thrifty phenotype hypothesis. Br Med Bull 2001;60:5-20.
423. STUEBE AM, RICH-EDWARDS JW. The Reset Hypothesis: Lactation and Maternal Metabolism. Am J Perinatol 2009;26:081-88.
424. JIANG M, GAO H, VINYES-PARES G, et al. Association between breastfeeding duration and postpartum weight retention of lactating mothers: A meta-analysis of cohort studies. Clin Nutr 2018;37:1224-31.
425. HARDER T, BERGMANN R, KALLISCHNIGG G, PLAGEMANN A. Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol 2005;162:397-403.
426. DALY B, TOULIS KA, THOMAS N, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study. PLoS Med 2018;15:e1002488.
427. BURGESS A, MCDOWELL W, EBERSOLD S. Association Between Lactation and Postpartum Blood Pressure in Women with Preeclampsia. MCN Am J Matern Child Nurs 2019;44:86-93.
428. GUNDERSON EP, LEWIS CE, WEI GS, WHITMER RA, QUESENBERRY CP, SIDNEY S. Lactation and changes in maternal metabolic risk factors. Obstet Gynecol 2007;109:729-38.
429. HORTA BL, LORET DE MOLA C, VICTORA CG. Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. Acta Paediatr 2015;104:30-7.
430. SCHWARZ EB, BROWN JS, CREASMAN JM, et al. Lactation and maternal risk of type 2 diabetes: a population-based study. Am J Med 2010;123:863 e1-6.
431. BUCHANAN TA, XIANG AH, PAGE KA. Gestational diabetes mellitus: risks and management during and after pregnancy. Nat Rev Endocrinol 2012;8:639-49.
432. SHOJI H, SHIMIZU T. Effect of human breast milk on biological metabolism in infants. Pediatr Int 2019;61:6-15.
433. LUCAS A, SARSON DL, BLACKBURN AM, ADRIAN TE, AYNSLEY-GREEN A, BLOOM SR. Breast vs bottle: endocrine responses are different with formula feeding. Lancet 1980;1:1267-9.
434. MOSS KM, DOBSON AJ, TOOTH L, MISHRA GD. Associations between feeding practices in infancy and fruit and vegetable consumption in childhood. Br J Nutr 2020:1-9.
435. OSMAN MW, NATH M, KHALIL A, WEBB DR, ROBINSON TG, MOUSA HA. Haemodynamic differences amongst women who were screened for gestational diabetes in comparison to healthy controls. Pregnancy Hypertens 2018;14:23-28.
436. MA RM, LAO TT. Maternal mean arterial pressure and oral glucose tolerance test results. Relationship in normotensive women. J Reprod Med 2001;46:747-51.
437. MIKAEL LR, PAIVA AMG, GOMES MM, et al. Vascular Aging and Arterial Stiffness. Arq Bras Cardiol 2017;109:253-58.

438. YU D, ZHAO Z, SIMMONS D. Interaction between Mean Arterial Pressure and HbA1c in Prediction of Cardiovascular Disease Hospitalisation: A Population-Based Case-Control Study. J Diabetes Res 2016;2016:8714745-45.
439. MCCLOSKEY K, VUILLERMIN P, PONSONBY AL, CHEUNG M, SKILTON MR, BURGNER D. Aortic intima-media thickness measured by trans-abdominal ultrasound as an early life marker of subclinical atherosclerosis. Acta Paediatr 2014;103:124-30.
440. YÜCEL O, CEVIK H, KINIK ST, TOKEL K, AKA S, DINC F. Abdominal aorta intima media thickness in obese children. J Pediatr Endocrinol Metab 2013;26:735-41.
441. DABELEA D, MAYER-DAVIS EJ, LAMICHHANE AP, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case-Control Study. Diabetes Care 2008;31:1422-6.
442. LAHTI-PULKKINEN M, BHATTACHARYA S, WILD SH, et al. Consequences of being overweight or obese during pregnancy on diabetes in the offspring: a record linkage study in Aberdeen, Scotland. Diabetologia 2019;62:1412-19.
443. WHO. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract 2014;103:341-63.
444. HAMEL C, LANG E, MORISSETTE K, et al. Screening for depression in women during pregnancy or the first year postpartum and in the general adult population: a protocol for two systematic reviews to update a guideline of the Canadian Task Force on Preventive Health Care. Syst Rev 2019;8:27-27.
445. YU M, ZHANG X, LU F, FANG L. Depression and Risk for Diabetes: A Meta-Analysis. Can J Diabetes 2015;39:266-72.
446. NOUWEN A, ADRIAANSE MC, VAN DAM K, et al. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabet Med 2019;36:1562-72.
447. MUSSELMAN DL, EVANS DL, NEMEROFF CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998;55:580-92.
448. ARAFA A, DONG JY. Depression and risk of gestational diabetes: A meta-analysis of cohort studies. Diabetes Res Clin Pract 2019;156:107826.
449. BEKA Q, BOWKER S, SAVU A, KINGSTON D, JOHNSON JA, KAUL P. Development of Perinatal Mental Illness in Women With Gestational Diabetes Mellitus: A Population-Based Cohort Study. Can J Diabetes 2018;42:350-55.e1.
450. WILSON CA, SANTORELLI G, DICKERSON J, et al. Is there an association between anxiety and depression prior to and during pregnancy and gestational diabetes? An analysis of the Born in Bradford cohort. J Affect Disord 2020;276:345-50.
451. SCHMITZ N, DESCHÊNES SS, BURNS RJ, et al. Depression and risk of type 2 diabetes: the potential role of metabolic factors. Mol Psychiatry 2016;21:1726-32.
452. LIU D, DE CRESPIGNY C, PROCTER N, et al. Comorbidity Action in the North: a study of services for people with comorbid mental health and drug and alcohol disorders in the northern suburbs of Adelaide. Australas Psychiatry 2016;24:592-97.
453. PHDIU. An atlas of mental health conditions in South Australia: Population patterns of prevalence, risk factors, service use and treatment. Adelaide: Public Health Information Development Unit, 2016.
454. AUSTIN MP, COLTON J, PRIEST S, REILLY N, HADZI-PAVLOVIC D. The antenatal risk questionnaire (ANRQ): acceptability and use for psychosocial risk assessment in the maternity setting. Women Birth 2013;26:17-25.
455. COX JL, HOLDEN JM, SAGOVSKY R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782-6.
456. COHEN S, KAMARCK T, MERMELSTEIN R. A global measure of perceived stress. J Health Soc Behav 1983;24:385-96.
457. AUERBACH SM. Trait-state anxiety and adjustment to surgery. J Consult Clin Psychol 1973;40:264-71.
458. SLAVIN V, CREEDY DK, GAMBLE J. Single Item Measure of Social Supports: Evaluation of construct validity during pregnancy. J Affect Disord 2020;272:91-97.
459. AHMED A, BOWEN A, FENG CX, MUHAJARINE N. Trajectories of maternal depressive and anxiety symptoms from pregnancy to five years postpartum and their prenatal predictors. BMC Pregnancy Childbirth 2019;19:26.
460. ATTORNEY-GENERAL. Domestic Violence Discussion Paper. South Australia:: Goverment of South Australia, 2016.
461. GILBERT L, GROSS J, LANZI S, QUANSAH DY, PUDER J, HORSCH A. How diet, physical activity and psychosocial well-being interact in women with gestational diabetes mellitus: an integrative review. BMC Pregnancy Childbirth 2019;19:60.

462. RIGGIN L. Association Between Gestational Diabetes and Mental Illness. Can J Diabetes 2020;44:566-71.e3.
463. MISHRA S, SHETTY A, RAO CR, NAYAK S, KAMATH A. Effect of maternal perceived stress during pregnancy on gestational diabetes mellitus risk: A prospective case-control study. Diabetes Metab Syndr 2020;14:1163-69.
464. HINKLE SN, BUCK LOUIS GM, RAWAL S, ZHU Y, ALBERT PS, ZHANG C. A longitudinal study of depression and gestational diabetes in pregnancy and the postpartum period. Diabetologia 2016;59:2594-602.
465. BYRN M, PENCKOFER S. The relationship between gestational diabetes and antenatal depression. J Obstet Gynecol Neonatal Nurs 2015;44:246-55.
466. WILSON CA, NEWHAM J, RANKIN J, et al. Is there an increased risk of perinatal mental disorder in women with gestational diabetes? A systematic review and meta-analysis. Diabet Med 2020;37:602-22.
467. BEKA Q, BOWKER SL, SAVU A, KINGSTON D, JOHNSON JA, KAUL P. History of mood or anxiety disorders and risk of gestational diabetes mellitus in a population-based cohort. Diabet Med 2018;35:147-51.
468. BOWERS K, LAUGHON SK, KIM S, et al. The association between a medical history of depression and gestational diabetes in a large multi-ethnic cohort in the United States. Paediatr Perinat Epidemiol 2013;27:323-8.
469. SILVEIRA ML, WHITCOMB BW, PEKOW P, et al. Perceived psychosocial stress and glucose intolerance among pregnant Hispanic women. Diabetes Metab 2014;40:466-75.
470. AIHW. Cardiovascular disease in Australian women—a snapshot of national statistics.

. Canberra: Australian Institute of Health and Welfare, 2019. (vol CDK 10.).
471. FAKHRZADEH H, ALATAB S, SHARIFI F, et al. Carotid intima media thickness, brachial flow mediated dilation and previous history of gestational diabetes mellitus. Journal of Obstetrics and Gynaecology Research 2012;38:1057-63.
472. ORGANIZATION WH. Cardiovascular Diseases (CVD). Geneva: World Health Organisation 2021 (vol 2021).
473. FEDERATION ID. IDF Diabetes Atlas. In: IDF, ed. Belgium, 2017

2007.
474. STALEY JR, BRADLEY J, SILVERWOOD RJ, et al. Associations of blood pressure in pregnancy with offspring blood pressure trajectories during childhood and adolescence: findings from a prospective study. J Am Heart Assoc 2015;4.
475. FAHY K LA, MILNE BJ. New Zealand Socio-economic index 2013. Auckland: Compass Research Centre The University of Auckland, 2013 (vol 2021).
476. GRUMMER-STRAWN LM, REINOLD C, KREBS NF. Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States. MMWR Recomm Rep 2010;59:1-15.
477. WHO. Waist cirumference and Waist-hip ratio: report of a WHO expert Consultation In: organisation Wh, ed. Geneva: World Health Organisation, 2008 (vol 2021).
478. SAIKIA B, DERRICK G, FORDHAM T, BRIERLEY J. 117: Validation of USCOM BP+ In Children and Adolescents: A Preliminary Report. Critical Care Medicine 2015;43:30-31.
479. ALDRIDGE E, MOLLEN J, VERBURG PE, et al. Agreement of aneroid and oscillometric blood pressure devices used in pregnancy. Pregnancy Hypertens 2019;17:43-48.
480. RESHETNIK A, GOHLISCH C, ABOU-DAKN M, TÖLLE M, ZIDEK W, VAN DER GIET M. Validation of noninvasive oscillometric blood pressure 2020 up pressure upper arm blood pressure monitoring technology according to the European Society of Hypertension International Protocol revision 2010. Blood Press Monit 2019;24:99-101.
481. SARAFIDIS PA, LASARIDIS AN, NILSSON PM, et al. Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. J Hum Hypertens 2007;21:709-16.
482. LAVIE CJ, ARENA R, ALPERT MA, MILANI RV, VENTURA HO. Management of cardiovascular diseases in patients with obesity. Nat Rev Cardiol 2018;15:45-56.
483. DENISON FC, ROBERTS KA, BARR SM, NORMAN JE. Obesity, pregnancy, inflammation, and vascular function. Reproduction 2010;140:373-85.
484. ROCA-RODRÍGUEZ MM, LÓPEZ-TINOCO C, MURRI M, et al. Postpartum development of endothelial dysfunction and oxidative stress markers in women with previous gestational diabetes mellitus. Journal of Endocrinological Investigation 2014;37:503-09.
485. CHARWAT-RESL S, YARRAGUDI R, HEIMBACH M, et al. Microvascular function in women with former gestational diabetes: A cohort study. Diab Vasc Dis Res 2017;14:214-20.

486. DAVIS CL, GUTT M, LLABRE MM, et al. History of Gestational Diabetes, Insulin Resistance and Coronary Risk. Journal of Diabetes and its Complications 1999;13:216-23.
487. VERMA A, BONEY CM, TUCKER R, VOHR BR. Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. J Clin Endocrinol Metab 2002;87:3227-35.
488. SHEN Y, LI W, LENG J, et al. High risk of metabolic syndrome after delivery in pregnancies complicated by gestational diabetes. Diabetes Res Clin Pract 2019;150:219-26.
489. AHMAD S, MORA S, RIDKER PM, HU FB, CHASMAN DI. Gene-Based Elevated Triglycerides and Type 2 Diabetes Mellitus Risk in the Women's Genome Health Study. Arterioscler Thromb Vasc Biol 2019;39:97-106.
490. JOSEFSON JL, CATALANO PM, LOWE WL, et al. The Joint Associations of Maternal BMI and Glycemia with Childhood Adiposity. J Clin Endocrinol Metab 2020;105:2177-88.
491. BALDWIN MK, HART KD, RODRIGUEZ MI. Predictors for follow-up among postpartum patients enrolled in a clinical trial. Contraception 2018;98:228-31.
492. SHARP GC, LAWLOR DA. Paternal impact on the life course development of obesity and type 2 diabetes in the offspring. Diabetologia 2019;62:1802-10.
493. WU HY, CHENG Y, JIN LY, et al. Paternal obesity impairs hepatic gluconeogenesis of offspring by altering Igf2/H19 DNA methylation. Mol Cell Endocrinol 2021;529:111264.
494. WU P, HATHTHOTUWA R, KWOK CS, et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes 2017;10.
495. RUCHAT S-M, HOUDE A-A, VOISIN G, et al. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. Epigenetics 2013;8:935-43.
496. HOUDE A-A, GUAY S-P, DESGAGNÉ V, et al. Adaptations of placental and cord blood ABCA1 DNA methylation profile to maternal metabolic status. Epigenetics 2013;8:1289-302.
497. KAZMI N, SHARP GC, REESE SE, et al. Hypertensive Disorders of Pregnancy and DNA Methylation in Newborns. Hypertension 2019;74:375-83.
498. WHO. Infant and you child feeding. Geneva, 2021.
499. PATHIRANA MM, ALI A, LASSI ZS, ARSTALL MA, ROBERTS CT, ANDRAWEERA PH. Protective Influence of Breastfeeding on Cardiovascular Risk Factors in Women With Previous Gestational Diabetes Mellitus and Their Children: A Systematic Review and Meta-Analysis. J Hum Lact 2021:8903344211034779.
500. SANTIAGO ACT, CUNHA L, VIEIRA NSA, et al. Breastfeeding in children born small for gestational age and future nutritional and metabolic outcomes: a systematic review. Journal de Pediatra 2019;95:264-74.
501. JÚLÍUSSON PB, ROELANTS M, NORDAL E, et al. Growth references for 0-19 year-old Norwegian children for length/height, weight, body mass index and head circumference. Ann Hum Biol 2013;40:220-7.
502. WHO. Waist cirumference and Waist-hip ratio: report of a WHO expert Consultation. Geneva, 2008.
503. PATHIRANA MM AA, LASSI ZL, ARSTALL MA, ROBERTS CT, ANDRAWEERA PH. Protective effect of breastfeeding on cardiovascular risk factors in women and children exposed to gestational diabetes mellitus: a systematic review and meta-analysis Journal of Human Lactation 2021 [In press].
504. WAGATA M, KOGURE M, NAKAYA N, et al. Hypertensive disorders of pregnancy, obesity, and hypertension in later life by age group: a cross-sectional analysis. Hypertens Res 2020;43:1277-83.
505. BLAIR RA, NEVES JS, NICKLAS JM, HORN CE, SKURNIK G, SEELY EW. Breastfeeding Associated with Lower Prevalence of Metabolic Syndrome in Women with Gestational Diabetes in the Very Early Postpartum Period. Am J Perinatol 2021.
506. YU J, PUDWELL J, DAYAN N, SMITH GN. Postpartum Breastfeeding and Cardiovascular Risk Assessment in Women Following Pregnancy Complications. J Womens Health (Larchmt) 2020;29:627-35.
507. SANTIAGO ACT, CUNHA L, COSTA ML, et al. Cardiometabolic evaluation of small for gestational age children: protective effect of breast milk. Nutr Hosp 2021;38:36-42.
508. LOWE WL, JR., SCHOLTENS DM, KUANG A, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Gestational Diabetes Mellitus and Childhood Glucose Metabolism. Diabetes Care 2019;42:372-80.
509. PHIDU. South Australia: Data by Population Health Area. In: University T, ed. *Social Health Atlas of Australia*: Torrens University, 2020.
510. GUNDERSON EP, GREENSPAN LC, FAITH MS, HURSTON SR, QUESENBERRY CP, JR. Breastfeeding and growth during infancy among offspring of mothers with gestational diabetes mellitus: a prospective cohort study. Pediatr Obes 2018;13:492-504.

511. SHONKOFF JP, GARNER AS. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012;129:e232-46.
512. JOHN CC, BLACK MM, NELSON CA, 3RD. Neurodevelopment: The Impact of Nutrition and Inflammation During Early to Middle Childhood in Low-Resource Settings. Pediatrics 2017;139:S59-S71.
513. WALSH K, MCCORMACK CA, WEBSTER R, et al. Maternal prenatal stress phenotypes associate with fetal neurodevelopment and birth outcomes. Proc Natl Acad Sci U S A 2019;116:23996-4005.
514. ÁLVAREZ-BUENO C, CAVERO-REDONDO I, LUCAS-DE LA CRUZ L, NOTARIO-PACHECO B, MARTÍNEZ-VIZCAÍNO V. Association between pre-pregnancy overweight and obesity and children's neurocognitive development: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2017;46:1653-66.
515. SANCHEZ CE, BARRY C, SABHLOK A, et al. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes Rev 2018;19:464-84.
516. PANGRAZZI L, BALASCO L, BOZZI Y. Oxidative Stress and Immune System Dysfunction in Autism Spectrum Disorders. Int J Mol Sci 2020;21.
517. RIZZO TA, DOOLEY SL, METZGER BE, CHO NH, OGATA ES, SILVERMAN BL. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol 1995;173:1753-8.
518. NOMURA Y, MARKS DJ, GROSSMAN B, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. Arch Pediatr Adolesc Med 2012;166:337-43.
519. XIANG AH, WANG X, MARTINEZ MP, et al. Maternal Gestational Diabetes Mellitus, Type 1 Diabetes, and Type 2 Diabetes During Pregnancy and Risk of ADHD in Offspring. Diabetes Care 2018;41:2502-08.
520. ORNOY A, RATZON N, GREENBAUM C, WOLF A, DULITZKY M. School-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment. J Pediatr Endocrinol Metab 2001;14 Suppl 1:681-9.
521. WANG P, XIE J, JIAO XC, et al. Maternal Glycemia During Pregnancy and Early Offspring Development: A Prospective Birth Cohort Study. J Clin Endocrinol Metab 2021;106:2279-90.
522. MADIGAN S, OATLEY H, RACINE N, et al. A Meta-Analysis of Maternal Prenatal Depression and Anxiety on Child Socioemotional Development. J Am Acad Child Adolesc Psychiatry 2018;57:645-57 e8.
523. VERBURG PE, TUCKER G, SCHEIL W, ERWICH JJ, DEKKER GA, ROBERTS CT. Sexual Dimorphism in Adverse Pregnancy Outcomes - A Retrospective Australian Population Study 1981-2011. PLoS One 2016;11:e0158807.
524. NETWORK. APH. Northern Adelaide *Understanding the health of the Adelaide Reigion*. South Australia: Public Health Network Adelaide, 2020 (vol 2020).
525. SQUIRES J, & BRICKER, D. . *Ages & Stages Questionnaires®, Third Edition (ASQ®-3): A Parent-Completed Child Monitoring System.* Baltimore: Brookes Publishing Co. Inc Number of pages.
526. SQUIRE J TM, BRICKER D, POTTER LW. . ASQ Technical Report. In: Publishing B, ed. Baltimore USA, 2009 (vol ASQ-3).
527. MARSDEN J, STEWART D, GOSSOP M, et al. Assessing Client Satisfaction with Treatment for Substance Use Problems and the Development of the Treatment Perceptions Questionnaire (TPQ). Addiction research 2000;8:455-70.
528. VISSER SN, DANIELSON ML, BITSKO RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. J Am Acad Child Adolesc Psychiatry 2014;53:34-46.e2.
529. HOSOKAWA R, KATSURA T. Effect of socioeconomic status on behavioral problems from preschool to early elementary school - A Japanese longitudinal study. PLoS One 2018;13:e0197961.
530. KOUTRA K, CHATZI L, BAGKERIS M, VASSILAKI M, BITSIOS P, KOGEVINAS M. Antenatal and postnatal maternal mental health as determinants of infant neurodevelopment at 18 months of age in a mother-child cohort (Rhea Study) in Crete, Greece. Soc Psychiatry Psychiatr Epidemiol 2013;48:1335-45.
531. SCHONHAUT L, PÉREZ M, ARMIJO I, MATURANA A. Comparison between Ages & Stages Questionnaire and Bayley Scales, to predict cognitive delay in school age. Early Hum Dev 2020;141:104933.
532. MAY T, ADESINA I, MCGILLIVRAY J, RINEHART NJ. Sex differences in neurodevelopmental disorders. Curr Opin Neurol 2019;32:622-26.
533. NUGENT BM, O'DONNELL CM, EPPERSON CN, BALE TL. Placental H3K27me3 establishes female resilience to prenatal insults. Nat Commun 2018;9:2555.

534. MURRAY AL, BOOTH T, EISNER M, AUYEUNG B, MURRAY G, RIBEAUD D. Sex differences in ADHD trajectories across childhood and adolescence. Dev Sci 2019;22:e12721.
535. HADDERS-ALGRA M. Early Diagnostics and Early Intervention in Neurodevelopmental Disorders-Age-Dependent Challenges and Opportunities. J Clin Med 2021;10.
536. GUMUSOGLU SB, CHILUKURI ASS, SANTILLAN DA, SANTILLAN MK, STEVENS HE. Neurodevelopmental Outcomes of Prenatal Preeclampsia Exposure. Trends Neurosci 2020;43:253-68.
537. SAVVIDOU MD, ANDERSON JM, KAIHURA C, NICOLAIDES KH. Maternal arterial stiffness in pregnancies complicated by gestational and type 2 diabetes mellitus. American journal of obstetrics and gynecology 2010;203:274. e1-74. e7.
538. MOODLEY S, ARUNAMATA A, STAUFFER KJ, et al. Maternal arterial stiffness and fetal cardiovascular physiology in diabetic pregnancy. Ultrasound Obstet Gynecol 2018;52:654-61.
539. MECACCI F, OTTANELLI S, VANNUCCINI S, et al. Maternal hemodynamic changes in gestational diabetes: a prospective case-control study. Arch Gynecol Obstet 2021.
540. KHALIL A, GARCIA-MANDUJANO R, CHIRIAC R, AKOLEKAR R, NICOLAIDES KH. Maternal hemodynamics at 11-13 weeks' gestation in gestational diabetes mellitus. Fetal Diagn Ther 2012;31:216-20.
541. SU WJ, CHEN YL, HUANG PY, et al. Effects of Prepregnancy Body Mass Index, Weight Gain, and Gestational Diabetes Mellitus on Pregnancy Outcomes: A Population-Based Study in Xiamen, China, 2011-2018. Ann Nutr Metab 2019;75:31-38.
542. FADL H, MAGNUSON A, ÖSTLUND I, MONTGOMERY S, HANSON U, SCHWARCZ E. Gestational diabetes mellitus and later cardiovascular disease: a Swedish population based case-control study. BJOG : an international journal of obstetrics and gynaecology 2014;121:1530-36.
543. CATALANO PM. The impact of gestational diabetes and maternal obesity on the mother and her offspring. J Dev Orig Health Dis 2010;1:208-15.
544. GRIEGER JA, BIANCO-MIOTTO T, GRZESKOWIAK LE, et al. Metabolic syndrome in pregnancy and risk for adverse pregnancy outcomes: A prospective cohort of nulliparous women. PLoS Med 2018;15:e1002710.
545. TAM WH, MA RC, YANG X, et al. Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: a 15-year follow-up study. Diabetes Care 2010;33:1382-4.
546. BONEY CM, VERMA A, TUCKER R, VOHR BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115:e290-6.
547. ZOU J, YANG Y, WEI Q, ZHANG Y, SHI H. Longitudinal Association of Maternal Pre-Pregnancy BMI and Third-Trimester Glycemia with Early Life Growth of Offspring: A Prospective Study among GDM-Negative Pregnant Women. Nutrients 2021;13.
548. CULLINAN J, GILLESPIE P, OWENS L, AVALOS G, DUNNE FP. Is there a socioeconomic gradient in the prevalence of gestational diabetes mellitus? Ir Med J 2012;105:21-3.
549. ALVAREZ-GALVEZ J, GOMEZ-BAYA D. Socioeconomic Context as a Moderator in the Relationship between Body Mass Index and Depression in Europe. Appl Psychol Health Well Being 2017;9:410-28.
550. NGUYEN B, JIN K, DING D. Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review. PLoS One 2017;12:e0187923.
551. ZHANG Z, LAI M, PIRO AL, et al. Intensive lactation among women with recent gestational diabetes significantly alters the early postpartum circulating lipid profile: the SWIFT study. BMC medicine 2021;19:241-41.
552. LAMBRINOU CP, KARAGLANI E, MANIOS Y. Breastfeeding and postpartum weight loss. Curr Opin Clin Nutr Metab Care 2019;22:413-17.
553. NAM GE, HAN K, KIM DH, et al. Associations between Breastfeeding and Type 2 Diabetes Mellitus and Glycemic Control in Parous Women: A Nationwide, Population-Based Study. Diabetes Metab J 2019;43:236-41.
554. CHAMBERLAIN C, MCLEAN A, OATS J, et al. Low rates of postpartum glucose screening among indigenous and non-indigenous women in Australia with gestational diabetes. Matern Child Health J 2015;19:651-63.
555. LI N, YANG Y, CUI D, et al. Effects of lifestyle intervention on long-term risk of diabetes in women with prior gestational diabetes: A systematic review and meta-analysis of randomized controlled trials. Obes Rev 2021;22:e13122.
556. ALDRIDGE E, VERBURG PE, SIERP S, et al. A Protocol for Nurse-Practitioner Led Cardiovascular Follow-Up After Pregnancy Complications in a Socioeconomically Disadvantaged Population. Front Cardiovasc Med 2019;6:184.

Appendix 1: Publication for Cardiovascular risk factors in women with a history of gestational diabetes mellitus: a systematic review and meta-analysis

Reviews in Endocrine and Metabolic Disorders (2021) 22:729–761
https://doi.org/10.1007/s11154-020-09587-0

Cardiovascular risk factors in women with previous gestational diabetes mellitus: A systematic review and meta-analysis

Maleesa M. Pathirana[1,2] · Zohra Lassi[1,2] · Anna Ali[2,3,4] · Margaret Arstall[2,5] · Claire T. Roberts[1,2,6] · Prabha H. Andraweera[1,2,5]

Accepted: 26 August 2020 / Published online: 27 October 2020

Abstract

This systematic review and meta-analysis aimed to synthesize evidence on conventional cardiovascular disease (CVD) risk factors among women with previous Gestational Diabetes Mellitus (GDM). The review protocol is registered with PROSPERO (CRD42019118149). PubMed, CINAHL, SCOPUS, and EMBASE databases were searched. Studies reporting on CVD risk factors in women with previous GDM compared to women without previous GDM were selected. A total of 139 studies were eligible, of which 93 were included in the meta-analysis. Women with previous GDM have significantly higher systolic blood pressure (2.47 mmHg 95% CI 1.74 to 3.40, n = 48, 50,118 participants) diastolic blood pressure (1.89 mmHg 95% CI 1.32 to 2.46, n = 48, 49,495 participants), BMI (1.54 kg/m^2 95% CI 1.32 to 2.46, n = 78, 255,308 participants), total cholesterol (0.26 SMD 95% CI 0.15 to 0.37, n = 48, 38,561 participants), LDL cholesterol (0.19 SMD 95% CI 0.08 to 0.30, n = 44, 16,980 participants), triglycerides (0.56 SMD 95% CI 0.42 to 0.70, n = 46, 13,175 participants), glucose (0.69 SMD 95% CI 0.56 to 0.81, n = 55, 127,900 participants), insulin (0.41 SMD 95% CI 0.23 to 0.59, n = 32, 8881 participants) and significantly lower HDL cholesterol (−0.28 SMD 95% CI −0.39 to −0.16, n = 56, 35,882 participants), compared to women without previous GDM. The increased blood pressure, total cholesterol, triglycerides and glucose are seen as early as <1 year post-partum.Women with previous GDM have a higher risk of CVD based on significant increases in conventional risk factors. Some risk factors are seen as early as <1 year post-partum. Women with GDM may benefit from early screening to identify modifiable CVD risk factors.

Keywords Gestational diabetes · Women's health · Cardiovascular disease · Cardiovascular risk factors

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11154-020-09587-0) contains supplementary material, which is available to authorized users.

✉ Prabha H. Andraweera
prabha.andraweera@adelaide.edu.au

1 Adelaide Medical School and The Robinson Research Institute, The University of Adelaide, Adelaide, SA, Australia

2 Faculty of Health and Medical Sciences, Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia

3 Basil Hetzel Institute, The Queen Elizabeth Hospital, Woodville, SA, Australia

4 Adelaide G-TRAC Centre & CRE Frailty & Healthy Ageing Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia

5 Department of Cardiology, Lyell McEwin Hospital, Elizabeth Vale, SA, Australia

6 Flinders Health and Medical Research Institute, Flinders University, Bedford Park, SA, Australia

Abbreviations

CVD cardiovascular disease
GDM gestational diabetes mellitus

1 Introduction

Cardiovascular disease (CVD) is a major global health burden. There are 17.9 million deaths annually, accounting for 31% of global mortality [1]. CVD is also a leading cause of death in women [2]. Research over the past decade has shown an association between the major pregnancy complications including preeclampsia, intrauterine growth restriction, preterm birth and gestational diabetes mellitus and increased risk of CVD, with each pregnancy complication incurring a 2-fold increased risk of developing CVD later in life [3].

Gestational diabetes mellitus (GDM) is defined as glucose intolerance, which is first recognised in pregnancy, hence different from both type I and type II diabetes mellitus. GDM is estimated to affect one in seven pregnancies [4]. Women with previous GDM are more likely to be obese, have dyslipidaemia and hypertension post-partum [3]. These women have an approximately seven-fold increased risk of developing type II diabetes mellitus (T2DM) later in life [5]. The definition of GDM changed in 2013, following a study by the Hyperglycaemia Adverse Pregnancy Outcomes (HAPO) cohort, which showed that adverse perinatal outcomes were seen even in women whose glycaemic levels were below the conventional GDM criteria [6]. This meant that women, who were not diagnosed with GDM based on previous guidelines, were still at risk for these adverse outcomes. With the implication of the new international guidelines for GDM, the rate of women classified as having GDM is expected to increase.

A recent meta-analysis by Kramer et al. (2019) based on more than a million participants, showed that women with GDM have a 2-fold increased risk of developing CVD, irrespective of the disease progression of T2DM [7]. Thus impaired glucose tolerance post-partum does not appear to be the only cardiovascular risk factor in women who experience GDM to warrant screening for CVD. A major mechanism that underlies the risk of CVD is metabolic syndrome, which is a collection of vascular derangements including obesity, dyslipidaemia, insulin resistance and hypertension [8]. Therefore, early identification of these modifiable risk factors is pertinent in order to offer targeted interventions/lifestyle modification advice to reduce the subsequent risk for CVD. It has been shown that minimal decreases in risk factors including systolic blood pressure, total cholesterol and adiposity can significantly reduce the risk of ischemic heart disease later in life [9, 10].

There has not been a systematic review and meta-analysis that has comprehensively evaluated all conventional CVD risk factors simultaneously in women with previous GDM, and none that has assessed the timeline of development of risk factors for CVD. This is particularly important as Kramer et al. (2019) showed an association between previous GDM and increased risk of CVD events as early as one year post-partum [8].

Therefore, our primary aim was to conduct a systematic review and meta-analysis on the association between GDM and major risk factors for CVD including blood pressure (BP), body mass index (BMI), fasting glucose, insulin and lipids using data from all eligible studies. Our secondary aim was to assess the risk factor profile based on the time elapsed post-partum at which assessments were conducted.

2 Methods

2.1 Search strategy

All studies describing the association between GDM and risk factors for CVD in women were identified by searching the following electronic databases: PubMed, CINAHL, SCOPUS and EMBASE with an end of search date of 5th November 2018. Subsequently, we updated the literature search to include all relevant articles published until 10th Jan 2020. The search was conducted by ZL. The review protocol is registered in PROSPERO (CRD42019118149).

The review was undertaken with reference to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [11]. The search strategy was as follows**:** ("gestational diabetes*" OR "pregnancy induced diabetes" OR "diabetic pregnancy") AND (pregnan* OR mother OR women OR woman) AND ("blood pressure" OR diabetes OR cardiovascular OR metabolic OR hypertension OR BMI or "body mass index" OR obesity OR overweight OR lipids OR lipid OR cholesterol OR triglyceride* OR glucose OR insulin OR vascular).

We included case-control studies, cross-sectional and cohort studies. Previous systematic reviews and meta-analyses on closely related topics, and references from eligible studies were checked for additional studies. All identified studies were assessed for relevance by four authors (MP, PA, AA, ZL). Data were independently extracted by two authors (MP, AA). Discrepancies were resolved by discussion with ZL and PA.

2.2 Inclusion criteria

Studies were selected if they compared CVD risk factors in women with a previous history of GDM compared to women with no history of GDM. We included studies that defined GDM based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [12]. However, since the diagnostic criteria have been revised recently, we included studies that used prior recommended diagnostic criteria of GDM including the 1999 World Health Organization definition, and other regional definitions. The definitions of GDM of included studies are detailed in Table 1. Studies that did not include a definition of GDM, those that did not define the case and control groups and those that compared women with GDM to another risk group were excluded.

Data were extracted independently and in duplicate for outcomes, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), lipid levels (total cholesterol, low density lipoprotein (LDL) high density lipoprotein (HDL), and triglycerides), blood glucose, and fasting insulin. We analysed all studies collectively as an overall analysis, and subsequently stratified into subgroups based on the

Table 1 Included studies in systematic review and meta-analysis

Author and year	Study design	Country	Exposed/Definition of GDM (n=)	Non exposed (n=)	Birthweight of offspring cases/controls (g)
< 1 year postpartum					
Albareda 2004 [57]	Prospective	Spain	696/50 g, 1 h GCT-	70	**NR**
Anastasiou 1998 [14]	Case-control	Greece	33/ADA	19	**NR**
Berglund 2016 [151]	Cohort	Spain	331/ NDDG or IDF	132	**NR**
Bowes 1996 [71]	Prospective	UK	7/75 g OGTT 2 h blood glucose > 9 mmol/1.	5	**NR**
Bozkurt 2010 - abstract (2) [152]	Cross-sectional	Italy	62/ 4th International Workshop conference on GDM	29	**NR**
Bozkurt 2012 (2) [72]	Cross-sectional	Vienna	54/4th International Workshop conference on GDM	**29**	**NR**
Cellina 1983 [21]	Observational Cohort	Italy	20/ O'Sullivan and Mahan	**15**	**NR**
Chan 1992 [153]	Retrospective	UK	15/ 75 g OGTT: 120 min venous plasma glucose >7.8 mmol/l.	15	**NR**
Davenport 2012 [23]	Prospective	Canada	10/ Canadian Diabetes Association	10	**NR**
Davis 1999 [24]	Cross-sectional	USA	21/medical records	39	**NR**
Eroglu 2006 [77]	Prospective	Turkey	36/ Abnormal 3 h 100 g OGTT at 24–28 weeks' gestation	33	Cases: 3308 ± 401, Control:3334 ± 373
Ferrada 2007 [26]	Case-control	Chile	58/GDM definition not explained	58	**NR**
Friere 2006 [154]	Cross-sectional	Brazil	13/ Carpenter and Coustan.	13	**NR**
Homko 2001 [155]	Cross-sectional	USA	7/ Carpenter and Coustan	8	**NR**
Kjos 1991 [100]	Prospective	USA	6–12 weeks ($n = 1340$), 1 year ($n = 157$)/ NDDG (1979)	6–12 wk. ($n = 43$) 1 year ($n = 36$)	**NR**
Ko 1999 [33]	Case-control	Hong Kong	19/ 75 g OGTT	10	**NR**
Lee 2015 [36]	Cross-sectional	Korea	36/75 g oral glucose tolerance test (OGTT)	19	**NR**
Maghbooli 2010 [156]	Case-control	Iran	92/50 g O'Sullivan and Mahan criteria after two step OGCT	100	**NR**
McLachlan 2005 [83]	Case-control	Australia	19/ 75-g OGTT (ADIPS)	19	**NR**
Morbiducci 2009 **(1)** [84]	Methodology study	Italy	122/ Not specified	19	**NR**
Noujah 2017 [157]	Population Based Cohort Study	Iran	176/ IADPSG criteria, or medical records	86	**NR**
Noujah 2018 [43]	Population Based Prospective Cohort Study	Iran	176/ IADPSG criteria, or medical records	86	**NR**
Pacini 2012 (2) [126]	Retrospective	Austria	104/Not specified	35	**NR**
Retnakaran 2009* [158]	Observational Study	Canada	137/NDDG (1979)	259	**NR**
Retnakaran 2010* [106]	Observational Study	Canada	107/NDDG (1979)	73	**NR**
Retnakaran 2010* [106]	Prospective observational Study	Canada	136/NDDG (1979)	87	**NR**
Retnakaran 2010* [106]	Observational Study	Canada	107/NDDG (1979)	Not reported	**NR**
Retnakaran 2011* [123]	Observational Study	Canada	137/NDDG (1979)	259	**NR**
Roca-Rodrigeuz 2012* [159]	Case-control	Spain	41/NDDG (1979)	21	**NR**
Roca-Rodrigeuz 2014* [45]	Case-control	Spain	41/NDDG (1979)	21	**NR**
Sartore 2011 [120]	Retrospective cohort	Italy	21/Carpenter and Coustan (1982)	21	**NR**
Seck 2018	Case-control	Sengal	20/ Not specified	20	**NR**
Sokup 2012* [115]	Prospective cohort	Poland	85/ WHO 1999	40	**NR**
Sokup 2012* [115]	Prospective cohort	Poland	125/WHO 1999	40	**NR**
Sung 2008 [49]	Cohort	South Korea	140/ Third International Workshop Conference on GDM	17	**NR**
Todoric 2012 [65]	Retrospective	Austria	10/Universal GDM Screening	6	**NR**

Table 1 (continued)

Tura 2006 (2) [127]	Prospective cohort	Austria	24/4th Workshop Conference on GDM	23	**NR**
Vitoratos 2001 [96]	Retrospective	Greece	24/ Carpenter and Coustan (1982)	19	**NR**
Wang 2019	Retrospective	China	30/ 75 g OGTT	15	3445.67/3362.85
Weisnagel 2013 abstract [160]	Abstract	Canada	20/ Not reported	27	**NR**
Winzer 2004**(1)**[99]	Cross-sectional	Austria	89/4th Workshop Conference of Gestational Diabetes	**19**	**NR**
Zajdenverg 2014 [55]	Cross- sectional analysis	Brazil	25/ADA criteria	20	**NR**
1–5 years post-partum					
Akinci 2008 [15]	Cross-sectional	Turkey	46/ 50 g-OGTT, ADA	30	**NR**
Akinci 2011* [130]	Cross-sectional	Turkey	195/ 50 g-OGTT, ADA	71	**NR**
Akini 2011* [130]	Cross-sectional case–control study	Turkey	128/ 50 g OGTT, ADA	67	**NR**
Akini 2013* [43]	Prospective	Turkey	141/ 50 g OGTT, ADA	49	**NR**
Albareda 2003 [57]	Prospective	Spain	696/ 50 g, 1 h glucose challenge test	70	**NR**
Albareda 2004 [57]	Prospective	Spain	262/50-g, 1 h glucose challenge test	66	**NR**
Banerjee 2012 [16]	Prospective	UK	8/75 g OGTT at 28 weeks pregnancy - WHO defined GDM (Fasting glucose >7 mmol/L or 2 h >7.8 mmol/L)	8	**NR**
Bently Lewis 2015* [58]	Cohort	USA	96/ Carpenter Coustain criteria	96	Normal GT: 3455 ± 464, GDM:3571 ± 525
Bently Lewis 2016* [17]	Cohort	USA	51/ Carpenter Coustain criteria	1810	Same as 2015
Cocilovo 1990 [73]	Cohort	Italy	41/ 3 h OGTT O'Sullivan criteria.	25	**NR**
Davis 1999 [24]	Cross-sectional	USA	21/medical records	39	**NR**
Demir 2016 [75]	Cohort study	Turkey	80/Carpenter Coustan criteria;	40	**NR**
Eroglu 2006 [77]	Prospective	Turkey	36/ 3 h 100 g OGTT O'Sullivan and Mahan	33	3308 ± 401/ 3334 ± 373
Fakhrzadeh 2012 [25]	Retrospective	Iran	O'Sullivan and Mahan	20	**NR**
Hakkariainen 2015** [161]	Hospital register base cohort study	Finland	489/ Fasting, 1 h, 2 h capillary whole blood glucose values 4.8, 10.0 and 8.7 mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1 h and 2 h respectively after Sept 2001	385	**NR**
Hakkariainen 2016** [30]	Hospital register base cohort study	Finland	489/Fasting, 1 h, 2 h capillary whole blood glucose values 4.8, 10.0 and 8.7 mmol/L respectively before Sept 2001 Values changed to 11.2 and 9.9 mmol/l for 1 h and 2 h respectively after Sept 2001	385	GDM (1) 3637 ± 571, GDM (2) 3671 ± 531/ Control:3581 ± 571
Hu 1998 [60]	Cross-sectional	Sweden	17/ 75 g OGTT capillary blood glucose > 9 mmol/UL	20	**NR**
Kjos 1991 [100]	Prospective cohort	USA	6–12 weeks (n = 1340), 1 year (n = 157)/ NDDG (1979)	6–12 wk. (n = 43) 1 year (n = 36)	Not reported
Kousta 2003 [79]	Reterospective	UK	34/ 75 g- OGTT, WHO (1999)	44	**NR**
Krishnaveni 2007 [34]	Prospective cohort	India	35/ Diagnosis made based on Carpenter and Coustain criteria	489	**NR**
Lee 2008 [35]	Cross-sectional	South Korea	620/ NDDG after two step OGTT	868	**NR**

Table 1 (continued)

Levka 2015* [62]	Prospective Cohort	Norway	50(IADPSG) and 31 (WHO) /IADPSG and WHO 1999	234 (IADPSG) and 253 (WHO)	Mean (SD): IADPSG: 3832 (530)/ 3588 (502) WHO: 3740 (455)/ 3640 (520)
Levka 2016* [162]	Prospective Cohort	Norway	50(IADPSG) and 31 (WHO) /IADPSG and WHO 1999	234 (IADPSG) and 253 (WHO)	**NR**
Levka 2017* [163]	Prospective Cohort	Norway	50(IADPSG) and 31 (WHO) /IADPSG and WHO 1999	234 (IADPSG) and 253 (WHO)	**NR**
Madarasz 2009 [37]	Retrospective	Hungary	68/WHO 1985	39	**NR**
Mai 2014 [38]	Case-control	China	190/ ADA 2004	80	**NR**
Noctor 2015** [164]	Prospective Cohort study (Based on Noctor 2013)	Ireland	265/ modified WHO 1999 (based on Noctor 2016)	378	**NR**
Noctor 2016** [42]	Prospective Cohort study (Based on Noctor 2013)	Ireland	270/WHO 1999	388	**NR**
Ozuguz 2011 [118]	Prospective case control	Turkey	61/Carpenter and Coustan (1982)	40	**NR**
Perrson 2015 [110]	Retrospective	Sweden	111/Not reported	333	**NR**
Pimenta 2004 [86]	Prospective	Brazil	20/ NDDG (1979)	20	**NR**
Prikoszovich 2011 [87]	Retrospective	Austria	23/Fourth Workshop Conference of Gestational Diabetes	8	**NR**
Rauito 2014 [44]	Multicentre Prospective cohort	Finland	115/Medical records	150	**NR**
Ruksasakul 2016 [64]	Case control	Thailand	56/Carpenter and Coustan (2007)	51	**NR**
Ryan 1995 [90]	Cross-sectional	Canada	14/ Hospital based definition	14	**NR**
Ryan 2013 [46]	Case-control	USA	20/History confirmed by health care provider	26	**NR**
Shen 2018 [92]	Observational Study	China	1263/WHO 1999	705	**NR**
Shen 2018 [92]	Observational Study	China	1263/WHO 1999	705	**NR**
Shen 2019	Observational Study	China	1263/WHO 1999	705	**NR**
Sokup 2012 [115]	Prospective cohort	Poland	85/ WHO 1999	40	**NR**
Sokup 2012 [115]	Prospective cohort	**Poland**	125/WHO 1999	40	**NR**
Stuebe 2011 [113]	Longitudinal cohort	USA	16/ Carpenter and Coustan	461	**NR**
Ueland 2018	Population based prospective cohort study	Norway	48/ IADPSG 2010	225	**NR**
Verma 2002 [52]	Prospective cohort	USA	58/Carpenter and Coustain modification of NDDG	51	**NR**
Vigneault 2015 [95]	Retrospective	Canada	216/Medical Records	83	**NR**
Vilmi-Kerala 2016 [53]	Cross-sectional	Finland	120/ Finnish Current Guidelines (2013)	120	**NR**
Wang 2015 [97]	Cross-sectional	China	48/ ADA (2013)	48	**NR**
Winhofer 2013* (1) [165]	Prospective Longitudinal Follow-Up	Austria	62/ ADA (based on Tura 2008)	10	**NR**
Winhofer 2013 abstract* (1) [166]	Longitudinal Follow-Up	Austria	43/ADA (based on Tura 2008)	10	**NR**
Winhofer 2014* (1) [54]	Prospective longitudinal follow-up	Austria	45/ (ADA based on Tura 2008)	18	**NR**
Winzer 2004 (1) [99]	Cross sectional	Austria	89/4th Workshop Conference of Gestational Diabetes	19	**NR**
Xiang 2012 [167]	Abstract Longitudinal	USA	76/Based on medical records (Watanabe 2007)	88	**NR**
Xiong 2013 [129]	Case control	USA	19/ACOG	20	**NR**
5–10 years postpartum					
Benjamin 1993 [107]	Case-control	India	47/O'Sullivan and Mahan	47	**NR**

Table 1 (continued)

Bian 2000 [169]	Retrospective	China	45/ >2 abnormalFPG > 5.8 mmol/L, at 1 h > 10.6 mmol/L, at 2 h > 9.2 mmol/L, at 3 h > 8. 1 mmol/L.	**39**	**NR**
Bo 2007 [18]	Cohort	Italy	82/ 50 g GCT Carpenter and Coustan	113	**NR**
Caliskan 2014 [19]	Case-control	Turkey	62/ Medical history	33	**NR**
Da 2016 (Abstract) [170]	Retrospective	Poland	199/ Based on OGTT values (not specified further)	50	**NR**
Donhorst 1990 [76]	Cohort	UK	56/ modification of O'Sullivan and Mahan	23	**NR**
Ferraz 2007 [101]	Cohort	Brazil	70/ 75-g OGTT, (WHO)	108	**NR**
Hakkariainen 2015** [161]	Hospital register base cohort study	Finland	489/ Fasting, 1 h, 2 h capillary whole blood glucose values 4.8, 10.0 and 8.7 mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1 h and 2 h respectively after Sept 2001	385	**NR**
Hakkariainen 2016** [30]	Hospital register base cohort study	Finland	489/ Fasting, 1 h, 2 h capillary whole blood glucose values 4.8, 10.0 and 8.7 mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1 h and 2 h respectively after Sept 2001	385	*Mean (SD)* GDM (1) 3637 ± 571, GDM (2) 3671 ± 531/ 3581 ± 571
Hunger Dathe 2006 [32]	Cohort	Germany	132/medical history	50	**NR**
Lauenborg 2005 [61]	Long term follow-up	Denmark	481/Based on 3 h 75 g OGTT - Damm et al. (1993)	1000	**NR**
Meier (2005). [39]	Case-control/experimental	Germany	15/ OGTT based on fasting glucose	**20**	*Mean (SD)* 3615 ± 661/3165 ± 289
Modela 2016* [41]	Retrospective cohort study	Poland	199/OGTT	50	**NR**
Osei 1998 [85]	Case-control	USA	15/ O'Sullivan criteria adapted by NDDG	15	Not reported
Pimenta 2004 [86]	Prospective	Brazil	20/NDDG (1979)	20	Not reported
Seghiri 2007 [91]	Retrospective	Italy	43/Carptenter and Coustan (1992)	22	**NR**
Sriharan 2002 [48]	Retrospective	Brazil	46/1999 WHO	50	**NR**
Tam 2007* [171]	Prospective cohort	Hong Kong	67/1999 WHO	136	*Mean (SD):* 3230 ± 485/3272 ± 429
Tam 2012** [125]	Prospective cohort	Hong Kong	94/WHO 1999	44	*Mean (SD):* 3230 (485)/ 3272(429)
Tam 2013** [122]	Prospective cohort	Hong Kong	94/WHO 1999	45	*Mean (SD):* 3230 (485)/ 3272(429)
Tehrani 2012 [121]	Nested longitudinal case control study	Iran	29/WHO 1999	*n* = 58 (Group 1) *n* = 570 (Group 2)	**NR**
Tobias 2017 [94]	Prospective cohort analysis	USA	5292/Self-reported GDM (validated method)	84,187	**NR**
Tutino 2014 [172]	Nested Case Control - Abstract	Hong Kong	124/ Self- reported GDM	372	**NR**
Verma 2002 [52]	Prospective cohort	USA	58/Carpenter and Coustain modification of NDDG	51	**NR**
Wender-Ozegowska 2007 [98]	Prospective cohort	Poland	153/Hospital records	155	**NR**
>10 years postpartum					
Ajala 2011 (abstract) [168]	Cohort	UK	*n* = 95/ GDM diagnosis not specified	Not specified (total n = 95)	**NR**

Table 1 (continued)

Ajala 2015 [68]	Cohort	Canada	90/ Canadian Diabetes Association	59	**NR**
Behboudi- Gandevani 2019	Long term longitudinal follow-up	Iran	801/WHO (1998)	2594	**NR**
Carr 2006 [20]	Cross-sectional	US	662/ Self-reported	332	**NR**
Charwat-Resl 2017 [22]	Cross-sectional	Vienna	55/ WHO (1998)	32	**NR**
Gobl 2011 (1) [173]	Prospective	Austria	120/ 75 g OGTT, Fourth International Workshop conference on GDM	40	**NR**
Gobl 2014 (1) [174]	Cross-sectional	Austria	108/75 g OGTT, Fourth International Workshop conference on GDM	41	**NR**
Gobl 2014 (1) [175]	Cross-sectional, prospective	Austria	77/75 g OGTT, Fourth International Workshop conference on GDM	41	**NR**
Gunderson 2014 [28]	Longitudinal observational study	Canada	119/ Self- reported GDM: confirmed by OGTT results from prenatal records to match definition by Diabetes Care 1997	364	**NR**
Hakkariainen 2015** [161]	Hospital register base cohort study	Finland	489/ abnormal fasting, 1 h, 2 h capillary whole blood glucose values 4,8, 10.0 and 8.7 mmol/l respectively (Until Sept 2001) Values changed to 11.2 and 9.9 mmol/l for 1 h and 2 h respectively after Sept 2001	385	**NR**
Hakkariainen 2016** [30]	Hospital register base cohort study	Finland	489/ Fasting, 1 h, 2 h capillary whole blood glucose values 4.8, 10.0 and 8.7 mmol/L respectively before Sept 2001. Values changed to 11.2 and 9.9 mmol/l for 1 h and 2 h respectively after Sept 20,019.9 mmol/l for 1 h and 2 h respectively after Sept 2001	385	GDM (1) 3637 ± 571, GDM (2) 3671 ± 531/ 3581 ± 571
Heida 2015 [31]	Prospective cohort study	Dutch	1089/ Self- reported questionnaire	15,560	**NR**
King 2009 [124]	Case-control	USA	20/Self-report of having GDM and OGTT	20	**NR**
Lee 2007 [80]	Retrospective	Australia	5740/75 g OGTT and 50 g OGTT. FPG: 5.5 mmol/l and/or a 2 h plasma glucose>8.0 mmol/	783	**NR**
Linne 2002 [81]	Retrospective	Stockholm	28/ 2- h oral glucose tolerance test (OGTT) with 75 g glucose, 2 h value over >9.0 mmol/L	52	**NR**
Minoee 2017 [176]	Prospective population follow-up	Iran	476/ WHO (1998)	1982	**NR**
Minoee 2017 [176]	Prospective population follow-up	Iran	476/ WHO (1998)	1982	**NR**
Pirkola 2010 [111]	Population based study	Finland	124/ 2 h 75 g OGTT one abnormal value – Fasting >5.5 mmol/l, 1 h >11.0 mmol/ 2 h > 8 mmol/l	5342	**NR**
Tam 2012 [125]	Prospective follow-up	Hong Kong	45/ WHO 1999 (Tam 2007)	94	**NR**
Tam 2013 [122]	Prospective follow-up	Hong Kong	67/WHO 1999	136	Baseline: Mean (SD): 3230 (485)/ 3272(429)
Verma 2002 [52]	Longitudinal follow-up study	USA	58/Carpentrr and Coustain modification of NDDG	51	**NR**
Wang 2012 [66]	Longitudinal database	USA	1142/ICD-9	18,856	**NR**
Winhofer 2014 (1) [54]	Prospective follow-up	Austria	35/4th Workshop Conference of Gestational Diabetes (Based on Winzer 2004)	14	**NR**

Table 1 (continued)

Xiang 2013 [128]	Observational longitudinal	USA	93/ Based on medical records	142	**NR**
Xiang 2013 [128]	Observational longitudinal	USA	93/ Based on medical records	142	**NR**
No specified postpartum follow-up					
Couch 1998 [74]	Cross-sectional	Ohio	20/ O'Sullivan and NDDG criteria used	20	**NR**
Gadgil 2017 [78]	Cross-sectional	USA	13/ Self reported	13	**NR**
Gunderson 2010 [28]	Longitudinal observational	Canada	154/ Self reported confirmed with OGTT	1655	**NR**
Han 2018	Retrospective cohort study	South Korea	4970/ diagnosed based on ICD-10 codes	97,930	**NR**
Shostrom 2017 [114]	Population base study	USA	555/Self reported	7572	**NR**
Simmons 2017 [93]	Follow-up study	New Zealand	52/ Self reported	2582	**NR**
Thomann 2008 [51]	Case control	Switzerland	18/ ADA (2004)	19	**NR**

Author and year	Parity cases/controls	Gestational age of delivery cases/controls	Years follow up postpartum	Outcome measure considered	Adjusted analysis for cardiovascular outcome
< 1 year postpartum					
Albareda 2004 [57]	446/694 (64.3)	**NR**	6 weeks and 5 year	Blood pressure BMI, Serum Lipids Blood Glucose Insulin	Independent predictors of GDM: previous hyperglycaemia, 4 abnormal values in diagnostic OGTT or overt diabetes during pregnancy, 2 h blood glucose in diagnostic OGTT 11/7 mmol/L, gestational age at diagnosis, pre-pregnancy BMI. Accumulates to 49.3% risk of diabetes in GDM women
Anastasiou 1998 [14]	*Mean (SD)* Normal: 1.6 ± 0.6, Non obese: 1.4 ± 0.6, Obese:1.7 ± 0.8	**NR**	3–6 months	Serum Lipids	Endothelium dependant dilation not associated with diagnosis of GDM
Berglund 2016 [151]	Parity>1 (n=): Normal weight: 55 Overweight: 24 Obese: 28 GDM:35	**NR**	At birth	BMI	**NR**
Bowes 1996 [71]	**NR**	*Mean (SD)* 30.9 + 0.8	2–3 months	BMI Blood glucose Fasting Plasma Insulin	**NR**
Bozkurt 2010 - abstract (2) [152]	**NR**	**NR**	3–6 months	BMI, Triglycerides	**NR**
Bozkurt 2012 (2) [72]	**NR**	**NR**	3–6months	Blood pressure, Triglycerides, Blood Glucose	**NR**
Cellina 1983 [21]	**NR**	**NR**	5 weeks	Blood pressure	**NR**
Chan 1992 [153]	**NR**	**NR**		Serum insulin Glucose	**NR**

Table 1 (continued)

			60 and 120 min after delivery		
Davenport 2012 [23]	**NR**	**NR**	2 month post-partum	Blood Pressure BMI Serum Lipids	**NR**
Davis 1999 [24]	**NR**	**NR**	3–18 months	Blood pressure BMI Serum Lipids Blood glucose Fasting Insulin	MANOVA adjusting for insulin metabolic syndrome variables - all significant for glucose sum, triglycerides, BMI and diastolic BP.
Eroglu 2006 [77]	Parity: Cases: 1.3 ± 0.7 Control: 1.4 ± 0.	**NR**	10–15 months after delivery	BMI, Serum Lipids Blood glucose, Fasting insulin	**NR**
Ferrada 2007 [26]	**NR**	**NR**	End of puerperal period	Blood pressure, BMI Serum Lipids	**NR**
Friere 2006 [154]	**NR**	**NR**	8 weeks	Blood pressure BMI	**NR**
Homko 2001 [155]	**NR**	**NR**	3 months postpartum	Blood Glucose Fasting insulin	**NR**
Kjos 1991 [100]	Mean (SD): GDM 3 (2)/Control: 3 (2)	**NR**	6–12 weeks,	BMI Serum Lipids	Women with DM had significantly elevated TG and reduced HDL than those who remained non-diabetic.
Ko 1999 [33]	**NR**	**NR**	6 weeks	Blood pressure BMI, SBP, DBP, Serum Lipids Blood Glucose Fasting Plasma Insulin (uU/mL)	GDM women had significantly higher risk of developing obesity, hypertension, hypercholesterolemia, dyslipidaemia, diabetes, and IGT (after excluding those with DM)
Lee 2015 [36]	**NR**	**NR**	6–8 weeks after delivery,	Blood Pressure BMI Serum Lipids Blood glucose Fasting Insulin	Multiple regression: b cell function significantly associated with parental diabetes history and waist-hip ratio after adjustment for age, BMI, BP and visceral adiposity in previous GDM women
Maghbooli 2010 [156]	1.4 ± 0.03 0.38 ± 0.59	**NR**	6–12 weeks	Serum Lipids Blood glucose	**NR**
McLachlan 2005 [83]	**NR**	**NR**	3–6 weeks	BMI, Blood glucose	**NR**
Morbiducci 2009 **(1)** [84]	**NR**	**NR**	4–6 months	BMI	**NR**
Noujah 2017 [157]	**NR**	**NR**	6–12 weeks	Serum Lipids	Univariate analysis – pre-pregnancy BMI > 35 and GDM history in first relatives associated with dyslipidaemia in GDM women. Multivariate analysis showed significance for BMI > 25 only
Noujah 2018 [43]	**NR**	**NR**	6–12 weeks	Blood pressure BMI, Blood Glucose	Backward linear regression - gravidity >2, pre-pregnancy overweight or obesity, systolic BP, and metformin or insulin use in pregnancy risk factors for MetS in univariate analysis.
Pacini 2012 (2) [126]	**NR**	**NR**	6 months	BMI (kg/m2), Blood Glucose Fasting Plasma Insulin	**NR**

Table 1 (continued)

Retnakaran 2009* [158]	Nulliparous: (GDM 50.4%/CON: 46.7%)	*Median (IQR)* 29 (28–31)/30 (28–32)	3 month	BMI Blood Glucose	Meta-regression analysis –IR post-partum associated with adiponectin levels in pregnancy after adjustment for various covariates
Retnakaran 2010* [106]	**NR**	**NR**	3 month	Blood Pressure BMI Blood Glucose	AUC associated with total cholesterol, LDL, HDL, triglycerides in adjusted model for age ethnicity and diabetes history
Retnakaran 2010* [106]	**NR**	34.4 (4.3)/34.0 (4.4)	3 month	Blood Pressure BMI	Multiple linear regression: GDM was negative predictor of change in beta cell function between 3 and 12 months postpartum, after adjustment for age, ethnicity, familial history of diabetes, breastfeeding and b cell function.
Retnakaran 2010* [106]	**NR**	**NR**	3 month	Blood Pressure BMI Blood glucose	Area under curve associated with total cholesterol, LDL, HDL, triglycerides in adjusted model for age ethnicity and diabetes history
Retnakaran 2011* [123]	**NR**	**NR**	3 month	Blood Pressure BMI Serum Lipids	Multiple linear regression performed for effect on adiponectin in metabolic status in GDM women adjusted for various covariates.
Roca-Rodrigeuz 2012* [159]	**NR**	**NR**	≤1 year	Blood Pressure BMI, Serum Lipids Blood glucose Fasting plasma insulin	Changes at 3 and 12 months post-partum not significant after adjusting for waist circumference, weight, insulinsensitivity and b cell function adjusted for baseline values.
Roca-Rodrigeuz 2014* [45]	**NR**	**NR**	≤1 year	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Relationship between AUC glucose and lipids adjusted for age, ethnicity and familial diabetes.
Sartore 2011 [120]	**NR**	**NR**	6 months	Serum Lipids, Blood Glucose	Adjusted *p* value reported, specified for age and waist circumference (based on Kruskall Wallis test)
Seck 2018	**NR**	**NR**	After delivery	Serum Lipids Blood Glucose	**NA**
Sokup 2012* [115]	**NR**	**NR**	2–24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Sokup 2012* [115]	**NR**	**NR**	2–24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Sung 2008 [49]	**NR**	**NR**	2 months	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Todoric 2012 [65]	**NR**	**NR**	6–12 weeks		

Table 1 (continued)

				Blood Pressure BMI Serum Lipids Fasting plasma insulin	Adjusted *p* values for BMI: Fasting plasma glucose (mmol/L): p = 0.000; TC (mmol/L): *p* = 0.9940; HDL-C (mmol/L) *p* = 0.0027, LDL-C *p* = 0.4022; TG *p* = 0.0006 Fasting plasma glucose:HDL-C *p* = 0.0049, TG p = <0.0001
Tura 2006 (2) [127]	Mean (SE) 1.26 (0.11)/1.48 (0.18)	**NR**	4–6 months	BMI, Blood glucose Fasting plasma insulin	**NR**
Vitoratos 2001 [96]	**NR**	Case: 38.6 (38–39.5)/ Control39.4 (39–40)	6 weeks	BMI	**NR**
Wang 2019	**NR**	**NR**	After delivery	BMI	**NA**
Weisnagel 2013 abstract [160]	**NR**	**NR**	2 months	Total cholesterol, HDL, Triglyceride, Fasting glucose, Fasting Insulin (not specified)	**NR**
Winzer 2004**(1)**[99]	**NR**	**NR**	3 month	BMI Serum Lipids Blood glucose Fasting plasma insulin	Adiponectin unadjusted is negatively associated with fasting glucose, triglycerides and positively associated with HDL cholesterol in pGDM and healthy control subjects, this correlation stays after adjustment for BFM, WHR and SI
Zajdenverg 2014 [55]	2.3 (1.22)/ 2.4 (1.4)	**NR**	≤ 1 year	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
1–5 years post-partum					
Akinci 2008 [15]	**NR**	**NR**	3 years	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Multiple regression analysis: Plasma PAI-1 antigen significantly correlated with BMI fasting and post load glucose, total cholesterol, triglyceride, HDL and LDL.
Akinci 2011* [130]	**NR**	**NR**	3 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	No association was seen between pre-pregnancy obesity (BMI >30 kg/m2) and postpartum diabetes association wasweak, controlled for age, parity and gestational week at the diagnosis of GDM.
Akini 2011* [130]	**NR**	**NR**	3 years	Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Akini 2013* [43]	**NR**	**NR**	3 years	Serum Lipids Blood glucose Fasting plasma insulin	Fasting glucose, post-load glucose - separate models run along with age,

Table 1 (continued)

					postpartum duration, smoking, BMI, waist circumference and HOMA index.
Albareda 2003 [57]	**NR**	**NR**	6 weeks and 5 year	Blood Glucose	Independent predictors of GDM: previous hyperglycaemia, 4 abnormal values in diagnostic OGTT or overt diabetes during pregnancy, 2 h blood glucose in diagnostic OGTT 11/7 mmol/L, gestational age at diagnosis, pre-pregnancy BMI. Accumulates to 49.3% risk of diabetes in GDM women
Albareda 2004 [57]	**NR**	**NR**	5 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Logistic regression: Metabolic syndrome significantly associated with all independent variables age, GDM/control status, obesity were independent variables. Second model included HOMA-IR, insulin secretion and resistance
Banerjee 2012 [16]	**NR**	**NR**	2 years	Blood Pressure BMI Serum Lipids Blood glucose	BMI directly correlated with arterial stiffness, inversely related to maximum endothelium dependant and independent dilation
Bently Lewis 2015* [58]	Nulliparous: GDM: 245 (47.0). Multiparous GDM: 273 (52.4)	≥37 weeks	4.1 years	Blood Pressure BMI Serum Lipids	**NR**
Bently Lewis 2016* [17]	Same as 2015	≥37 weeks	4.1 years	Blood Pressure BMI	Risk of essential hypertension higher in women with GDM adjusted for demographic (age, race gravidity, parity) + clinical features (SBP, BMI, GWG, BW and GA percentile) + SES (smoking status, breastfeeding as discharge, marital status, education years)
Cocilovo 1990 [73]	**NR**	**NR**	1 year	BMI	**NR**
Davis 1999 [24]	**NR**	**NR**	3–18 months	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	MANOVA 2: Insulin and metabolic syndrome variables - all significant adjusting for glucose sum, triglycerides, BMI and diastolic BP. MACOVA: Insulin metabolic variables, significant for glucose, triglycerides, BMI and diastolic blood pressure
Demir 2016 [75]	**NR**	**NR**	**3–4 years**		**NR**

Table 1 (continued)

				Blood Pressure BMI Serum Lipids Blood glucose	
Eroglu 2006 [77]	1.3 ± 0.7/ 1.4 ± 0.	**NR**	10–15 months after delivery	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Fakhrzadeh 2012 [25]	1.45 ± 0.76/ 1.95 ± 1.05	**NR**	4 years	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Logistic regression -. Stratified analysis showed association of CVD with GDM was only seen among women with BMI > 25, but only women with BMI < 30 accounted for the increased risk.
Hakkariainen 2015** [161]	**NR**	**NR**	5-10 years	BMI Blood glucose Fasting plasma insulin	**NR**
Hakkariainen 2016** [30]	Primiparity (%): GDM (1) 35.9 (2) 37.9/ 54.7	Days: GDM (1) 278 ± 10 (2) 278 ± 10/ Control 279 ± 11	5-10 years	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Hu 1998 [60]	**NR**	**NR**	2 years	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Kjos 1991 [100]	3 (2)/3 (2)	Not reported	1 year	BMI Serum Lipids,	N/A
Kousta 2003 [79]	Median (IQR) 2 (1–3)/ 2 (1–3)	**NR**	2 years	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Krishnaveni 2007 [34]	Parity 2+: GDM: NGT: 1 (9%) IGT: 2 (18%) DM:3 (23%) No GDM: NGT:65 (16%) IGT:14 (19%)DM: 4 (50%)	30 weeks	>5 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Lee 2008 [35]	**NR**	**NR**	Median 2.1 years	Blood Pressure BMI Serum Lipids Blood glucose	Logistic regression: T2DM risk higher for women with GDM risk compared to general population (stratified by race status). GDM status indepdently and significantly associated with diabetes development (3.7-fold increase risk)
Levka 2015* [62]	Primipara (%) IADPSG: 44%/60% WHO: 60.0%/48.6	Median (IQR): IADPSG: 40.4 (39.0–41.3)/ 40.4 (39.3–41.1)	5 years	Blood Pressure Serum Lipids	Adjusted p value for age, smoking frequency and BMI HDL-C (mmol/L) $p = 0.058$ LDL-C (mmol/L) $p = 0.405$ TG (mmol/L) $p = 0.261$ Multivariate analysis: Pulse Wave Velocity at 5 years is associated with age, GDM systolic blood pressure. TG/HDL-C ratio is associated with BMI, GDM status, SBP
Levka 2016* [162]	IADPSG: 6 (12.0)/26 (11.1) WHO: 6 (19.3)/26 (10.3)	**NR**	5 years	Blood Pressure BMI	**NR**

Table 1 (continued)

Levka 2017* [163]	IADPSG: 6 (12.0)/26 (11.1) WHO: 6 (19.3)/26 (10.3)	**NR**	**5**	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Univariate analysis showed LDL at 5 years postpartum negatively associated with insulin sensitivity and resistance, b cell function
Madarasz 2009 [37]	**NR**	**NR**	**3.5 years**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Adjusted p value specified for age and BMI: Systolic blood pressure p = 0.40 Diastolic blood pressure ***p*** **= 0.017** HDL-C: $p = 0.68$ LDL-C: $p = 0.18$
Mai 2014 [38]	*Mean (SD)*2.5 (1.8)/2.6 (1.9)	**NR**	2.5 years	Blood Pressure Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Noctor 2015** [164]	**NR**	**NR**	≤3 years	Blood Pressure BMI Serum Lipids Blood glucose	BMI > 30, first degree relative with GDM, macrosomic baby in previous pregnancy associated with GDM
Noctor 2016** [42]	**NR**	**NR**	≤3 years	Blood Pressure BMI Serum Lipids Blood glucose	Abnormal glucose tolerance at any time 5 years postpartum associated with fasting glucose, 1-h glucose values on pregnancy OGTT, and family history of diabetes. BMI >30 at follow-up associated with abnormal glucose tolerance
Ozuguz 2011 [118]	*Mean (SD)* 2.63 (1.36)/ 2.64 (1.13)	*Mean (SD)* 26.23 (1.73)/26.54 (1.81)	1 year	Serum Lipids Blood glucose Fasting plasma insulin	
Perrson 2015 [110]	*Mean (SD)* 1.3 (0.8)/1.3 (1.3)	**NR**	4 years	BMI	**NR**
Pimenta 2004 [86]	Median (IQR): 2 (1)/ 2 (2)	**NR**	5 years	Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Prikoszovich 2011 [87]	**NR**	**NR**	3 to 5 years	BMI Serum Lipids Blood glucose Fasting plasma insulin	Adjustment for Body Fat Mass attenuated after adjusting for HDL-C in pGDM compared to control
Rauito 2014 [44]	**NR**	**NR**	**1**	Blood Pressure BMI Serum Lipids	Adjusted p value for age, outcome variable and BMI at baseline
Ruksasakul 2016 [64]	**NR**	**NR**	≤3 years	Blood Pressure BMI Serum Lipids Fasting plasma insulin	Metabolic syndrome associated significantly with BMI >25 and age > 35, but not previous GDM
Ryan 1995 [90]	**NR**	**NR**	≤4.9 years	BMI Blood glucose	**NR**
Ryan 2013 [46]	**NR**	**NR**	≤5 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Shen 2018 [92]	**NR**	**NR**	3.65 years	Serum Lipids, Blood Glucose	NR
Shen 2018 [92]	**NR**	**NR**	3 years	BMI Blood Glucose	pGDM women have 13.fold multivariable adjusted risk for diabetes
Shen 2019	**NR**	**NR**	3.65 years	Serum Lipids, Blood Glucose	Women with GDM had higher risk of postpartum metabolic syndrome by NCEP ATPIII criteria (2.79, 95% CI 2.00 to 3.89) even with adjustment for various covariates:

Table 1 (continued)

					(central obesity hypertriglyceridemia, high blood pressure, low HDL cholesterol hyperglycaemia
Sokup 2012 [115]	**NR**	**NR**	2–24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	Adjusted *p*-values for BMI reported
Sokup 2012 [115]	**NR**	**NR**	2–24 months	BMI Serum Lipids Blood glucose Fasting plasma insulin	hsCRP associated with BMI, serum e-selectin associated with TG, Serum TC and HDL associated with LDL
Stuebe 2011 [113]	*(n=)*GDM P1 = 7; P2 = 6, P3 = 3/ CON: P1 = 131; P2 = 227; P3 + = 112	**NR**	3 years	BMI Serum Lipids Blood glucose Fasting plasma insulin	Adjusted analyses performed for age, parity, race, parental history of diabetes and maternal BMI at 3 years postpartum
Ueland 2018	**NR**	**NR**	5 years	Blood Pressure BMI	Adiponectin significantly lower in women with GDM than controls even after adjustment for BMI, age, parity, diabetes in family and C- Reactive Protein
Verma 2002 [52]	P1 (n=) 42/49 P2 (n=) 64/52 >= P3 (n=) 23 (22)/16 (16)	**NR**	4 to 5 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Risk of developing MetS in subsequent 2 years was 26 times higher in women with GDM with PPO (cumulative HR: 1.3) compared to controls without PPO (cumulative HR: 0.05)
Vigneault 2015 [95]	Normal Weight *(Mean (SD))* 2.14 (0.89)/2.12 (0.13) Overweight 1.93 (0.11)/2.38 (0.17) Obese: 3.57 (0.25)/2.85 (0.51)	**NR**	≤4	BMI Blood glucose Fasting plasma insulin	**NR**
Vilmi-Kerala 2016 [53]	Nulliparous: (GDM 23 (19.2%)/CON: 23 (19.2%)	**NR**	≤4 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Previous GDM is not an important influencing factor for the primary outcome measurements in study.
Wang 2015 [97]	**NR**	**NR**	**1**	Blood Pressure BMI Serum Lipids	**NR**
Winhofer 2013* (1) [165]	**NR**	**NR**	5 years	Blood Pressure BMI Serum Lipids	pGDM group had increased waist circumference, HBA1C and increased fasting glucose but was attenuated after adjusting for BMI (Values not shown)
Winhofer 2013 abstract* (1) [166]	**NR**	**NR**	5	HDL-C (mg/dl),	**NR**
Winhofer 2014* (1) [54]	**NR**	**NR**	5 years	BMI Blood Glucose	**NR**
Winzer 2004 (1) [99]	**NR**	**NR**	1 years	BMI Serum Lipids Blood glucose Fasting plasma insulin	Fasting glucose adjusted Mean: 89.00/82.33 -adjusted

Table 1 (continued)

					for waist circumferenceMean: 89.93/81.36 - adjusted for body fat mass
Xiang 2012 [167]	**NR**	**NR**	≤5 years	BMI	Plasma glucose and insulin not significantly different between GDM and controls for adjusted values (Adjusted age, age at first pregnancy, baseline percentage body fat, baseline calorie intake and physical activity, additional pregnancy).
Xiong 2013 [129]	Nulliparous *(n=)*: 2 (10.5%)/ 4(20%) Multiparous(n=): 17 (89.5%) 16 (80.0%)	**NR**	1.9 years	Blood glucose Fasting plasma insulin	**NR**
5–10 years postpartum					
Benjamin 1993 [107]	*Mean:*GDM, 3.2 Non GDM: 3.4	**NR**	9 years	BMI	**NR**
Bian 2000 [169]	**NR**	**NR**	5–10 years	Rate of T2DM	T2DM is higher in GDM women with antepartum BMI < 25kgm/2 and > 25 kg/m2
Bo 2007 [18]	*Mean:* Control: 1.6 GDM: 1.9	**NR**	6.5 year	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Multiple regression analysis showed e-selectin, ICAM-1, IL-6 and hsCRP associated with Mean IMT after adjustment for BMI, waist circumference, blood pressure and blood glucose
Caliskan 2014 [19]	**NR**	**NR**	6 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Carotid intima medial thickness (cIMT), total cholesterol, BMI, HBA1C, and HOMA-IR independently correlated with epicardial fat thickness
Da 2016 (Abstract) [170]	**NR**	**NR**	5–12 years	BMI Serum Lipids Blood glucose	**NR**
Donhorst 1990 [76]	Recurrent GDM:1–4. Known diabetics DM:2–8, IGT:2–6, NGT:1–5	**NR**	6–12 years	BMI	**NR**
Ferraz 2007 [101]	**NR**	**NR**	6.2 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Average of CRP levels were statistically high in subjects with previous GDM and abdominal obesity and elevated fasting glucose.
Hakkariainen 2015** [161]	**NR**	**NR**	>10 years	BMIBlood glucose Fasting plasma insulin	**NR**
Hakkariainen 2016** [30]	Primiparity (%): GDM (1) 35.9 (2) 37.9/ 54.7	Days: GDM (1) 278 ± 10 (2) 278 ± 10/ 279 ± 11	>10 years	Blood Pressure BMI Serum Lipids Blood glucose	**NR**

Table 1 (continued)

Hunger Dathe 2006 [32]	**NR**	**NR**	6 years	Blood Pressure BMI Blood glucose	**NR**
Lauenborg 2005 [61]	**NR**	*Median (IQR)* 227 (197–249)/ 227 (197–249)	9.8 years	Blood Pressure BMI Fasting plasma insulin	**NR**
Meier (2005). [39]	**NR**	26 ± 6 (mean ± SD)	4.1	Blood pressure Blood glucose	Multivariate analysis adjusted for age and BMI
Modela 2016* [41]	**NR**	Not reported	**7**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Osei 1998 [85]	Parity similar between groups	**NR**	7 years	BMI Blood glucose Fasting plasma insulin	**NR**
Pimenta 2004 [86]	*Mean (SD):* 2(1)/2(2)	**NR**	5–8 years	BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Seghiri 2007 [91]	*Mean (SD):* 2 (1)/ 1.6 (0.8)	**NR**	7.5 years	BMI	**NR**
Sriharan 2002 [48]	*Mean (SD):* 1.8 (2.2)/2.2 (1.8)	**NR**	6.8 years	Blood PressureBMISerum Lipids Blood glucose	Multiple logistic analysis adjusted for age, time from previous pregnancy, BMI, and family history of diabetes
Tam 2007* [171]	Nulliparous (n=) 40/74	*Mean (SD):* 39.3 ± 2.1 /39.5 ± 1.6	8 years	Blood Pressure BMI Serum Lipids	Triglyceride in linear regression model adjusted for age, race, school years, metabolic syndrome
Tam 2012** [125]	**NR**	*Mean (SD):* 39.3 (2.1) /39.5 (1.6)	8 years	BMI Serum Lipids	**NR**
Tam 2013** [122]	**NR**	*Mean (SD):* 39.3 (2.1) /39.5 (1.6)	8 years	BMI Serum Lipids	Relative and absolute risk for subgroups of various glycaemic indices mid-gestation - adjusted for various factors
Tehrani 2012 [121]	*Mean (SD)* 30.0 (1.7)/ Control 1 2.8 (1.5) Control 2 4.6 (2.3)	**NR**	9 years	Blood Pressure BMI Serum Lipids Blood glucose	Relative and absolute risk for subgroups of various glycaemic indices mid-gestation - adjusted for various factors
Tobias 2017 [94]	*Mean (SD)* 1.9 (1.2)/ 1.8 (1.1)	**NR**	6 to 8 years	BMI	Adjusted analysis for baseline parameters
Tutino 2014 [172]	**NR**	**NR**	8 years	Blood Glucose	Multivariable models for CVD risk:Adjusted for age, years since pregnancy, menopausal status, hormone use, white race/ethnicity, family history of MI, or stroke, history of pregnancy hypertensive disorders, BMI and parity
Verma 2002 [52]	P1 (n=) 42/49 P2 (n=) 64/52 > = P3 (n=) 23 (22)/16 (16)	**NR**	6, 7, 8, 9 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	**NR**
Wender-Ozegowska 2007 [98]	**NR**	**NR**	6 years	Blood Pressure BMI Serum Lipids	**NR**

Table 1 (continued)

>10years postpartum					
Ajala 2011 (abstract) [168]	**NR**	**NR**	10 years	Blood Pressure BMI Serum Lipids	**NR**
Ajala 2015 [68]	**NR**	**NR**	4 to 10year	BMI Serum Lipids Blood glucose	After controlling for adiposity, BP, lipids, CRP glycaemic status did not contribute to vascular function.
Behboudi- Gandevani 2019	**NR**	**NR**	13years	Serum Lipids	NA
Carr 2006 [20]	**NR**	**NR**	29.9years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	CVD and coronary heart disease specifically higher in women with prior GDM compared to no GDM. Adjusted for age, menopausal status and proband clustering.
Charwat-Resl 2017 [22]	**NR**	*Mean (SD)* 16.2 ± 5.2/ 14.2 ± 4.8	16years	Blood Pressure BMI Serum Lipids	**NR**
Gobl 2011 (1) [173]	**NR**	**NR**	10years	Serum Lipids Blood Glucose	Fasting glucose, fasting insulin: Various models adjusted for age, age at first pregnancy, baseline percentage body fat baseline calorie intake and physical activity, % body fat and additional pregnancy during follow-up
Gobl 2014 (1) [174]	**NR**	**NR**	10years	BMI	2h OGTT >140mg/dL, age > 35 and HDL cholesterol <50mg/dL were best predictors of metabolic syndrome up to 10years follow-up
Gobl 2014 (1) [175]	**NR**	**NR**	10years	BMIFasting plasma insulin	Moderate associations of HbA1c with measurements of plasma glucose during the OGTT.
Gunderson 2014 [28]	*Mean (SD):* 2.3 (0.95)/ 2.2 (1.1)	**NR**	20	Blood Pressure BMI Serum Lipids Blood glucose	Adjusted and unadjusted mean (95% CI) for cIMT by GDM history stratified by women with diabetes or metabolic syndrome. No significant differences seen in adjusted models.
Hakkariainen 2015** [161]	**NR**	**NR**	>10 years	BMI Blood glucose Fasting plasma insulin	**NR**
Hakkariainen 2016** [30]	Primiparity (%): GDM (1) 35.9 (2) 37.9/ 54.7	Days: GDM (1) 278 ± 10 (2) 278 ± 10/ 279 ± 11	>10 years	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Heida 2015 [31]	No of pregnancy: 1: Not exposed: 1781 (11.5) HDP: 572 (9.3)GDM: 106 (9.7). 2: 5977 (38.4) 2226 (36.2) 360 (33.1), 3/ >:7802 (50.1) 3359 (54.5) 623 (57.2)	**NR**	Mean 29years since index pregnancy	Blood Pressure Serum Lipids	GDM associated with increased OR of having CVD, IHD, stroke or T2D. Model III adjusted for cohort, HDP, age, BMI, current smoking and alcohol consumption at study enrolment, total cholesterol/HDL ratio, prevalent hypertension, and T2D (for stroke, IHD and CVD outcomes only).

Table 1 (continued)

King 2009 [124]	GDM: 2.45 (0.9) No GDM: 2.25(0.6)	**NR**	15years (based on child's index age)	BMI Blood Pressure Serum Lipids	Adjusted results shown for age, current use of estrogen, BMI before first child, current BMI
Lee 2007 [80]	GDM: 2 (2–3) Control: 3 (2–3),	GDM 38.4 (2.7) Control39.2 (3.4)	15years	BMI, fasting glucose	**NR**
Linne 2002 [81]	**NR**	**NR**	15years	BMI	**NR**
Minoee 2017 [176]	Mean (SD): 2.7 ± 1.45/2.25 ± 1.24	**NR**	15 years	Blood Pressure BMI Blood glucose	T2DM progression is 2.15 fold higher in GDM women than controls after adjustment for age, BMI and family history of diabetes.
Minoee 2017 [176]	Mean (SD): 2.7 ± 1.45/2.25 ± 1.24	**NR**	15 years	Serum Lipids	**NR**
Pirkola 2010 [111]	**NR**	**NR**	20 years	BMI	GDM causes increased risk of diabetes in normal weight and overweight women, and hypertension in women who are overweight pre-pregnancy. In women with normal OGTT during pregnancy, hypertension and diabetes risk didn't differ between GDM women compared to women with no risk factors for GDM
Tam 2012 [125]	P1 (n=) 10/9, > = P2 (n=)84/36	**NR**	15 years	Total cholesterol (mmol/L)	Insulin sensitivity indices are independent predictors of diabetes and metabolic syndrome at 15years postpartum even with adjustment for b cell function or abnormal glucose tolerance status at 8years postpartum. History of GDM at index pregnancy increased the odds of progression to abnormal glucose tolerance, T2DM and hypertension.
Tam 2013 [122]	**NR**	Mean (SD): 39.3 (2.1) /39.5 (1.6)	15 years	BMI Serum Lipids	All glycaemic indices were predicative of abnormal glucose tolerance, diabetes mellitus and hypertension, but 2-h plasma glucose and glucose challenge tolerance is predictive of hypertension at 8 and 15years postpartum. Metabolic syndrome at 15years postpartum risk predicted by fasting plasma glucose
Verma 2002 [52]	P1 (n=) 42/49P2 (n=) 64/52 > = P3 (n=) 23 (22)/16 (16)	**NR**	11 years	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Fasting plasma glucose risk adjusted for maternal age, BMI at booking, AGT at 8years, familial history of DM, gestational hypertension, preeclampsia during indexpregnancy and subsequent term pregnancy (n=)
Wang 2012 [66]	Parity >1: GDM 53.5%/Non GDM: 36.1%	**NR**	13–50 years	Blood Pressure BMI	Metabolic syndrome increased in women with GDM with increasing age.
Winhofer 2014 (1) [54]	**NR**	**NR**	10 years	Blood Pressure BMI Serum Lipids Blood glucose	**NR**

Table 1 (continued)

Xiang 2013 [128]	Mean (SD) 3.1(1.3)/2.9 (1.2)	**NR**	>10 years	BMI Blood glucose Fasting plasma insulin	**NR**
Xiang 2013 [128]	*Mean (SD)* 3.1(1.3)/2.9 (1.2)	**NR**	>10 years	BMI Fasting plasma glucose Fasting plasma insulin	**NR**
No specified postpartum follow-up					
Couch 1998 [74]	**NR**	**NR**	**NR**	Serum Lipids	**NR**
Gadgil 2017 [78]	GDM: 2.2 (0.6), no GDM:2.1 (0.8)	**NR**	**NR**	Blood Pressure BMI Serum Lipids	Adjustment for age and weight at 40. Women with GDM history have 3.3 fold increased risk of having diabetes
Gunderson 2010 [28]	**NR**	**NR**	**NR**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Pre-pregnancy cardiometabolic risk factors adjusted for familial diabetes parity at conception, births during interval, time to first conception, smoking age at preconception examination and race
Han 2018	**NR**	**NR**	**NR**	BMI Blood Glucose	NA
Shostrom 2017 [114]	**NR**	**NR**	**NR**	BMI	GDM is associated with higher risk of CVD compared to women without CVD as a reference for all models (Adjusted for age, race/ethnicity, education, family income-poverty ratio, smoking/drinking, physical activity, total energy, BMI).
Simmons 2017 [93]	**NR**	**NR**	**NR**	Blood Pressure BMI Serum Lipids Blood glucose	**NR**
Thomann 2008 [51]	**NR**	**NR**	**NR**	Blood Pressure BMI Serum Lipids Blood glucose Fasting plasma insulin	Difference shown between groups in fat distribution, estimates ofinsulin resistance, serum levels of lipids and parameters of low-grade chronic inflammation after adjusting for age and percent body fat.

Abbreviations = OGTT = oral glucose tolerance test, GCT = glucose challenge test, OGCT = oral glucose tolerance test. FPG: Fasting plasma glucose. BMI (body mass index), SBP (Systolic blood pressure), DBP (diastolic blood pressure), TC (total cholesterol), HDL (high density lipopprotein-cholesterol), LDL (low density lipoprotein-cholesterol), TG (triglycerides)

ADA: American Diabetes Association, ADIPS: Australian Diabetes in Pregnancy Society, IADPSG – International Association of Diabetes in Pregnancy Society

(+)BMI kg/m2, SBP/DBP mmHg units, all other units specified each study

Lipids collectively refers to study including total cholesterol, HDL, LDL and triglycerides

* - papers of same author are the same study

** - paper looked at two different time points

(1) Studies with this subscript part of the same cohort but Winzer 2004 was used in overall meta-analysis,Winzer < 1 year postpartum, Winhofer + 10 years

(2) Studies with this subscript part of the same cohort but Bozkurt 2012 used in overall meta-analysis and < 1 year postpartum subgroup

time of follow up post-partum as: <1 year, 1–5 years, 5–10 years and 10+ years from the index pregnancy. Studies that did not provide details on when the follow up assessment was conducted, were only included in the overall analysis. When the same cohort was assessed at multiple times post-partum, the study with the largest sample size was used in the overall analysis and in the relevant subgroup analyses. When outcome measures of the same cohort at one follow up time point were reported in multiple publications, the one with the largest sample size was used in the overall analysis.

We considered studies published in English, and studies that could be translated to English. We contacted authors via email to obtain missing data and clarifications when required. We included abstracts of cohort studies, but only abstracts which provided data for relevant outcomes were included in the meta-analysis and non-meta-analysis table (Supplementary Table 1).

2.3 Statistical analysis

The following data were collected from each included study: definition of GDM, time of post-partum follow up (number of years since index pregnancy), number of cases (those who experienced GDM) and controls (those who did not experience GDM), child birthweight, and gestational age at delivery of cases and controls, and data on the variables considered in any adjusted analyses/variables used to match cases with controls.

The meta-analysis was performed using RevMan software (Review Manager Version 5.3) based on an inverse variance method. As per protocol, the random-effects model was selected to account for the differences in diagnostic criteria of GDM. For each outcome measure, unadjusted mean and standard deviation (SD) were used in meta-analyses. When mean and SD were not reported, Standard Error of Mean (SEM) was converted to SD using RevMan software. The Standard Mean Difference (SMD) was used when the outcome was measured in different units across studies and Mean Difference (MD) when units were consistent.

Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the Chi^2 P value was less than 0.1. The studies that reported on outcome measures using median and IQR are detailed in Supplementary Table 1. To assess publication bias, funnel plots were used for the primary outcomes. The methodological quality was assessed using the Newcastle - Ottawa Quality Assessment Scale (NOS) and graphically illustrated in the supplementary data (Supplementary Fig. 1) [13]. Sensitivity analyses were performed to evaluate heterogeneity for outcomes after excluding low quality studies (i.e. scored 1–3 on the NOS) and excluding abstracts that were included in the meta-analyses. Two authors (MP, AA) independently assessed the quality of each study included in the review. The discrepancies were resolved through discussions with ZL and PA.

3 Results

The literature search identified 12,248 articles. Four hundred and thirteen (413) articles were eligible for full text review. Of these, 139 were included in the review and 93 were included in the meta-analyses. The reasons for excluding 274 studies are detailed in Fig. 1. We contacted 24 authors for additional data; we received a 17% response rate ($n = 4$ studies). Of the included studies, 33 were of high quality (scored 7–8), 79 were of moderate quality (scored 4–6), and 28 were of low quality (scored 1–3) (Supplementary Table 2). The results of the overall meta-analyses for all CVD risk factors in women with previous GDM compared to those without previous GDM are shown in Table 2.

Blood pressure Systolic blood pressure (SBP) and diastolic blood pressure (DBP) data were available from 60 studies, of which 48 were included in the overall meta-analysis. Quantitative summary measures showed that women with previous GDM have 2.47 mmHg (95% CI 1.74 to 3.40) higher mean SBP compared to controls (n (total) = 50,118; heterogeneity: Chi^2 $P < 0.00001$, $I^2 = 80\%$) (Table 1) (Supplementary Fig. 1A) [14–56]. Of the 12 studies with data not included in the meta-analysis [52, 57–67], eight reported higher SBP in women with previous GDM compared to the control group [52, 57–60, 63, 64, 67], with five studies showing statistical significance [52, 57, 60, 64, 66] (Supplementary Table 1). Sensitivity analysis after excluding the low quality studies showed a marginal increase in heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 82\%$). (Supplementary Table 3A).

Women with previous GDM have 1.89 mmHg (95% CI 1.32 to 2.46) higher DBP compared to women without previous GDM ($n = 49{,}495$, heterogeneity: Chi^2 $P < 0.00001$, $I^2 = 83\%$) (Table 2) (Supplementary Fig. 1B) [14–56]. Of the 12 studies not included in the meta-analysis [2, 52, 57–67], six reported higher DBP in women with previous GDM compared to the control group [52, 57, 58, 60, 63], with three studies showing statistical significance [57, 60, 61]. Sensitivity analysis after excluding low quality studies showed a marginal increase in heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 85\%$). (Supplementary Table 3B).

Body mass index Body Mass Index (BMI) data were available from 102 studies, of which 78 were included in the overall meta-analysis. BMI was 1.54 kg/m^2 higher in women with previous GDM compared to women without previous GDM (95% CI 1.17 to 1.91; $n = 255{,}308$, heterogeneity: Chi^2 $P < 0.00001$, $I^2 = 97\%$) [14, 16, 18–20, 22, 23, 25, 26, 28, 29, 38, 39, 41–43, 45, 46, 48–53, 55, 56, 58, 68–104]

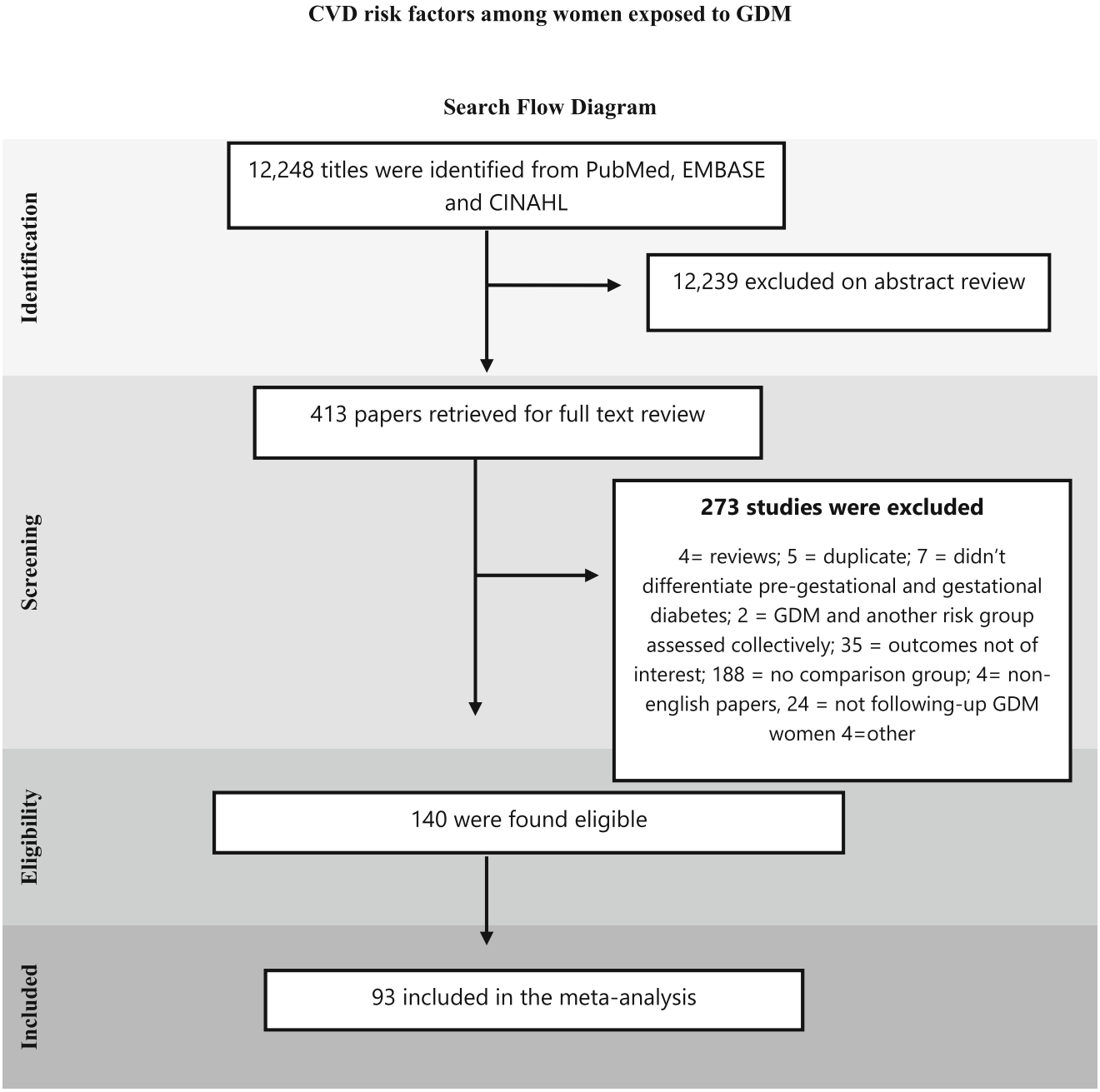


Fig. 1 PRISMA flow chart of study selection

(Table 1) (Supplementary Fig. 2). Of the 24 studies not included in the meta-analysis [37, 52, 57, 59–61, 63–67, 100, 105–117], 12 studies reported that women with previous GDM had significantly higher BMI or were more obese than women without previous GDM [37, 52, 60, 61, 64, 66, 67, 69, 100, 106, 108–111, 114–117]. Sensitivity analysis after excluding low quality studies showed a decrease in heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 95\%$) (Supplementary Table 3C).

Lipids Total cholesterol data were available from 59 studies, 48 studies were included in the overall meta-analysis. Women with previous GDM had 0.26 SMD higher total cholesterol compared to women without previous GDM, (95% CI 0.15 to 0.37; $n = 38{,}561$, heterogeneity: Chi^2 $P < 0.00001$, $I^2 = 89\%$) [14, 16, 19, 20, 22–25, 29, 31, 33, 35, 36, 38, 41, 42, 44, 46, 47, 49, 52, 53, 55, 56, 64, 69, 70, 75, 77, 78, 86, 97, 100, 101, 118–122] (Table 1) (Supplementary Fig. 3). Of the 11 studies not included in the meta-analysis [52, 57, 59, 60, 65, 74, 100, 113, 115, 116, 123], three reported that women with previous GDM had significantly higher total cholesterol compared to the control group [52, 100, 116]. Sensitivity analysis after excluding low quality studies showed a marginal increase in

Table 2 Mean differences for cardiovascular outcomes overall in women with previous gestational diabetes mellitus compared to women without previous GDM

Outcome	Odds Ratio MD/SMD	95% CI	n = (studies)	n = (GDM/ control)	n = (total)	Heterogeneity
Systolic Blood Pressure (mmHg)	**MD 2.47**	**1.74, 3.40**	48	7332/42,786	50,118	$I^2 = 79\%$ $P < 0.00001$
Diastolic Blood Pressure (mmHg)	**MD 1.89**	**1.32, 2.46**	48	7025/42,470	49,495	$I^2 = 83\%$ $P < 0.00001$
BMI (kg/m^2)	**MD 1.54**	**1.17, 1.91**	78	26,689/ 228,619	255,308	$I^2 = 97\%$ $P < 0.00001$
Total cholesterol (SMD)	**SMD 0.26**	**0.15, 0.37**	48	6817/31,744	38,561	$I^2 = 89\%$ $P < 0.00001$
Low density Lipoprotein (SMD)	**SMD 0.19**	**0.08, 0.30**	44	5846/11,134	16,980	$I^2 = 83\%$ $P < 0.00001$
High density lipoprotein (SMD)	**SMD -0.28**	**-0.39, −0.16**	56	7203/28,679	35,882	$I^2 = 89\%$ $P < 0.00001$
Triglycerides (SMD)	**SMD 0.56**	**0.42, 0.70**	45	4110/9065	13,175	$I^2 = 88\%$ $P < 0.00001$
Glucose (SMD)	**SMD 0.69**	**0.56, 0.81**	55	17,180/110,720	127,900	$I^2 = 94\%$ $P < 0.00001$
Insulin (SMD)	**SMD 0.41**	**0.23, 0.59**	32	2994/5887	8881	$I^2 = 90\%$ $P < 0.00001$

Abbreviations: MD – mean difference, 95% CI – 95% Confidence Interval

Bold MD (95% CI) highlights significant result

heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 90\%$). (Supplementary Table 3D).

Low density lipoprotein (LDL) cholesterol data were available from 57 studies, of which 44 were included in the overall meta-analysis. Women with previous GDM had 0.19 SMD higher LDL compared to women without previous GDM (95% CI 0.08 to 0.30; $n = 16{,}980$, heterogeneity: Chi^2 P < 0.00001, $I^2 = 83\%$) (Table 1) (Supplementary Fig. 4) [8, 14, 15, 18–20, 22–25, 28, 29, 33, 36–39, 41–45, 47, 49, 52, 54, 56, 58, 64, 68, 70, 75, 78, 86, 97, 100, 118, 120–122, 124]. Of the 13 studies not included in the meta-analysis [52, 57, 59, 62, 65, 74, 100, 113, 115, 116, 122, 123, 125], four reported that women with previous GDM had significantly higher LDL compared to the control group [52, 62, 100, 116]. Sensitivity analysis after excluding low quality studies showed an increase in heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 85\%$). (Supplementary Table 3E).

High density lipoprotein (HDL) cholesterol data were available from 70 studies, of which 56 were included in the overall meta-analysis. Women with previous GDM had lower HDL compared to those without previous GDM, a − 0.28 SMD (95% CI -0.39 to −0.16; $n = 35{,}882$, heterogeneity: Chi^2 P < 0.00001, $I^2 = 89\%$) [15, 16, 18–20, 22–26, 29–31, 33, 35–39, 41–48, 52, 55, 58, 64, 70, 75, 77–79, 86, 87, 99–101, 118, 120–122] (Table 1) (Supplementary Fig. 5). Of the 14 studies not included in the meta-analysis [34, 49, 52, 57, 59, 61, 62, 65, 74, 84, 100, 113, 115, 122], five reported that women with previous GDM had significantly lower HDL than the control group [14, 52, 61, 115, 116, 122]. Sensitivity analysis after excluding low quality studies showed a marginal increase in heterogeneity (Chi^2 $P < 0.0001$, $I^2 = 90\%$). (Supplementary Table 3F).

Triglyceride data were available from 64 studies, of which 45 were included in the overall meta-analysis. Women with previous GDM had 0.56 SMD higher triglycerides compared to those without previous GDM (95% CI 0.42 to 0.70; $n =$ 13,175, heterogeneity: Chi^2 $p < 0.00001$, $I^2 = 88\%$) [14–16, 19, 20, 22–25, 29, 30, 35, 36, 39, 41, 42, 44–47, 55, 58, 68, 70, 72, 75, 77–79, 86, 87, 99–101, 103, 118, 120] (Table 1) (Supplementary Fig. 6). Of the 19 studies not included in the meta-analysis [34, 51, 52, 57, 59–62, 65, 74, 97, 100, 113, 115, 116, 121–123], seven studies reported that women with previous GDM had significantly higher triglycerides than those without previous GDM [51, 52, 61, 100, 108, 115, 116]. Sensitivity analysis after excluding low quality studies showed no difference in heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 88\%$). (Supplementary Table 3G).

Glucose Blood glucose data were available from 72 studies, of which 55 were included in the overall meta-analysis. Women with previous GDM had 0.69 SMD higher blood glucose compared to those without previous GDM (95% CI 0.56 to 0.81; $n = 127{,}900$, heterogeneity: Chi^2 $P < 0.00001$, $I^2 = 94\%$) [8, 16, 18–20, 22, 24, 25, 28–30, 32, 33, 35, 36, 38, 41–49,

51–54, 56, 68, 71, 72, 75, 77, 79, 80, 83, 85, 92, 95, 101, 118–121, 124, 126–129](Table 1) (Supplementary Fig. 7). Of the 17 studies not included in the meta-analysis [34, 37, 52, 57, 59–61, 63, 78, 91, 106, 113, 115, 116, 122, 130, 131], 10 studies reported that women with previous GDM had significantly higher glucose than those without previous GDM [34, 52, 57, 61, 64, 115, 116, 122, 130, 131]. Sensitivity analysis after excluding low quality studies showed no difference in heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 94\%$). (Supplementary Table 3H).

3.1 Insulin

Serum insulin data were available from 44 studies, of which 32 were included in the overall meta-analysis. Women with previous GDM had 0.41 SMD higher insulin compared to those without previous GDM (95% CI 0.23 to 0.59; $n =$ 8881, heterogeneity: Chi^2 $P < 0.00001$, $I^2 = 90\%$) [15, 22, 24, 25, 29, 30, 36, 38, 41, 45, 46, 53, 56, 70, 71, 75, 77, 85, 95, 99, 101, 118, 119, 124, 126–128]. (Table 1) (Supplementary Fig. 8). Of the 12 studies not included in the meta-analysis [20, 32, 37, 49, 51, 52, 61, 64, 86, 113, 115, 116], five studies reported that women with previous GDM had significantly higher glucose than those without previous GDM [20, 32, 37, 52, 61, 107]. Sensitivity analysis after excluding low quality studies showed no difference in heterogeneity (Chi^2 $P < 0.00001$, $I^2 = 90\%$). (Supplementary Table 3I).

Subgroup analyses We conducted subgroup analyses based on the time of post-partum follow up (<1 year post-partum, 1–5 years post-partum, 5–10 years post-partum and > 10 years post-partum). The results are shown in Table 3. Systolic blood pressure, diastolic blood pressure, triglycerides and blood glucose were higher in women with previous GDM compared to those without previous GDM as early as <1 year post-partum. Triglycerides and blood glucose remained significantly elevated at 1–5 years, 5–10 years and > 10 years post-partum (Table 2).

4 Discussion

CVD is a global concern and contributes to the majority of deaths due to non-communicable disease (NCDs) (approximately 17.9 million deaths annually) [132]. Early detection, prevention and treatment of risk factors are critical in reducing the incidence of CVD. Pregnancy complications, such as pre-eclampsia and GDM are now identified as risk factors for NCDs including T2DM and CVD [3]. Women may be susceptible to long-life CVD, due to a genetic predisposition or poor lifestyle choices or a combination. Thus, pregnancy may act as a second hit for CVD in these women who already have a predisposition to metabolic syndrome, before phenotypic expression [3]. Furthermore, it is known that exposure to gestational diabetes mellitus in utero increases the risk of cardiovascular risk factors in offspring [133]. Therefore, we sought to determine the CVD risk factors and well as the timeline for manifestation of risk factors among women with previous GDM. Synthesizing the published evidence on conventional CVD risk factors in women with previous GDM and assessing the timeline for manifestation of risk factors, thus, provide strong evidence to plan screening strategies to identify those at risk for CVD. This review also signifies the importance of considering pregnancy complications in CVD risk stratification, thus providing an opportunity for primordial prevention.

4.1 Key findings

Women with previous GDM have an increase in all conventional CVD risk factors. Blood pressure (both systolic and diastolic), serum triglycerides and blood glucose are also higher in women with GDM compared to those without GDM as early as <1 year post-partum.

4.2 Comparison to other studies

Our meta-analysis showed that women with previous GDM have an increase in systolic and diastolic blood pressure. It has been shown that GDM increases the risk of developing hypertension in different populations [111, 134, 135]. Daly et al. (2018) showed that the cumulative incidence of hypertension and ischemic heart disease was higher in women with previous GDM compared with controls, and that this difference persisted over a 25-year study period [109].

Our analysis showed that BMI was 1.57 kg/m^2 higher in women with previous GDM compared to controls based on a sample size of nearly 300,000 women. While we do not know whether the women with previous GDM were obese prior to pregnancy and during pregnancy, it is likely the case for many of these women. A large scale meta-analysis showed that the unadjusted ORs of developing GDM were 2.14 (CI% 1.82 to 2.53), 3.56 (3.05–4.21) and 8.56 (5.07–16.04) for overweight, obese and severely obese women respectively, compared to normal weight pregnant women [136].Obese women have substantially higher liver fat content, and this is consistent with the impairment of fat sequestration by adipocytes in individuals developing GDM [137].

Women with previous GDM were also demonstrated to have higher total cholesterol, LDL, triglycerides and a decrease in HDL demonstrating an “at risk phenotype” compared to women without previous GDM. During the third trimester of pregnancy, women with GDM show an exaggerated elevation in serum lipids, and this may result in transient metabolic disease. [137, 138]. Studies have shown that triglycerides are significantly elevated in women with GDM

Table 3 Subgroup analysis for all cardiovascular outcomes in women with previous GDM compared to those with no previous GDM

Outcome	<1 year postpartum (95% CI)	1–5 years postpartum (95% CI)	5–10 years postpartum (95% CI)	>10 years postpartum (95% CI)
Systolic Blood Pressure (mmHg)	**3.47 (1.26–5.68)** n(total) = 1826 $n = 1237$ $I^2 = 50\%$, $p = 0.02$	**2.26 (0.27, 4.25)** n(total) = 19,701; $n = 2567$ $I^2 = 93\%$, $p < 0.00001$	**3.96 (2.36, 5.56)** n(total) = 1965; n(exposed) = 805 $I^2 = 17\%$, $p = 0.27$	**2.58 (1.05, 4.11)** n(total) = 4941; n(exposed) = 1157 $I^2 = 23\%$, $p = 0.23$
Diastolic Blood Pressure (mmHg)	**2.48 (0.58–4.37)** n(total) = 1749 n(exposed) = 1137 $I^2 = 64\%$, $p = 0.01$	**1.37 (0.20–2.54)** n(total) = 19,676 n(exposed) = 2428 $I^2 = 89\%$, $p < 0.0001$	**7.17 (−1.69–16.03)** n(total) = 2184 n(exposed) = 916 $I^2 = 99\%$, $p < 0.00001$	**1.23 (1.03–1.96)** n(total) = 4948 n(exposed) = 1122 $I^2 = 97\%$, $p < 0.00001$
BMI (kg/m^2)	1.56 (−0.28–3.41) n(total) = 2534 n(exposed) = 1640 $I^2 = 98\%$, $p < 0.00001$	**2.01 (1.24, 2.79)** n(total) = 22,326; n(exposed)=,4329 $I^2 = 96\%$, $p < 0.00001$	**0.73 (0.22, 1.27)** n(total) = 91,844 n(exposed) = 6161 $I^2 = 91\%$, $p < 0.00001$	**1.39 (1.05, 1.73)** n(total) = 13,989; n(exposed) = 8015 $I^2 = 0\%$, $p = 0.64$
Total Cholesterol (SMD)	0.41 (−0.02,0.84) n(total) = 1722 n(exposed) = 1149 $I^2 = 84\%$, $p < 0.00001$	**0.42 (0.21,0.64)** n(total) = 3836; n(exposed) = 1886 $I^2 = 86\%$, $p < 0.00001$	0.04 (−0.13, 0.20) n(total) = 907; n(exposed) = 485 $I^2 = 24\%$, $p = 0.24$	0.04 (−0.09, 0.17) n(total) = 6469; n(exposed) = 1555 $I^2 = 51\%$, $p = 0.02$
LDL (SMD)	0.33 (0.06–0.60) n(total) = 2458 n(exposed) = 1534 $I^2 = 84\%$, $p < 0.0001$	0.25 (−0.05,0.55) n(total) = 1780 n(exposed) = 1062 $I^2 = 87\%$, $p < 0.00001$	0.05 (−0.08–0.19) n(total) = 989 n(exposed) = 520 $I^2 = 0\%$, $p = 0.47$	0.09 (−0.02, 0.19) n(total) = 5546 n(exposed) = 1383 $I^2 = 28\%$, $p = 0.10$
HDL (SMD)	−0.18 (−0.23–0.59) n(total) = 1788 n(exposed) = 1146 $I^2 = 87\%$, $p = <0.00001$	**−0.49 (−0.73, −0.24)** n(total) = 4506 n(exposed) = 2327 $I^2 = 92\%$, $p < 0.00001$	−0.40 (−0.80–0.01) n(total) = 2164 n(exposed) = 810 $I^2 = 93\%$, $p = <0.00001$	**−0.14 (−0.25, −0.03)** n(total) = 6805 n(exposed) = 1647 $I^2 = 49\%$, $p = 0.02$
Triglycerides (SMD)	**0.53 (0.16–0.91)** n(total) = 706 n(exposed) = 459 $I^2 = 76\%$, $p < 0.00001$	**0.65 (0.42,0.89)** n(total) = 4334 n(exposed) = 2234 $I^2 = 90\%$, $p < 0.00001$	**0.56 (0.04–1.08)** n(total) = 1086 n(exposed) = 561 $I^2 = 94\%$, $p < 0.00001$	**0.31 (0.16, 0.46)** n(total) = 3520 n(exposed) = 865 $I^2 = 53\%$, p-0.02
Glucose (SMD)	**1.12 (0.62,1.62)** n(total) = 2187 n(exposed) = 1461 $I^2 = 93\%$, $p < 0.00001$	**0.67 (0.45, 0.90)** n(total) = 6233; n(exposed) = 3457 $I^2 = 92\%$, $p < 0.00001$	**0.75 (0.20, 1.30)** n(total) = 1152 n(exposed) = 606 $I^2 = 94\%$, $p < 0.00001$	**0.58 (0.44, 0.72)** n(total) = 8807 n(exposed) = 6234 $I^2 = 62\%$, $p = 0.002$
Insulin (SMD)	1.10 (−0.37, 2.57) n(total) = 293 n(exposed) = 191 $I^2 = 95\%$, $p < 0.00001$	**0.53 (0.08–0.99)** n(total) = 1762 n(exposed) = 1073 $I^2 = 94\%$, $p < 0.00001$	**0.22 (0.06, 0.37)** n(total) = 1036 n(exposed) = 542 $I^2 = 24\%$, $p = 0.24$	**0.28 (0.07, 0.50)** n(total) = 817 n(exposed) = 308 $I^2 = 45\%$, $p = 0.10$

Units as specified in above table

Abbreviations: 95% CI – 95% Confidence Interval

Bold value highlights significant result

compared to controls across each trimester. It has also been shown that elevated first trimester maternal triglyceride level (adjusted for BMI) is a strong predictor for future GDM [138]. Consistent with these finding, our study showed that triglycerides were elevated as early as <1 year post-partum.

We also observed a significant increase in glucose and insulin in women with previous GDM compared to controls. GDM results in a dysregulation of cytokines (particularly a reduction in adiponectin, and elevation in interleukin-6 and tumour necrosis factor-alpha) and an increase in free fatty acids which promote insulin resistance (IR) and a state of metabolic dysfunction [137]. The study by Daly et al. (2018) also showed that women with GDM are more likely to develop T2DM later in life over a 25-year period. In some populations, 50% of women with GDM progress to T2DM [139], and approximately one third of women with T2DM have had previous GDM [140].

4.3 Strengths and limitations

This systematic review and meta-analysis is the first to observe all conventional CVD risk factors in women who experienced GDM. Our study provides robust evidence that women who experience GDM have an increase in all CVD risk factors compared to controls, based on evidence from 139 studies. Furthermore, subgroup analysis demonstrated that blood pressure, glucose and triglycerides are already elevated as early as <1 year post-partum, thereby highlighting the importance of early screening for CVD risk factors after a pregnancy complicated by GDM.

There are limitations to our findings that need acknowledgement. Firstly, GDM is a multifactorial disease, with many environmental and genetic components contributing to disease risk. Both obesity and GDM share the same causal pathway of elevated FFAs and dysregulation of cytokines leading to insulin resistance [137, 141]. Common risk factors such as advanced maternal age, familial history of T2DM or GDM in a first-degree relative (mother or sister) and Asian ethnicity contribute to a higher risk of GDM [142]. There are certain candidate genes that are associated with type II diabetes mellitus and GDM, mainly influencing insulin secretion [143]. Therefore, it is difficult to elucidate whether CVD in obese/overweight women with previous GDM is attributed to GDM alone or other pre-existing predispositions. Another limitation was the inability to adjust for important confounders such as BMI, age, and sex. Due to non-availability of data on adjusted mean values and the differences in the confounders used in studies, we were not able to use adjusted values in our meta-analyses. However, Table 1 demonstrates various regression analyses used in studies that are adjusted for these important covariates. Secondly, substantial heterogeneity was seen for most overall outcomes, based on I^2 and Chi^2 P values. Observational studies may be subject to publication bias, although visual analysis of funnel plots showed no heterogeneity (Supplementary Fig. 9A-9I). Heterogeneity was further explored through subgroup analysis, however for some subgroups heterogeneity was still evident (Table 3). After sensitivity analysis of overall outcomes after excluding low quality studies, heterogeneity was increased for most outcomes (Supplementary Table 3A, 3B, 3D, 3E, 3F). It is difficult to elucidate the reasons for heterogeneity for aggregate data. It is conventionally explained by significant differences between studies, which in our study can include definition of GDM, time of post-partum screening, methodology and study design. We can only attribute the heterogeneity seen due to genetic and environmental factors that could not be adjusted for, and recommend that more longitudinal, large scale studies are conducted to contribute to this evidence and reduce the overall heterogeneity.

Future direction and clinical relevance Our findings signify the importance of early post-partum CVD risk screening for women who experience GDM. Metabolic syndrome is defined as a cluster of conditions including hypertension, dyslipidaemia, dysglycemia and obesity that significantly increases the risk of type II diabetes and cardiovascular disease. Our study demonstrates that women with GDM in pregnancy show clinical phenotypes that can contribute to metabolic syndrome and type II diabetes as early as within one year post-partum. Approximately 10% of women with GDM are known to develop diabetes soon after delivery. Therefore, it is necessary to implement interventions and treatment strategies as early as practical in these women in order to significantly reduce the risk of CVD later in life. A study in the UK in 2013, showed that risk factors such as SBP and total cholesterol decreased in those who attended such CVD screening, with an overall CVD risk reduction of 6.8% [144].

While the values seen in our meta-analysis for blood pressure are within a normal range, increase in blood pressure poses a continuous risk of CVD. It has been shown that a 10 mmHg increase in systolic blood pressure is associated with a 30% higher risk of ischemic heart disease [10]. We demonstrated that at <1 year post-partum, SBP in women with previous GDM was nearly 4 mmHg higher than in controls. This suggests that women with previous GDM may benefit from monitoring of blood pressure as early as <1 year post-partum to reduce the risk of subsequent hypertension.

Persistence of high BMI in women with previous GDM is likely due to post-partum behaviours, and it may be beneficial to target reduction of obesity prior to gestation. A meta-analysis by Baptise-Roberts et al. showed that for every 1 kg increase in pre-pregnancy weight, the increased odds of developing type II diabetes mellitus increased by 40% [145]. The Diabetes Prevention Program, a multi-centre randomized controlled trial, showed that intensive lifestyle changes, targeting a 7% reduction in enrolment weight, and increased

physical activity in women with previous GDM, reduced the risk of diabetes incidence by 50% at 12 years post-partum [146]. Interestingly, it was shown that women with GDM lost the most amount of weight at 6 months post randomization, and increased weight again afterwards. These weight patterns correlated with a decrease in physical activity (women in the active GDM group were achieving 1.5 h of exercise from baseline in the first year, but by the third year, they were reporting less than 30 min of physical activity a week, correlating with a mean weight loss of only 1.6 kg). In our subgroup analysis, there was no difference in BMI between women with previous GDM and controls at <1 year post-partum, and then for the subsequent subgroups, there were significant differences in BMI [146]. Therefore, it appears that lifestyle guidance during pregnancy promotes weight loss in the first year post-partum, and compliance decreases beyond this point. Strategies to maintain a healthy weight in women with previous GDM beyond the first post-partum year, may significantly reduce their overall CVD risk.

Women with GDM experience insulin resistance (IR) and hypertriglyceridemia, which are both promoted by elevated free fatty acids (FFAs) in response to increased adiposity [137]. IR is a marker of essential hypertension, as it promotes a pro-atherogenic state through marked dyslipidaemia and elevation in inflammatory markers [147]. Atherosclerosis is also promoted by elevations in any non-HDL cholesterols. [148] The higher total cholesterol and triglycerides and the lower HDL cholesterol evident in women with previous GDM suggest an adverse serum lipid profile and as such, women with previous GDM may be at higher risk for CVD. While the values seen in this meta-analysis are minimal, it is important to recognize that serum lipids are strong predictors of hypertension and IHD mortality, with total cholesterol/HDL ratio being the strongest predictor of IHD mortality overall [149, 150]. In our meta-analysis we observed a minimal but significant increase in non HDL cholesterols and a decrease in HDL cholesterol, therefore suggesting that women with GDM are likely to exhibit a poor lipid profile and may benefit from regular monitoring of serum lipids.

Women with previous GDM will also benefit from regular screening of blood glucose and insulin. Towards the end of the second trimester, insulin resistance is elevated to facilitate the delivery of glucose to the fetus down a concentration gradient via placental transfer. Women who are normoglycemic during this period, have adequate β-cell function through compensatory hyperplasia of the beta cells, which causes increased insulin release upon glucose stimulation [141]. However in women with GDM, there is a failure of β-cell compensation to protect against the increased insulin resistance and as such blood glucose is significantly elevated. This insulin resistance may not resolve after delivery and blood glucose remains elevated post-partum [141]. Therefore, monitoring and screening women for type II diabetes mellitus is very important.

5 Conclusion

Women with previous GDM have a higher risk for CVD as evidenced by an increase in risk factor profile compared to women with no history of GDM. Most of these risk factors are seen as early as <1 year post-partum. Therefore, women who experience GDM may benefit from CVD risk screening commencing in the early post-partum period to enable detection of modifiable risk factors.

Funding ZSL is supported by a NHMRC Australia Public Health Early Career Fellowship (GNT1141382). MMP is supported by a Divisional Scholarship by The Faculty of Health Sciences, University of Adelaide.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

References

1 Organization WH. Cardiovascular diseases (CVD). In: Cardiovascular diseases. World Health Organization, Geneva. 2017. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed 20 Jan 2020.
2 Cardiovascular disease in women—a snapshot of national statistics. In: AIHW, editor. Canberra: AIHW; 2019.
3 Andraweera PH, Dekker GA, Arstall M, Bianco-Miotto T, Roberts CT. Complications of Pregnancy and Future Cardiovascular Risk. Encylopedia of Cardiovascular Research and Medicine. Netherlands: Oxford; 2018. p. 643–50.
4 Federation ID. IDF diabetes atlas. Vol 8th edition. International Diabetes Federation: Belgium, Brussels; 2017.
5 Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373(9677):1773–9. https://doi.org/10.1016/s0140-6736(09)60731-5.
6 Coustan DR, Lowe LP, Metzger BE, Dyer AR. International Association of D, Pregnancy Study G. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Am J Obstet Gynecol. 2010;202(6):654.e1–654.e6546. https://doi.org/10.1016/j.ajog.2010.04.006.
7 Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia. 2019;62(6):905–14. https://doi.org/10.1007/s00125-019-4840-2.
8 Zimmet PZ, Alberti KG, Shaw JE. Mainstreaming the metabolic syndrome: a definitive definition. Med J Aust. 2005;183(4):175–6.
9 Chen Z, Iona A, Parish S, Chen Y, Guo Y, Bragg F, et al. Adiposity and risk of ischaemic and haemorrhagic stroke in 0·5 million Chinese men and women: a prospective cohort study. Lancet Glob Health. 2018;6(6):e630–e40. https://doi.org/10.1016/s2214-109x(18)30216-x.
10 Lacey B, Lewington S, Clarke R, Kong XL, Chen Y, Guo Y, et al. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0·5 million adults in China: a prospective cohort study. Lancet Glob Health. 2018;6(6):e641–e9. https://doi.org/10.1016/s2214-109x(18)30217-1.
11 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA

statement. BMJ. 2009;339:b2535. https://doi.org/10.1136/bmj.b2535.
12 Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676–82. https://doi.org/10.2337/dc09-1848.
13 Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. http://www.ohrica/programs/clinical_epidemiology/oxford asp. 2001. Accessed 15 May 2019.
14 Anastasiou E, Lekakis JP, Alevizaki M, Papamichael CM, Megas J, Souvatzoglou A, et al. Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. Diabetes Care. 1998;21(12):2111–5.
15 Akinci B, Celtik A, Yener S, Yesil S. Is fasting glucose level during oral glucose tolerance test an indicator of the insulin need in gestational diabetes? Diabetes Res Clin Pract. 2008;82(2):219–25. https://doi.org/10.1016/j.diabres.2008.07.023.
16 Banerjee M, Anderson SG, Malik RA, Austin CE, Cruickshank JK. Small artery function 2 years postpartum in women with altered glycaemic distributions in their preceding pregnancy. Clin Sci (London, England : 1979). 2012;122(2):53–61. https://doi.org/10.1042/cs20110033.
17 Bentley-Lewis R, Claggett B, Liu J, Maggioni AP, McMurray JJV, Tardif JC, et al. Baseline characteristics and cardiovascular outcomes in women with a history of gestational diabetes in the evaluation of lixisenatide in acute coronary syndrome trial. Diabetes. 2016;65:A356–60. https://doi.org/10.2337/db16-861-1374.
18 Bo S, Valpreda S, Menato G, Bardelli C, Botto C, Gambino R, et al. Should we consider gestational diabetes a vascular risk factor? Atherosclerosis. 2007;194(2):e72–9. https://doi.org/10.1016/j.atherosclerosis.2006.09.017.
19 Caliskan M, Caklili OT, Caliskan Z, Duran C, Ciftci FC, Avci E, et al. Does gestational diabetes history increase epicardial fat and carotid intima media thickness? Echocardiography (Mount Kisco, NY). 2014;31(10):1182–7. https://doi.org/10.1111/echo.12597.
20 Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care. 2006;29(9):2078–83.
21 Cellina G, Lo Cicero G, Brina A, Zanchetti A. Reversible alteration of myocardial function in gestational diabetes. Eur Heart J. 1983;4(1):59–63. https://doi.org/10.1093/oxfordjournals.eurheartj.a061372.
22 Charwat-Resl S, Yarragudi R, Heimbach M, Leitner K, Leutner M, Gamper J, et al. Microvascular function in women with former gestational diabetes: a cohort study. Diab Vasc Dis Res. 2017;14(3):214–20. https://doi.org/10.1177/1479164116683148.
23 Davenport MH, Goswami R, Shoemaker JK, Mottola MF. Influence of hyperglycemia during and after pregnancy on postpartum vascular function. Am J Phys Regul Integr Comp Phys. 2012;302(6):R768–75. https://doi.org/10.1152/ajpregu.00115.2011.
24 Davis CL, Gutt M, Llabre MM, Marks JB, O'Sullivan MJ, Potter JE, et al. History of gestational diabetes, insulin resistance and coronary risk. J Diabetes Complicat. 1999;13(4):216–23.
25 Fakhrzadeh H, Alatab S, Sharifi F, Mirarefein M, Badamchizadeh Z, Ghaderpanahi M, et al. Carotid intima media thickness, brachial flow mediated dilation and previous history of gestational diabetes mellitus. J Obstet Gynaecol Res. 2012;38(8):1057–63. https://doi.org/10.1111/j.1447-0756.2011.01829.x.
26 Ferrada C, Molina M, Cid L, Riedel G, Ferrada C, Arevalo R. Relationship between gestational diabetes and metabolic syndrome. Rev Med Chil. 2007;135(12):1539–45.
27 Freire CM, Nunes Mdo C, Barbosa MM, Longo JR, Nogueira AI, Diniz SS, et al. Gestational diabetes: a condition of early diastolic abnormalities in young women. J Am Soc Echocardiogr : Off Publ Am Soc Echocardiogr. 2006;19(10):1251–6. https://doi.org/10.1016/j.echo.2006.04.021.
28 Gunderson EP, Chiang V, Pletcher MJ, Jacobs DR, Quesenberry CP, Sidney S, et al. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the coronary artery risk development in Young adults study. J Am Heart Assoc. 2014;3(2):e000490. https://doi.org/10.1161/jaha.113.000490.
29 Gunderson EP, Jacobs DR Jr, Chiang V, Lewis CE, Feng J, Quesenberry CP Jr, et al. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-year prospective study in CARDIA (coronary artery risk development in Young adults). Diabetes. 2010;59(2):495–504. https://doi.org/10.2337/db09-1197.
30 Hakkarainen H, Huopio H, Cederberg H, Paakkonen M, Voutilainen R, Heinonen S. The risk of metabolic syndrome in women with previous GDM in a long-term follow-up. Gynecol Endocrinol : Off J Int Soc Gynecol Endocrinol. 2016;32(11):920–5. https://doi.org/10.1080/09513590.2016.1198764.
31 Heida KY, Franx A, van Rijn BB, Eijkemans MJC, Boer JMA, Verschuren MWM, et al. Earlier Age of Onset of Chronic Hypertension and Type 2 Diabetes Mellitus After a Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus. Hypertension (0194911X). 2015;66(6):1116–22. https://doi.org/10.1161/HYPERTENSIONAHA.115.06005.
32 Hunger-Dathe W, Mosebach N, Samann A, Wolf G, Muller UA. Prevalence of impaired glucose tolerance 6 years after gestational diabetes. Exp Clin Endocrinol Diabetes : Off J, German Soc Endocrinol German Diabetes Association. 2006;114(1):11–s. https://doi.org/10.1055/s-2005-873015.
33 Ko GTC, Chan JCN, Tsang LWW, Li CY, Cockram CS. Glucose intolerance and other cardiovascular risk factors in Chinese women with a history of gestational diabetes mellitus. Aust N Z J Obstet Gynaecol. 1999;39(4):478–83.
34 Krishnaveni GV, Hill JC, Veena SR, Geetha S, Jayakumar MN, Karat CL, et al. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in south Indian women. Diabetes Res Clin Pract. 2007;78(3):398–404.
35 Lee H, Jang HC, Park HK, Metzger BE, Cho NH. Prevalence of type 2 diabetes among women with a previous history of gestational diabetes mellitus. Diabetes Res Clin Pract. 2008;81(1):124–9.
36 Lee V, Burwick R, Pilliod R, Shaffer B, Cheng Y, Caughey A. Outcomes of late preterm pregnancies complicated by gestational diabetes mellitus and polyhydramnios. Am J Obstet Gynecol. 2015;212(1):S352. https://doi.org/10.1016/j.ajog.2014.10.929.
37 Madarász E, Tamás G, Tabák AG, Kerényi Z. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. Diabetes Res Clin Pract. 2009;85(2):197–202. https://doi.org/10.1016/j.diabres.2009.05.001.
38 Mai C, Wang B, Wen J, Lin X, Niu J. Lipoprotein-associated phospholipase A2 and AGEs are associated with cardiovascular risk factors in women with history of gestational diabetes mellitus. Gynecol Endocrinol. 2014;30(3):241–4. https://doi.org/10.3109/09513590.2013.871522.
39 Meier JJ, Gallwitz B, Askenas M, Vollmer K, Deacon CF, Holst JJ, et al. Secretion of incretin hormones and the insulinotropic effect of gastric inhibitory polypeptide in women with a history of gestational diabetes. Diabetologia. 2005;48(9):1872–81. https://doi.org/10.1007/s00125-005-1863-7.
40 Minooee S, Ramezani Tehrani F, Rahmati M, Mansournia MA, Azizi F. Diabetes incidence and influencing factors in women with and without gestational diabetes mellitus: a 15year population-

based follow-up cohort study. Diabetes Res Clin Pract. 2017;128: 24–31. https://doi.org/10.1016/j.diabres.2017.04.003.
41 Moleda P, Fronczyk A, Safranow K, Majkowska L. Is uric acid a missing link between previous gestational diabetes mellitus and the development of type 2 diabetes at a later time of life? PLoS One. 2016;11(5):e0154921. https://doi.org/10.1371/journal.pone.0154921.
42 Noctor E, Crowe C, Carmody LA, Saunders JA, Kirwan B, O'Dea A, et al. Abnormal glucose tolerance post-gestational diabetes mellitus as defined by the international association of diabetes and pregnancy study groups criteria. Eur J Endocrinol. 2016;175(4):287–97. https://doi.org/10.1530/EJE-15-1260.
43 Nouhjah S, Shahbazian H, Shahbazian N, Jahanfar S, Jahanshahi A, Cheraghian B, et al. Early postpartum metabolic syndrome in women with or without gestational diabetes: results from life after gestational diabetes Ahvaz cohort study. Diabetes Metab Syndr Clin Res Rev. 2018;12(3):317–23. https://doi.org/10.1016/j.dsx.2017.12.027.
44 Rautio N, Jokelainen J, Korpi-Hyovalti E, Oksa H, Saaristo T, Peltonen M, et al. Lifestyle intervention in prevention of type 2 diabetes in women with a history of gestational diabetes mellitus: one-year results of the FIN-D2D project. J Women's Health (Larchmt). 2014;23(6):506–12. https://doi.org/10.1089/jwh.2013.4520.
45 Roca-Rodriguez MM, Lopez-Tinoco C, Murri M, Fernandez-Deudero A, Garcia-Palacios MV, Garcia-Valero MA, et al. Postpartum development of endothelial dysfunction and oxidative stress markers in women with previous gestational diabetes mellitus. J Endocrinol Investig. 2014;37(6):503–9. https://doi.org/10.1007/s40618-013-0045-6.
46 Ryan AS, McLenithan JC, Zietowski GM. Accelerated metabolic susceptibility to type 2 diabetes in older women with a history of gestational diabetes. Endocr Connect. 2013;2(2):79–86. https://doi.org/10.1530/EC-12-0072.
47 Simmons D, Kumar S, Crook N, Rush E. Diabetes among Māori women with self-reported past gestational diabetes mellitus in a New Zealand Māori community. Aust N Z J Obstet Gynaecol. 2017;57(6):599–603. https://doi.org/10.1111/ajo.12639.
48 Sriharan M, Reichelt AJ, Opperman MLR, Duncan BB, Mengue SS, Crook MA, et al. Total sialic acid and associated elements of the metabolic syndrome in women with and without previous gestational diabetes. Diabetes Care. 2002;25(8):1331–5. https://doi.org/10.2337/diacare.25.8.1331.
49 Sung HC, Soo HK, Youn BS, Lim S, Young JP, Lee H, et al. High plasma retinol binding protein-4 and low plasma adiponectin concentrations are associated with severity of glucose intolerance in women with previous gestational diabetes mellitus. J Clin Endocrinol Metab. 2008;93(8):3142–8. https://doi.org/10.1210/jc.2007-1755.
50 Ramezani Tehrani F, Hashemi S, Hasheminia M, Azizi F. Follow-up of women with gestational diabetes in the Tehran lipid and glucose study (TLGS): a population-based cohort study. J Obstet Gynaecol Res. 2012;38(4):698–704. https://doi.org/10.1111/j.1447-0756.2011.01767.x.
51 Thomann R, Rossinelli N, Keller U, Tirri BF, De Geyter C, Ruiz J, et al. Differences in low-grade chronic inflammation and insulin resistance in women with previous gestational diabetes mellitus and women with polycystic ovary syndrome. Gynecol Endocrinol : Off J Int Soc Gynecol Endocrinol. 2008;24(4):199–206. https://doi.org/10.1080/09513590801893398.
52 Verma A, Boney CM, Tucker R, Vohr BR. Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. J Clin Endocrinol Metab. 2002;87(7):3227–35. https://doi.org/10.1210/jc.87.7.3227.
53 Vilmi-Kerala T, Palomaki O, Kankkunen P, Juurinen L, Uotila J, Palomaki A. Oxidized LDL, insulin resistance and central blood pressure after gestational diabetes mellitus. Acta Obstet Gynecol Scand. 2016;95(12):1425–32. https://doi.org/10.1111/aogs.13029.
54 Winhofer Y, Krssak M, Wolf P, Tura A, Anderwald CH, Kosi L, et al. Hepatic rather than cardiac steatosis relates to glucose intolerance in women with prior gestational diabetes. PLoS One. 2014;9(3):e91607. https://doi.org/10.1371/journal.pone.0091607.
55 Zajdenverg L, Rodacki M, Faria JP, Pires MLE, Oliveira JEP, Halfoun VLC. Precocious markers of cardiovascular risk and vascular damage in apparently healthy women with previous gestational diabetes. Diabetol Metab Syndr. 2014;6(1). https://doi.org/10.1186/1758-5996-6-63.
56 Lim S, Choi SH, Park YJ, Park KS, Lee HK, Jang HC, et al. Visceral fatness and insulin sensitivity in women with a previous history of gestational diabetes mellitus. Diabetes Care. 2007;30(2):348–53.
57 Albareda M, de Leiva A, Corcoy R. Reproducibility of diabetes mellitus diagnosis (WHO 1999 criteria) in women. Acta Diabetol. 2004;41(1):14–7. https://doi.org/10.1007/s00592-004-0138-y.
58 Bentley-Lewis R, Huynh J, Xiong G, Lee H, Wenger J, Clish C, et al. Metabolomic profiling in the prediction of gestational diabetes mellitus. Diabetologia. 2015;58(6):1329–32. https://doi.org/10.1007/s00125-015-3553-4.
59 Hannemann MM, Liddell WG, Shore AC, Clark PM, Tooke JE. Vascular function in women with previous gestational diabetes mellitus. J Vasc Res. 2002;39(4):311–9. https://doi.org/10.1159/000065543.
60 Hu J, Björklund A, Nyman M, Gennser G. Mechanical properties of large arteries in mother and fetus during normal and diabetic pregnancy. J Matern-Fetal Investig. 1998;8(4):185–93.
61 Lauenborg J, Mathiesen E, Hansen T, Glümer C, Jørgensen T, Borch-Johnsen K, et al. The prevalence of the metabolic syndrome in a Danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. J Clin Endocrinol Metab. 2005;90(7):4004–10. https://doi.org/10.1210/jc.2004-1713.
62 Lekva T, Bollerslev J, Godang K, Roland MCP, Friis CM, Voldner N, et al. β-Cell dysfunction in women with previous gestational diabetes is associated with visceral adipose tissue distribution. Eur J Endocrinol. 2015;173(1):63–70. https://doi.org/10.1530/EJE-15-0153.
63 Retnakaran R, Qi Y, Connelly PW, Sermer M, Hanley AJ, Zinman B. The graded relationship between glucose tolerance status in pregnancy and postpartum levels of low-density-lipoprotein cholesterol and apolipoprotein B in young women: implications for future cardiovascular risk. J Clin Endocrinol Metab. 2010;95(9):4345–53. https://doi.org/10.1210/jc.2010-0361.
64 Ruksasakul R, Tharavanij T, Sritipsukho P. Metabolic syndrome in Thai women previously diagnosed with gestational diabetes. J Med Assoc Thail. 2016;99:S195–202.
65 Todoric J, Handisurya A, Perkmann T, Knapp B, Wagner O, Tura A, et al. Circulating progranulin levels in women with gestational diabetes mellitus and healthy controls during and after pregnancy. Eur J Endocrinol. 2012;167(4):561–7. https://doi.org/10.1530/EJE-12-0060.
66 Wang Y, Chen L, Horswell R, Xiao K, Besse J, Johnson J, et al. Racial differences in the association between gestational diabetes mellitus and risk of type 2 diabetes. J Women's Health (Larchmt). 2012;21(6):628–33. https://doi.org/10.1089/jwh.2011.3318.
67 Ueland T, Michelsen AE, Aukrust P, Henriksen T, Bollerslev J, Lekva T. Adipokines and macrophage markers during pregnancy-possible role for sCD163 in prediction and progression of gestational diabetes mellitus. Diabetes Metab Res Rev. 2019;35(3):e3114. https://doi.org/10.1002/dmrr.3114.
68 Ajala O, Jensen LA, Ryan E, Chik C. Women with a history of gestational diabetes on long-term follow up have normal vascular function despite more dysglycemia, dyslipidemia and adiposity.

Diabetes Res Clin Pract. 2015;110(3):309–14. https://doi.org/10.1016/j.diabres.2015.10.004.
69 Akinci B, Celtik A, Genc S, Yener S, Demir T, Secil M, et al. Evaluation of postpartum carbohydrate intolerance and cardiovascular risk factors in women with gestational diabetes. Gynecol Endocrinol. 2011;27(5):361–7. https://doi.org/10.3109/09513590.2010.492885.
70 Akinci B, Celtik A, Tunali S, Genc S, Yuksel F, Secil M, et al. Circulating apelin levels are associated with cardiometabolic risk factors in women with previous gestational diabetes. Arch Gynecol Obstet. 2014;289(4):787–93. https://doi.org/10.1007/s00404-013-3070-y.
71 Bowes SB, Hennessy TR, Umpleby AM, Benn JJ, Jackson NC, Boroujerdi MA, et al. Measurement of glucose metabolism and insulin secretion during normal pregnancy and pregnancy complicated by gestational diabetes. Diabetologia. 1996;39(8):976–83.
72 Bozkurt L, Gobl CS, Tura A, Chmelik M, Prikoszovich T, Kosi L, et al. Fatty liver index predicts further metabolic deteriorations in women with previous gestational diabetes. PLoS One. 2012;7(2):e32710. https://doi.org/10.1371/journal.pone.0032710.
73 Cocilovo G, Tomasi F, Guerra S, Zampini A, Cocurullo A. Risk factors associated with persistence of glucose intolerance one year after gestational diabetes. Diabetes Metab. 1990;16(3):187–91.
74 Couch SC, Philipson EH, Bendel RB, Wijendran V, Lammi-Keefe CJ. Maternal and cord plasma lipid and lipoprotein concentrations in women with and without gestational diabetes mellitus: predictors of birth weight? J Reprod Med Obstet Gynecologist. 1998;43(9):816–22.
75 Demir T, Akinci B, Yener S, Argun L, Özcan M, Eraslan S. Endothelium-Dependent Hemostatic Factors in Women with Previous Gestational. Turkish J Endocrinol Metab. 2016;20(2). https://doi.org/10.4274/tjem.3477.
76 Dornhorst A, Bailey PC, Anyaoku V, Elkeles RS, Johnston DG, Beard RW. Abnormalities of glucose tolerance following gestational diabetes. Q J Med. 1990;77(284):1219–28.
77 Eroglu D, Zeyneloglu HB. Metabolic disorders in patients with recent gestational diabetes mellitus. J Obstet Gynaecol Res. 2006;32(4):408–15. https://doi.org/10.1111/j.1447-0756.2006.00418.x.
78 Gadgil MD, Oza-Frank R, Kandula NR, Kanaya AM. Type 2 diabetes after gestational diabetes mellitus in South Asian women in the United States. Diabetes/Metabolism Research and Reviews. 2017;33(5). https://doi.org/10.1002/dmrr.2891.
79 Kousta E, Lawrence NJ, Godsland IF, Penny A, Anyaoku V, Millauer BA, et al. Insulin resistance and β-cell dysfunction in normoglycaemic European women with a history of gestational diabetes. Clin Endocrinol. 2003;59(3):289–97. https://doi.org/10.1046/j.1365-2265.2003.01820.x.
80 Lee AJ, Hiscock RJ, Wein P, Walker SP, Permezel M. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. Diabetes Care. 2007;30(4):878–83. https://doi.org/10.2337/dc06-1816.
81 Linne Y, Barkeling B, Rossner S. Natural course of gestational diabetes mellitus: long term follow up of women in the SPAWN study. BJOG : Int J Obstet Gynaecol. 2002;109(11):1227–31.
82 Magenheim R, El Hadj OT, Schäfer-Graf UM, Pálffy A, Papp M, Kovács M, et al. Arterial stiffness of young women with previous gestational diabetes. Arch Gynecol Obstet. 2010;282:S146–S7. https://doi.org/10.1007/s00404-010-1634-7.
83 McLachlan KA, Alford FP. The impact of acute elevation of non-esterified fatty acids on insulin sensitivity and secretion in women with former gestational diabetes. Clin Endocrinol. 2005;62(1):79–84. https://doi.org/10.1111/j.1365-2265.2004.02177.x.
84 Morbiducci U, Di Benedetto G, Kautzky-Willer A, Deriu MA, Pacini G, Tura A. Identification of a model of non-esterified fatty acids dynamics through genetic algorithms: the case of women with a history of gestational diabetes. Comput Biol Med. 2011;41(3):146–53. https://doi.org/10.1016/j.compbiomed.2011.01.004.
85 Osei K, Gaillard TR, Schuster DP. History of gestational diabetes leads to distinct metabolic alterations in nondiabetic African-American women with a parental history of type 2 diabetes. Diabetes Care. 1998;21(8):1250–7. https://doi.org/10.2337/diacare.21.8.1250.
86 Pimenta WP, Calderon IMP, Cruz NS, Santos ML, Aragon FF, Padovani CR. Subclinical abnormalities of glucose metabolism in Brazilian women with a history of gestational diabetes mellitus. Acta Obstet Gynecol Scand. 2004;83(12):1152–8. https://doi.org/10.1111/j.0001-6349.2004.00444.x.
87 Prikoszovich T, Winzer C, Schmid AI, Szendroedi J, Chmelik M, Pacini G, et al. Body and liver fat mass rather than muscle mitochondrial function determine glucose metabolism in women with a history of gestational diabetes mellitus. Diabetes Care. 2011;34(2):430–6.
88 Rawal S, Tsai MY, Hinkle SN, Zhu Y, Bao W, Lin Y, et al. A longitudinal study of thyroid markers across pregnancy and the risk of gestational diabetes. J Clin Endocrinol Metab. 2018;103(7):2447–56. https://doi.org/10.1210/jc.2017-02442.
89 Rivas A, Landon M, Gaillard T, Schuster D, Osei K. Awareness of risk factors for type 2 diabetes in women with current and former gestational diabetes mellitus (GDM): implications for future primary diabetes prevention. Diabetes Metab Syndr Clin Res Rev. 2010;4(2):89–94. https://doi.org/10.1016/j.dsx.2010.05.007.
90 Ryan EA, Imes S, Liu D, McManus R, Finegood DT, Polonsky KS, et al. Defects in insulin secretion and action in women with a history of gestational diabetes. Diabetes. 1995;44(5):506–12.
91 Seghieri G, Tesi F, Bianchi L, Loizzo A, Saccomanni G, Ghirlanda G, et al. Taurine in women with a history of gestational diabetes. Diabetes Res Clin Pract. 2007;76(2):187–92.
92 Shen Y, Wang P, Wang L, Zhang S, Liu H, Li W, et al. Gestational diabetes with diabetes and prediabetes risks: a large observational study. Eur J Endocrinol. 2018;179(1):51–8. https://doi.org/10.1530/eje-18-0130.
93 Simmons D, Kumar S, Crook N, Rush E. Diabetes among Maori women with self-reported past gestational diabetes mellitus in a New Zealand Maori community. Aust N Z J Obstet Gynaecol. 2017;57(6):599–603. https://doi.org/10.1111/ajo.12639.
94 Tobias DK, Stuart JJ, Shanshan L, Chavarro J, Rimm EB, Rich-Edwards J, et al. Association of History of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. JAMA Intern Med. 2017;177(12):1735–42. https://doi.org/10.1001/jamainternmed.2017.2790.
95 Vigneault J, Lemieux S, Garneau V, Weisnagel SJ, Tchernof A, Robitaille J. Association between metabolic deteriorations and prior gestational diabetes according to weight status. Obesity (Silver Spring, Md). 2015, 23(2):345–50. https://doi.org/10.1002/oby.20940.
96 Vitoratos N, Salamalekis E, Kassanos D, Loghis C, Panayotopoulos N, Kouskouni E, et al. Maternal plasma leptin levels and their relationship to insulin and glucose in gestational-onset diabetes. Gynecol Obstet Investig. 2001;51(1):17–21. https://doi.org/10.1159/000052884.
97 Wang YM, Zhao LH, Su JB, Qiao HF, Wang XH, Xu F et al. Glycemic variability in normal glucose tolerance women with the previous gestational diabetes mellitus. Diabetology and Metabolic Syndrome. 2015;7(1). https://doi.org/10.1186/s13098-015-0077-5.
98 Wender-Ozegowska E, Sporna M, Zawiejska A, Sporna A, Brazert J. Components of metabolic syndrome in women after gestational diabetes. Pol Arch Med Wewn. 2007;117(10):457–62.

99 Winzer C, Wagner O, Festa A, Schneider B, Roden M, Bancher-Todesca D, et al. Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus. Diabetes Care. 2004;27(7):1721–7.

100 Kjos SL, Buchanan TA, Montoro M, Coulson A, Mestman JH. Serum lipids within 36 mo of delivery in women with recent gestational diabetes. Diabetes. 1991;40(SUPPL. 2):142–6.

101 Ferraz TB, Motta RS, Ferraz CL, Capibaribe DM, Forti AC, Chacra AR. C-reactive protein and features of metabolic syndrome in Brazilian women with previous gestational diabetes. Diabetes Res Clin Pract. 2007;78(1):23–9.

102 Seck A, Hichami A, Doucoure S, Diallo Agne F, Bassene H, Ba A, et al. Th1/Th2 dichotomy in obese women with gestational diabetes and their Macrosomic babies. J Diabetes Res. 2018;2018:8474617–7. https://doi.org/10.1155/2018/8474617.

103 Behboudi-Gandevani S, Ramezani Tehrani F, Rahmati M, Amiri M, Azizi F. Trend of various adiposity indices in women with and without history of gestational diabetes: a population-based cohort study. BMC Endocr Disord. 2019;19(1):24. https://doi.org/10.1186/s12902-019-0348-5.

104 Han KT, Cho GJ, Kim EH. Evaluation of the Association between Gestational Diabetes Mellitus at First Pregnancy and Cancer within 10 Years Postpartum Using National Health Insurance Data in South Korea. Int J Environ Res Public Health. 2018;15(12). https://doi.org/10.3390/ijerph15122646.

105 Bentley-Lewis R, Powe C, Ankers E, Wenger J, Ecker J, Thadhani R. Effect of race/ethnicity on hypertension risk subsequent to gestational diabetes mellitus. Am J Cardiol. 2014;113(8):1364–70. https://doi.org/10.1016/j.amjcard.2014.01.411.

106 Retnakaran R, Qi Y, Sermer M, Connelly PW, Hanley AJ, Zinman B. Beta-cell function declines within the first year postpartum in women with recent glucose intolerance in pregnancy. Diabetes Care. 2010;33(8):1798–804. https://doi.org/10.2337/dc10-0351.

107 Benjamin E, Winters D, Mayfield J, Gohdes D. Diabetes in pregnancy in Zuni Indian women: prevalence and subsequent development of clinical diabetes after gestational diabetes. Diabetes Care. 1993;16(9):1231–5.

108 Cheung NW, Lih A, Lau SM, Park K, Padmanabhan S, McElduff A. Gestational diabetes: a red flag for future type 2 diabetes in pregnancy? A retrospective analysis. Diabet Med. 2015;32(9):1167–71. https://doi.org/10.1111/dme.12723.

109 Daly B, Toulis KA, Thomas N, Gokhale K, Martin J, Webber J et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study. PLoS Med. 2018;15(1). https://doi.org/10.1371/journal.pmed.1002488.

110 Persson M, Winkvist A, Mogren I. Lifestyle and health status in a sample of Swedish women four years after pregnancy: A comparison of women with a history of normal pregnancy and women with a history of gestational diabetes mellitus. BMC Pregnancy and Childbirth. 2015;15(1). https://doi.org/10.1186/s12884-015-0487-2.

111 Pirkola J, Pouta A, Bloigu A, Miettola S, Hartikainen AL, Jarvelin MR, et al. Prepregnancy overweight and gestational diabetes as determinants of subsequent diabetes and hypertension after 20-year follow-up. J Clin Endocrinol Metab. 2010;95(2):772–8. https://doi.org/10.1210/jc.2009-1075.

112 Tura A, Benedetto GD, Morbiducci U, Winhofer Y, Montevecchi F, Pacini G, et al. Non-esterified fatty acids dynamics during an oral glucose tolerance test in women with a history of gestational diabetes. Diabetologia. 2009;52(S1):S32–S3. https://doi.org/10.1007/s00125-009-1445-1.

113 Stuebe AM, Mantzoros C, Kleinman K, Gillman MW, Rifas-Shiman S, Seely EW, et al. Gestational glucose tolerance and maternal metabolic profile at 3 years postpartum. Obstet Gynecol. 2011;118(5):1065–73. https://doi.org/10.1097/AOG.0b013e3182325f5a.

114 Shostrom DCV, Sun Y, Oleson JJ, Snetselaar LG, Bao W. History of gestational diabetes mellitus in relation to cardiovascular disease and cardiovascular risk factors in US women. Frontiers in Endocrinology. 2017;8(JUN). https://doi.org/10.3389/fendo.2017.00144.

115 Sokup A, Góralczyk B, Góralczyk K, Rosc D. Triglycerides as an early pathophysiological marker of endothelial dysfunction in non-diabetic women with a previous history of gestational diabetes. Acta Obstet Gynecol Scand. 2012;91(2):182–8. https://doi.org/10.1111/j.1600-0412.2011.01289.x.

116 Sokup A, Ruszkowska B, Góralczyk B, Góralczyk K, Szymański M, Grabiec M, et al. Elevation of sE-selectin levels 2-24 months following gestational diabetes is associated with early cardiometabolic risk in nondiabetic women. Int J Endocrinol. 2012;2012:1–6. https://doi.org/10.1155/2012/278050.

117 Wang H, She G, Zhou W, Liu K, Miao J, Yu B. Expression profile of circular RNAs in placentas of women with gestational diabetes mellitus. Endocr J. 2019;66(5):431–41. https://doi.org/10.1507/endocrj.EJ18-0291.

118 Ozuguz U, Isik S, Berker D, Arduc A, Tutuncu Y, Akbaba G, et al. Gestational diabetes and subclinical inflammation: evaluation of first year postpartum outcomes. Diabetes Res Clin Pract. 2011;94(3):426–33. https://doi.org/10.1016/j.diabres.2011.08.024.

119 Pokropek C, Sobolewski P, Getachew R, Paul A, Boura J, Ogunyemi D. Dietary intake patterns and insulin resistance in women with a history of gestational diabetes in the National Health and nutrition examination survey (NHANES) 2000-2010. Am J Obstet Gynecol. 2015;212(1):S308. https://doi.org/10.1016/j.ajog.2014.10.827.

120 Sartore G, Dalfrà M, Barison A, Marin R, Chilelli NC, Burlina S, et al. Plasma phospholipid fatty acid composition and desaturases indices in women with gestational diabetes mellitus before and after delivery. Diabetologia. 2011;54:S481–S2. https://doi.org/10.1007/s00125-011-2276-4.

121 Tehrani FR, Hashemi S, Hasheminia M, Azizi F. Follow-up of women with gestational diabetes in the Tehran lipid and glucose study (TLGS): a population-based cohort study. J Obstet Gynaecol Res. 2012;38(4):698–704. https://doi.org/10.1111/j.1447-0756.2011.01767.x.

122 Tam WH, Ma RC, Yang X, Ko GT, Lao TT, Sahota DS, et al. Prediction of women's long-term cardiometabolic risks using glycemic indices during pregnancy. J Obstet Gynaecol Res. 2013;39(2):484–91. https://doi.org/10.1111/j.1447-0756.2012.01976.x.

123 Retnakaran R, Qi Y, Sermer M, Connelly PW, Hanley AJ, Zinman B. The postpartum cardiovascular risk factor profile of women with isolated hyperglycemia at 1-hour on the oral glucose tolerance test in pregnancy. Nutrition, Metab, Cardiovasc Dis : NMCD. 2011;21(9):706–12. https://doi.org/10.1016/j.numecd.2011.02.010.

124 King KB, Gerich JE, Guzick DS, King KU, McDermott MP. Is a history of gestational diabetes related to risk factors for coronary heart disease? Res Nurs Health. 2009;32(3):298–306. https://doi.org/10.1002/nur.20325.

125 Tam WH, Ma RC, Yang X, Ko GT, Lao TT, Chan MH, et al. Cardiometabolic risk in Chinese women with prior gestational diabetes: a 15-year follow-up study. Gynecol Obstet Investig. 2012;73(2):168–76. https://doi.org/10.1159/000329339.

126 Pacini G, Tura A, Winhofer Y, Kautzky-Willer A. Incretin effect in women with former gestational diabetes within a short period after delivery. Int J Endocrinol. 2012;2012:1–4. https://doi.org/10.1155/2012/247392.

127 Tura A, Mari A, Winzer C, Kautzky-Willer A, Pacini G. Impaired beta-cell function in lean normotolerant former gestational diabetic women. Eur J Clin Investig. 2006;36(1):22–8. https://doi.org/10.1111/j.1365-2362.2006.01587.x.

128 Xiang AH, Takayanagi M, Black MH, Trigo E, Lawrence JM, Watanabe RM, et al. Longitudinal changes in insulin sensitivity and beta cell function between women with and without a history of gestational diabetes mellitus. Diabetologia. 2013;56(12):2753–60. https://doi.org/10.1007/s00125-013-3048-0.

129 Xiong X, Elkind-Hirsch KE, Xie Y, Delarosa R, Maney P, Pridjian G, et al. Periodontal disease as a potential risk factor for the development of diabetes in women with a prior history of gestational diabetes mellitus. J Public Health Dent. 2013;73(1):41–9. https://doi.org/10.1111/jphd.12004.

130 Akinci B, Celtik A, Yuksel F, Genc S, Yener S, Secil M, et al. Increased osteoprotegerin levels in women with previous gestational diabetes developing metabolic syndrome. Diabetes Res Clin Pract. 2011;91(1):26–31. https://doi.org/10.1016/j.diabres.2010.09.028.

131 Tutino GE, Tam WH, Yang X, Chan JC, Lao TT, Ma RC. Diabetes and pregnancy: perspectives from Asia. Diabet Med. 2014;31(3):302–18. https://doi.org/10.1111/dme.12396.

132 Organization WH. Noncommunicable diseases. World Health Organization Geneva 2018. Accessed 1 June 2018.

133 Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. J Dev Orig Health Dis. 2020:1–18. https://doi.org/10.1017/s2040174419000850.

134 Kaul P, Savu A, Nerenberg KA, Donovan LE, Chik CL, Ryan EA, et al. Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. Diabet Med. 2015;32(2):164–73. https://doi.org/10.1111/dme.12635.

135 Pace R, Brazeau A-S, Meltzer S, Rahme E, Dasgupta K. Conjoint associations of gestational diabetes and hypertension with diabetes, hypertension, and cardiovascular disease in parents: a retrospective cohort study. Am J Epidemiol. 2017;186(10):1115–24. https://doi.org/10.1093/aje/kwx263.

136 Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007;30(8):2070–6. https://doi.org/10.2337/dc06-2559a.

137 Abell SK, De Courten B, Boyle JA, Teede HJ. Inflammatory and other biomarkers: role in pathophysiology and prediction of gestational diabetes mellitus. Int J Mol Sci. 2015;16(6):13442–73. https://doi.org/10.3390/ijms160613442.

138 Ryckman KK, Spracklen CN, Smith CJ, Robinson JG, Saftlas AF. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. BJOG : Int J Obstet Gynaecol. 2015;122(5):643–51. https://doi.org/10.1111/1471-0528.13261.

139 Kjos SL, Peters RK, Xiang A, Henry OA, Montoro M, Buchanan TA. Predicting future diabetes in Latino women with gestational diabetes. Utility of early postpartum glucose tolerance testing. Diabetes. 1995;44(5):586–91. https://doi.org/10.2337/diab.44.5.586.

140 Cheung NW, Byth K. Population health significance of gestational diabetes. Diabetes Care. 2003;26(7):2005–9. https://doi.org/10.2337/diacare.26.7.2005.

141 Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci. 2018;19(11). https://doi.org/10.3390/ijms19113342.

142 Pons RS, Rockett FC, de Almeida Rubin B, Oppermann MLR, Bosa VL. Risk factors for gestational diabetes mellitus in a sample of pregnant women diagnosed with the disease. Diabetol Metab Syndr. 2015;7(Suppl 1):A80-A. https://doi.org/10.1186/1758-5996-7-S1-A80.

143 Wu L, Cui L, Tam WH, Ma RC, Wang CC. Genetic variants associated with gestational diabetes mellitus: a meta-analysis and subgroup analysis. Sci Rep. 2016;6:30539. https://doi.org/10.1038/srep30539.

144 Alageel S, Wright AJ, Gulliford MC. Changes in cardiovascular disease risk and behavioural risk factors before the introduction of a health check programme in England. Prev Med. 2016;91:158–63. https://doi.org/10.1016/j.ypmed.2016.08.025.

145 Baptiste-Roberts K, Barone BB, Gary TL, Golden SH, Wilson LM, Bass EB, et al. Risk factors for type 2 diabetes among women with gestational diabetes: a systematic review. Am J Med. 2009;122(3):207–14 e4. https://doi.org/10.1016/j.amjmed.2008.09.034.

146 Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008;93(12):4774–9. https://doi.org/10.1210/jc.2008-0772.

147 Semenkovich CF. Insulin resistance and atherosclerosis. J Clin Invest. 2006;116(7):1813–22. https://doi.org/10.1172/JCI29024.

148 Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. Int J Prev Med. 2014;5(8):927–46.

149 Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. Jama. 2009;302(18):1993–2000. https://doi.org/10.1001/jama.2009.1619.

150 Mørkedal B, Romundstad PR, Vatten LJ. Informativeness of indices of blood pressure, obesity and serum lipids in relation to ischaemic heart disease mortality: the HUNT-II study. Eur J Epidemiol. 2011;26(6):457–61. https://doi.org/10.1007/s10654-011-9572-7.

151 Berglund SK, Garcia-Valdes L, Torres-Espinola FJ, et al. Maternal, fetal and perinatal alterations associated with obesity, overweight and gestational diabetes: an observational cohort study (PREOBE). BMC Public Health. 2016;16:207.

152 Bozkurt L, Göbl CS, Tura A, et al. Assessment of fatty liver index (FLI) in relation to insulin sensitivity in women with prior gestational diabetes. In: Diabetes; 2010.

[153 Chan SP, Gelding SV, McManus RJ, et al. Abnormalities of intermediary metabolism following a gestational diabetic pregnancy. Clin Endocrinol. 1992;36:417–20.

154. Freire CM, Nunes Mdo C, Barbosa MM, et al. Gestational diabetes: a condition of early diastolic abnormalities in young women. J Am Soc Echocardiog. 2006;19:1251–6.

[155 Homko C, Sivan E, Chen X, Reece EA, Boden G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. J Clin Endocrinol Metab. 2001;86:568–73.

[156 Maghbooli Z, Hossein-Nezhad A, Mirzaei K, et al. Association between retinol-binding protein 4 concentrations and gestational diabetes mellitus and risk of developing metabolic syndrome after pregnancy. Reprod Sci. 2010;17:196–201.

[157 Nouhjah S, Shahbazian H, Amoori N, et al. Postpartum screening practices, progression to abnormal glucose tolerance and its related risk factors in Asian women with a known history of gestational diabetes: A systematic review and meta-analysis. Diabetes Metab Syndr Clin Res Rev. 2017;11:S703–12.

[158 Retnakaran R, Qi Y, Connelly PW, Sermer M, Hanley AJ, Zinman B (2009) Low adiponectin concentration in pregnancy predicts postpartum beta-cell dysfunction: Pathophysiologic implications for the link between gestational diabetes (GDM) and future type 2 diabetes (T2DM). Diabetes 58

[159 Roca-Rodriguez MM, Lopez-Tinoco C, Fernandez-Deudero A, et al. Adipokines and metabolic syndrome risk factors in women

with previous gestational diabetes mellitus. Diabetes Metab Res Rev. 2012;28:542–8.
160. Weisnagel SJ, Dubé MC, Morisset AS, Tchernof A. Prolactin, breastfeeding and the metabolic profile of women with or without previous gestational diabetes. Can J Diabetes. 2013;37:S80.
161. Hakkarainen H, Huopio H, Cederberg H, Paakkonen M, Voutilainen R, Heinonen S. Post-challenge glycemia during pregnancy as a marker of future risk of type 2 diabetes: a prospective cohort study. Gynecological endocrinology: the official journal of the International Society of. Gynecol Endocrinol. 2015;31:573–7.
162. Lekva T, Michelsen AE, Bollerslev J, et al. Low circulating pentraxin 3 levels in pregnancy is associated with gestational diabetes and increased apoB/apoA ratio: A 5-year follow-up study. Cardiovasc Diabetol. 2016;15.
163. Lekva T, Michelsen AE, Aukrust P, Henriksen T, Bollerslev J, Ueland T. Leptin and adiponectin as predictors of cardiovascular risk after gestational diabetes mellitus. Cardiovasc Diabetol. 2017;16:5.
164. Noctor E, Crowe C, Carmody LA, et al. ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. Acta Diabetol. 2015;52:153–60.
165. Winhofer Y, Tura A, Prikoszovich T, et al. The impact of recurrent gestational diabetes on maternal metabolic and cardiovascular risk factors. Eur J Clin Investig. 2013;43:190–7.
166. Winhofer Y, Tura A, Thomas A, et al. Metabolic characterisation of women with prior gestational diabetes maintaining normal glucose tolerance up to five years postpartum. Diabetologia. 2013;56:S510.
167. Xiang AH, Takayanagi M, Black MH, Trigo E, Watanabe RM, Buchanan TA. Women with recent gestational diabetes have faster decline in insulin sensitivity and beta-cell compensation than their normal parous siblings and cousins. Diabetes. 2012;61:A343.
168. Ajala O, Stenhouse E, Shaw N, Carr S, Millward A. Cardiovascular risk following diagnosis of gestational diabetes: Diabetes in Pregnancy Mother Baby Study 3. Diabet Med. 2011;28:173.
169. Bian X, Gao P, Xiong X, Xu H, Qian M, Liu S. Risk factors for development of diabetes mellitus in women with a history of gestational diabetes mellitus. Chin Med J. 2000;113:759–62.
170. Da PM, Fronczyk A, Safranow K, Majkowska L. Uric acid and glucose metabolism disorders in women with previous gestational diabetes mellitus. Diabetes. 2016;65:A590.
171. Tam WH, Yang XL, Chan JC, et al. Progression to impaired glucose regulation, diabetes and metabolic syndrome in Chinese women with a past history of gestational diabetes. Diabetes/Metabolism Research & Reviews. 2007;23:485–9.
172. Tutino EG, Zhang YY, Luk A, et al. Metabolic profile of women with diabetes type 2 with and without a history of gestational diabetes mellitus - Hong Kong joint Asia diabetes evaluation (JADE). Diabetes Res Clin Pract. 2014;106:S77.
173. Gobl CS, Bozkurt L, Prikoszovich T, Winzer C, Pacini G, Kautzky-Willer A. Early possible risk factors for overt diabetes after gestational diabetes mellitus. Obstet Gynecol. 2011;118:71–8.
174. Göbl CS, Bozkurt L, Prikoszovich T, Tura A, Pacini G, Kautzky-Willer A. Biomarkers of endothelial dysfunction in relation to impaired carbohydrate metabolism early after pregnancy with gestational diabetes mellitus. Diabetologia. 2014;57:S456.
175. Gobl CS, Bozkurt L, Yarragudi R, Tura A, Pacini G, Kautzky-Willer A. Is early postpartum HbA1c an appropriate risk predictor after pregnancy with gestational diabetes mellitus? Acta Diabetol. 2014;51:715–22.
176. Minooee S, Ramezani Tehrani F, Rahmati M, Mansournia MA, Azizi F. Dyslipidemia incidence and the trend of lipid parameters changes in women with history of gestational diabetes: a 15-year follow-up study. Endocrine. 2017;58:228–35.

Appendix 2: Publication for Cardiovascular risk factors in children exposed to gestational diabetes mellitus *in utero:* a systematic review and meta-analysis

Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis

Maleesa M. Pathirana, Zohra S. Lassi, Claire T. Roberts and Prabha H. Andraweera

Adelaide Medical School, The Robinson Research Institute, The University of Adelaide, Adelaide, Australia

Review

Cite this article: Pathirana MM, Lassi ZS, Roberts CT, and Andraweera PH. (2020) Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis. *Journal of Developmental Origins of Health and Disease* **11**: 599–616. doi: 10.1017/S2040174419000850

Received: 23 July 2019
Revised: 5 November 2019
Accepted: 10 November 2019
First published online: 6 January 2020

Keywords:
pregnancy; gestational diabetes mellitus; cardiovascular disease; child health

Address for correspondence:
Prabha Andraweera, Adelaide Medical School, Robinson Research Institute, The University of Adelaide, Adelaide, SA 5005, Australia.
Email: prabha.andraweera@adelaide.edu.au

Abstract

Gestational diabetes mellitus (GDM) is a pregnancy complication that affects one in seven pregnancies. Emerging evidence demonstrates that children born of pregnancies complicated by GDM may be at increased risk of cardiovascular disease (CVD) in adulthood. Therefore, the aim of this study was to determine cardiovascular risk factors in offspring exposed to GDM *in utero*. PubMed, CINAHL, SCOPUS, and EMBASE databases were searched. Information was extracted on established CVD risk factors including blood pressure, lipids, blood glucose, fasting insulin, body mass index (BMI), and endothelial/microvascular function. The review protocol is registered in PROSPERO (CRD42018094983). Prospective and retrospective studies comparing offspring exposed to GDM compared to controls (non-GDM pregnancies) were considered. We included studies that defined GDM based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) definition, or prior definitions. The PRISMA guidelines were followed in conducting this systematic review. Methodological quality was assessed using the Newcastle–Ottawa Quality Assessment Scale. Study selection, data extraction, and quality assessment were done by two independent reviewers. The data were pooled using a random-effects model. Of 59 eligible studies, 24 were included in the meta-analysis. Offspring exposed to GDM had higher systolic blood pressure (mean difference (MD): 1.75 mmHg, 95% CI 0.57–2.94; eight studies, 7264 participants), BMI *z*-score (MD 0.11, 95% CI 0.02–0.20; nine studies, 8759 participants), and glucose (standard MD 0.43, 95% CI 0.08–0.77; 11 studies, 6423 participants) than control participants. In conclusion, offspring exposed to GDM have elevated systolic blood pressure, BMI, and glucose. Those exposed to GDM *in utero* may benefit from early childhood blood pressure measurements.

Introduction

The incidence of cardiovascular disease (CVD) has shown a rapid increase over the last decade. In 2012, there were an estimated 17.6 million deaths from CVD, accounting for 31.43% of global mortality.[1] Emerging evidence demonstrates an association between gestational diabetes mellitus (GDM) and CVD with risk factors for CVD being more prevalent among women who experienced gestational diabetes (GDM) compared to those who did not.[1,2]

Prevalence of GDM varies between populations, but it is estimated to affect one in seven pregnancies.[3] The definition of GDM has changed over recent years, as it has become apparent that mild glucose intolerance in pregnancy which was not formerly considered as GDM increases the risk of developing type 2 diabetes mellitus (T2DM) and CVD in later life.[4] A recent meta-analysis showed a 7.5-fold increase in the risk of T2DM among women who experience GDM.[2]

Emerging evidence also suggests that children born after pregnancies complicated by GDM may also be at increased risk of CVD in adult life. Tam *et al.* showed that for every 1-SD (standard deviation) increase in maternal glycemic level, there was an increase in the adjusted odds ratio for impaired glucose tolerance in the offspring.[5] A meta-analysis conducted by Aceti *et al.* and colleagues demonstrated that systolic blood pressure (SBP) was higher in offspring of women who experienced GDM than controls.[6]

At present, there is no systematic review comparing the main conventional CVD risk factors between offspring exposed to GDM *in utero* compared to controls. Both vascular and metabolic CVD risk factors constitute metabolic syndrome which is a well-established risk factor for CVD.[1] Therefore, synthesizing evidence on all CVD risk factors will provide important information that can guide preventive strategies to reduce the global burden of CVD.

The primary objective of this study was to conduct a comprehensive systematic review and meta-analyses of all relevant studies published until October 2018 to assess conventional CVD risk factors including SBP and diastolic blood pressure (DBP), body mass index (BMI), lipids,

blood glucose, and insulin levels. As a secondary objective, we aimed to assess all relevant studies that assessed microvascular function.

Methods

Search strategy

All studies describing the association between GDM and offspring CVD risks were identified by searching the following electronic databases: PubMed CINAHL, SCOPUS, and EMBASE with an end of search date of April 18, 2018. Subsequently, we updated the literature search to include all relevant articles published until October 17, 2018. The review protocol is registered in PROSPERO (CRD42018094983). No amendments have been made to the current protocol.

The review was undertaken with reference to the PRISMA guidelines.[7] The search strategy is as follows: ("gestational diabetes*" OR "pregnancy induced diabetes" OR "diabetic pregnancy") AND (offspring OR newborn OR baby OR babies OR children OR infant OR neonate* OR adolescent* OR adult) AND ("blood pressure" OR diabetes OR cardiovascular OR metabolic OR hypertension OR BMI or "body mass index" OR obesity OR overweight OR lipids OR lipid OR cholesterol OR triglyceride* OR glucose OR insulin OR vascular). We included case–control studies, cohort studies, and clinical trials. Conference abstracts were also screened. Previous systematic reviews and meta-analyses on relevant topics were identified, and references from eligible reviews were checked for additional studies. All identified studies were assessed for relevance by two independent authors (MMP and PHA). Data were independently extracted by two authors (MMP and PHA). Discrepancies were resolved by discussion.

Inclusion criteria

The population of interest and exposure were offspring at any follow-up visit born to women who experienced GDM during pregnancy. We selected studies that assessed conventional CVD risk factors in offspring exposed to GDM *in utero* compared to offspring not exposed to GDM *in utero*. The CVD risk factor outcomes were blood pressure, BMI, serum and cord blood lipids, and serum and cord blood insulin and glucose.

We included studies that defined GDM based on the IADPSG. However, as diagnostic criteria have recently changed, we included studies that used prior diagnostic criteria of GDM including the 1999 World Health Organization definition, and other regional definitions. The definitions of GDM of included studies are detailed in Table 1. Studies that did not have the above definition/s of GDM, those that did not define study groups, and those that compared GDM and another risk group collectively were excluded. Studies that compared offspring exposed to GDM with offspring exposed to impaired glucose tolerance *in utero* were included in the review but were not included in the meta-analysis. The data from these studies are presented in Supplementary Table S1.

Data were extracted independently and in duplicate for outcomes SBP, DBP, BMI, serum and cord lipid levels (total cholesterol, low-density lipoprotein (LDL) high-density lipoprotein (HDL), non-HDL, and triglycerides), blood glucose, fasting insulin, and measures of vascular/endothelial function. When the same cohort was reported in multiple publications at different ages, the study reporting on the older age group was included in the meta-analysis. We considered both studies published in English and studies that could be translated to English. We contacted authors via email for missing information or data clarification if necessary, and if authors did not respond, then any relevant data from their respective studies are included in Supplementary Table S1.

Statistical analysis

The following data were collected from each included study: definition of GDM, age of offspring at follow-up, number of cases/exposed to GDM *in utero* and controls/not exposed to GDM *in utero*, and birthweight and gestational age at birth of cases and controls. For each outcome measure, mean and SD were used in meta-analyses. When mean and SD were not reported, standard error of mean and 95% CI were converted to SD via statistical software.[8] For studies reporting using median and interquartile range, the results are detailed in Supplementary Table S1. The standard mean difference (SMD) or mean difference (MD) and the 95% CI were calculated using a random-effects model. SMD was used when the outcome was measured in different units across trials and MD when units were consistent.

The meta-analysis was performed using Cochrane Collaborations RevMan software (Review Manager, Version 5.3, The Nordic Cochrane Centre, Copenhagen) based on an inverse variance method. As per protocol, the random-effects model was selected to account for the variation in different criteria used to diagnose GDM among the studies. However, to ensure that the results were not influenced by the choice of model, each analysis was repeated using a fixed-effects model. No difference in results was seen between the two models (results not shown). Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the χ^2 P value was less than 0.1. To assess publication bias, funnel plots were used. The methodological quality and risk of bias were assessed using Newcastle–Ottawa Quality Assessment Scale (Supplementary Table S2).[9] Sensitivity analyses were performed to evaluate heterogeneity for outcomes when omitting low-quality studies. Two authors (MMP, PHA) independently assessed the quality of each study included in the review. The discrepancies were resolved through discussions.

Results

A total of 4359 articles were identified from the literature search. One hundred and twelve articles were eligible for full-text review. Of these, 59 were included in the review and 25 were included in the meta-analyses. The reasons for excluding 53 studies are detailed in Fig. 1. We contacted nine authors for additional data, with responses from four authors (44.4% response); however, the authors of these four studies did not have data that could be used in the meta-analyses and hence are included in Supplementary Table S1.

The assessment of methodological quality identified 25 studies of high quality (scored 7–8), 25 studies of moderate quality (scored 4–6), and 9 studies of low quality (scored 1–3) (Supplementary Table S2). No publication bias was evident for relevant outcomes. Studies were found for all relevant outcomes, except microvascular function, and therefore, we could not report on this outcome in the review.

Systolic blood pressure

SBP data were available from 15 studies, of which 8 were included in the meta-analysis. The age of follow-up of offspring ranged from 3 to 16 years. Based on quantitative summary measures, the meta-analysis demonstrated that offspring exposed to GDM *in utero*

Table 1. Characteristics of the included studies

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Kaseva *et al.*[79]	2018	Multicohort study	Finland	(Both cohorts): OGTT at 26–28 weeks: indications for screening: glycosuria, prior GDM, suspected fetal macrosomia, previous macrosomic infant (birthweight 4500 g), maternal prepregnancy BMI ≥25 kg/m^2, and maternal age ≥40 years Overnight fasting by using a 75-g oral glucose load. Cutoff limits for GDM were used for venous blood glucose: >5.5mmol/l at fasting, >11.0 mmol/l and >8.0mmol/l, 1 and 2 h after the glucose load, respectively. A diagnosis of GDM was made with one abnormal value in the OGTT	191/547	ESTER cohort: 3651 (601)/3519 (466) ALYS cohort: 3881 (648)/3555 (462)	ESTER cohort: 39.0 (1.8)/39.8 (1.5) ALYS cohort: 39.0 (1.5)/40.0 (1.3)	23–25 years after delivery	BMI (kg/m^2)
Kearney *et al.*[26]	2017	Cohort study	USA	Based on hospital records from two major hospitals with a neonatal care unit in the metropolitan area of Québec City (Hôpital Saint-François d'Assise, Centre Hospitalier de l'Université Laval – CHUL) or according to administrative data from the provincial health plan registry (Régie de l'assurance maladie du Québec)	56/30	3346 ± 442/3267 ± 558	38.8 ± 1.4/ 39.5 ± 1.2	Between 3 and 12 years after delivery	BMI (kg/m^2) BMI *z*-score
Le Moullec *et al.*[47]	2018	Cohort study	France	Confirmed based on hospital, medical records with following criteria: positive screening for GDM based on a OGTT (1-h postload 50-g plasma glucose, 11.1 mmol/l), had a diagnosis of GDM based on a 100-g OGTT (OGTT with at least two pathologic values defined as: fasting, −5.3 mmol/l; 1 h, 10.0 mmol/l; 2 h, 8.6 mmol/l; 3 h, 7.8 mmol/l), and/or had received insulin treatment during pregnancy. A small number of participants (<0.5%; $n = 6$) with no available data were also classified into the GDM group if they combined high fasting (or postprandial) glycemic values with intense medical monitoring during pregnancy	600/600	3183 ± 563/ 3047 ± 500	Not reported	Average 6 years after delivery	BMI centile
Miettinen *et al.*[50]	2018	Cohort study	Finland	An oral 75-g, 2-h glucose tolerance test (OGTT) was performed for all subjects at weeks 22–29 of pregnancy, with the exception of three subjects with OGTT performed at weeks 31–33. OGTT was considered diagnostic for GDM if any of the measures were pathological. The following diagnostic thresholds were used: fasting plasma glucose >5.3 mmol/ l, 1-h plasma glucose (10.0 mmol/l) or 2-h plasma glucose (8.6 mmol/l)	15/13	3500 ± 120/ 3540 ± 130	39.8 ± 0.33/ 40.54.7 ± 0.32	After birth	Cord blood total cholesterol, lipids (mmol/l)

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Wang *et al.*[78]	2019	Population-based cohort study	China	Based on American diabetes association	1500/23,471	Not reported	39.1 ± 1.1/ 39.3 ± 1.1	6 years	BMI *z*-score
Hammoud *et al.*[80]	2017	Cohort study	The Netherlands	75-g OGTT or elevated fasting glucose (exact cutoffs not shown)	24/T1D: 27, T2D: 22	3582 ± 576/T1D: 3506 ± 556, T2D: 3701 ± 509	39 ± 2.0/T1D: 37 ± 1.3, T2D: 38 ± 1.7	5 years after delivery	Overweight/obese
Li *et al.*[37]	2017	Prospective cohort study	USA	Self-reported questionnaire	756/14,253	No mean reported	Not reported	11 years after delivery	BMI
Tam *et al.*[5]	2017	Longitudinal cohort study	Hong Kong	All women underwent a standard 75-g OGTT between 24 and 32 weeks of gestation, GDM diagnosed based on *HAPO criteria*	132/794	Not reported	Not reported	7 years after delivery	BMI (kg/m^2) BMI percentile SBP (mmHg) DBP (mmHg) Glucose (mmol/l) Lipids (mmol/l)
Bozkurt *et al.*[53]	2016	Descriptive study	Austria	Fourth International Workshop Conference on GDM criteria	32/DM: (26), Control: (18)	63.0 ± 24.0/DM: (71.3 ± 29.3), Control: (66.6 ± 22.1)[a]	Not reported	Average 6 years after birth	BMI-SDS, insulin (µU/ml)
Hakanen *et al.*[81]	2016	Longitudinal study	Finland	Diagnosed by hospital records	520/T1D: 67, Control: 6316	3600 (600)/Control: 3500 (500), T1D: 3700 (700)	39.4 (2.5)/Control: 39.7 (2.4), T1D: 38.5 (2.0)	Average 1–12 after delivery	BMI peak (kg/m^2)
López Morales *et al.*[49]	2016	Cross sectional	Spain	Diagnosed in medical records	38/women with normal gestation (still pregnant) = 38	Not reported	Not reported	Infant (after birth)	Cord blood glucose (mg/dl) Cord blood insulin (U/ml) Cord blood lipids (mg/dl)
Zhao *et al.*[36]	2016	Cross-sectional	Multicenter (Australia, Brazil, Canada, China Colombia, Finland, India, Kenya, Portugal, South Africa, UK, USA)	Varied between international centers but included WHO, ADA, modified ADA, and modified WHO definitions – women would self-report GDM and the research team confirmed the diagnostic criteria at the time of diagnosis	206/4.354	3415 (623)/ 3274 (576)	38.3 (2.1)/ 38.6 (2.2)	9–11 years after delivery	BMI
Chang *et al.*[12]	2015	Retrospective cohort study	China	*American Diabetes Association:* Women with abnormal 50-g OGTT (>7.8 mmol/l) underwent further fasting 3-h 75-g OGTT. GDM diagnosed with criteria: (BG > 5.3 mmol/l at baseline, >10 mmol/l at 1 h, >8.6 mmol/l at 2 h, 7.8 mmol/l at 3 h	356/500	3700 ± 120/3200 ± 800	Not reported	6 years after birth	BMI (kg/m^2) SBP (mmHg)
Krishnaveni *et al.*[13]	2015	Cohort study	India	*Carpenter and Coustan:* two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min) (reported in 2005 study)	26/CTRL: 165, Offspring of diabetic fathers: 22	Not reported	Not reported	13.5 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) Lipids (mmol/l)
Page *et al.*[82b]	2015	Cohort study	USA	Based on protocol[31]	10/9	Not reported	Not reported	Average 9–10 years after delivery	BMI (kg/m^2) BMI percentile
Rutkowska *et al.*[46b]	2015	Prospective cohort	Poland	Not specified	261/153	3330 ± 53/3420 ± 54	Not reported	Approximately 3 years after delivery	BMI percentile

Wilk *et al.*[57]	2015	Cohort study	Poland	Hospital records	50/46	Not reported	Not reported	7–15 years after delivery	BMI SDS BMI percentile Glucose (mg/dl) Insulin (mg/dl)
Zhao *et al.*[83]	2015	Cohort study	China	Women with risk factors for GDM underwent 85-g OGTT at <12-week gestation, OGTT repeated at 24–28 weeks if normal results. All women with low risk for GDM did normal 24- to 32-week gestation. 1999 WHO diagnostic criteria for GDM since January 1, 2003. GDM diagnosis based on IGT (fasting blood glucose <7.0 mmol/l and 2-h postprandial blood glucose ≥7.8–11.0 mmol/l) or DM (fasting blood glucose ≥7.0 mmol/l or 2-h postprandial blood glucose ≥11.1 mmol/l) positive results	LGA: 149/284 AGA: 771/1401 SGA: 148/180	GDM (followed) 3256 ± 405, GDM (not followed) 3172 ± 509/ Control followed: 3261 ± 391, Control not followed: 3254 ± 417	GDM (followed) 38.9 ± 0.9 (not followed) 38.4 ± 1.5/Control followed: 39.5 ± 1.0, Control not followed: 39.1 ± 0.7	5–10 years after delivery	BMI percentile
Holder *et al.*[25]	2014	Cohort study	USA	Self-reported	45/210	3242.54 ± 959.59/ 3297.93 ± 603.99	Not reported	Average 15 years after delivery	BMI (kg/m^2) BMI *z*-score Plasma glucose (mmol/l)
Köing *et al.*[35]	2014	Retrospective case-control	Germany	Three women were diagnosed with *Hesse Diabetes Society diagnosis:* Fasting: ≥90 mg/dl, 1-h postprandial: ≥160 mg/dl, 2-h postprandial ≥140 mg/dl in venous plasma. Some women were diagnosed who exceeded only one of these three threshold values in a venous blood specimen. Other women referred to by clinicians, based on DDG and AGA values: GDM was diagnosed if at least two measured values exceeded the limits of *Carpenter and Coustan* after ingestion of 75-g glucose, only one exceeded value was declared as impaired glucose tolerance. GDM can also be diagnosed if only one of the predetermined cutoffs is exceeded, whereas these values – based on the results of the *HAPO Study* – differ slightly from the former criteria: Fasting: ≥92 mg/dl, 1-h postprandial: ≥180 mg/dl, 2-h postprandial: ≥153 mg/dl	130/77	3406.62 ± 463.69/ 3456.09 ± 463.25	Not reported	6 months after delivery	BMI (kg/m^2) BMI percentile
Page *et al.*[27]	2014	Cohort study	USA	Based on protocol[31]	37/25	3186 ± 113/ 3454 ± 79	Not reported	5–16 years old (average 7–9 years after delivery)	BMI (kg/m^2) BMI *z*-score BMI percentile
Davis *et al.*[24]	2013	Longitudinal cohort	USA	Self-reported	47/163	3900 (800)/ 3700 (600)	Not reported	Average 10–11 years after birth	BMI (kg/m^2) BMI percentile BMI *z*-score Glucose (mg/dl) Insulin (μU/ml)

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Eslamian *et al.*[33]	2013	Cohort study	Iran	*World Health Organization*, diagnosed as either: fasting plasma glucose 5.1–6.9 mmol/l or: 1-h plasma glucose 10.0 mmol/l. Following a 75-g oral glucose load 2-h plasma glucose 8.5–11.0 mmol/l following a 75-g oral glucose load	112/159	3336.07 ± 630/ 3259.75 ± 490	37.72 ± 1.7/ 39.1.33	Infant (after birth)	BMI (kg/m^2) Cord blood glucose (mg/dl) Cord blood insulin (µU/ml) Cord blood lipids (mg/dl)
Farfel *et al.*[45b]	2013	Cohort study	Israel	159 males, 113 females/diagnosed by hospital records	Female (113), male (159)/PGDM male (34) female (23) control, male (198), control (147)	Male 3423 ± 537, female 3230 ± 510, PGDM male 3451 ± 535, female 3210 ± 364. CTRL male 3344 ± 372, female 3228 ± 324	Not reported	17 years after delivery	BMI >85th percentile
Nehring *et al.*[39]	2013	Retrospective cohort study	Germany	GDM cases found from medical records	195/7160	3479 (3417–3540)/ 3413 (3403–3424)	3413 (3403–3424)/ 39.4 (39.3–39.4)	Average 5.8 years after delivery	BMI (kg/m^2)
Nielsen *et al.*[40]	2012	Population-based cohort study	Denmark	*Rigshospitalet University Hospital modification of the White classification:* Oral glucose challenge test (OGTT) in gestational weeks 24–26 if they met one of the following criteria: (1) previous birth of a baby with birthweight >4500 g; (2) maternal overweight >130%; (3) family history of diabetes; (4) glycosuria; or (5) previous obstetrical complications or late miscarriage (diagnostic values not specified)	34/previous GDM (185), control (737)	3803 (780)/PREGDM: 3327 (648), control: 3482 (551)	38.9 (1.9)/PREGDM: 36.5 (1.8), control: 38.8 (2.0)	18–20 years after delivery	BMI (kg/m^2)
Page *et al.*[20b]	2013	Cohort study	USA	Based on protocol[31]	10/19	Not reported	Not reported	Average 9 years after delivery	BMI *z*-score SBP (mmHg) Glucose (mg/dl) Insulin (ulU/ml)
Pham *et al.*[84]	2013	Retrospective cohort study	USA	Normal screening at 24–28 weeks (unless considered at risk, tested in first trimester). 50-g, 1-h glucose challenge test of greater/equal to 140 mg/dl, then given a 100-g, 3-h glucose tolerance test if 1-h challenge was positive. Needed 1/4 of the possible measurements to be diagnosed. Diagnosis followed *National Diabetes Data Group* prior to April 2007, then changed to *Carpenter and Coustan* criteria after April 2007	459/2185	3406 ± 496/3404 ± 442	39.3 ± 1.0/ 39.6 ± 0.9	2–4 years after delivery	BMI percentile
Retnakaran *et al.*[32]	2013	Substudy of prospective observational study	Canada	Those with and without an abnormal 50-g glucose challenge screening test undergo 3-h, 100-g OGTT for ascertainment of antepartum glucose intolerance status (i.e., either GDM or non-GDM) based on NDDG, measurements at 20 min 1, 2, and 3 h	36/68	3411 (3110–3635)/ 3415 (3144–3628)	Not reported	1 year after delivery	BMI *z*-score Fasting glucose (mmol/l) Lipids (mmol/l)

Baptise-Roberts *et al.*[29]	2012	Prospective cohort	USA	All women provided fasting blood specimen if it was 120 mg/dl or higher, or if it rose to over 175 mg/dl at the end of 1 h and did not return to normal in the 2- and 3-h specimens. GDM diagnosed based on these criteria: (1) she was newly diagnosed with diabetes during pregnancy; (2) she initiated insulin during pregnancy; (3) she displayed an abnormal glucose tolerance test result; or (4) she had a blood glucose level of 200 mg/dl or more at any time during pregnancy	484/27,874	3302 ± 584/ 3190 ± 484	Not reported	7 years after birth	BMI (kg/m^2) BMI *z*-score BMI percentile
Borgoño *et al.*[52]	2012	Prospective cohort	Canada	*National Diabetes Data Group* criteria	36/68	3411 (3110–3635)/ 3415 (3144–3628)	Not included	1 year after birth	Fasting glucose (mmol/l) Fasting insulin (pmol/l)
Chandler Laney *et al.*[51]	2012	Cohort study	USA	Self-reported, confirmed with hospital records	Normal weight: (11), Overweight: (13)/Normal weight: (19), Overweight: (8)	Not reported	Not reported	Average 7–8 years after birth	BMI percentile Glucose (mg/dl)^2 Insulin (mg/dl)^2
Page *et al.*[31b]	2012	Cohort study	USA	Not reported in abstract (based on protocol): Fasting glucose <126 mg/dl (7 mM) from families of a proband with GDM diagnosed within the previous 5 years)	35/14	Not reported	Not reported	Average 8 years after delivery	BMI (kg/m^2) BMI *z*-score
Patel *et al.*[14]	2012	Prospective population-based cohort study	England	GDM was defined as any record of a diagnosis of gestational diabetes at any time during the pregnancy in women without existing diabetes at the start of pregnancy. (At time of study recruitment: all pregnant women to have urine tested for glycosuria and proteinuria at every antenatal clinic visit. Glycosuria was defined as a record of at least ++ (equal to 13.9 mmol/l or 250 mg/100 ml) on at least two occasions at any time during the pregnancy.) GDM was tested further to these results, diagnosed in the medical records as GDM with no history of existing diabetes.	27/Control: (4384), existing diabetes: (23), glycosuria: (154)	1.45 (1.28)/Control: 0.038 (0.97), existing diabetes: 0.28 (1.32), glycosuria: 0.18 (1.04)	38.6 (1.48)/control: 39.4 (1.85), existing diabetes: 37.5 (1.86), glycosuria: 39.7 (1.63)	15 years after delivery	BMI *z*-score SBP and DBP (mmHg) Glucose (mmol/l) Insulin (IU/l) Lipids (mmol/l)
Jahan *et al.*[85]	2011	Cohort study	Bangladesh	Diagnosed with fasting blood glucose, and 2 h after 75-g OGTT. Women who had repeatedly elevated fasting (>7.0 mmol/l) or postprandial (9 mmol/l) blood glucose values.	30/DM: ($n = 45$), control: ($n = 30$)	3000 (2100–4500)/ DM: 3100 (1700–4800), NDM: 2700 (2000–3800)	Not reported	Infant (after birth)	Insulin (mmol/l)
Tsadok *et al.*[22]	2011	Population-based cohort	Israel	Reported on hospital records	293/59,499	3411 ± 616/3301 ± 483	Not reported	17 years after delivery	BMI (kg/m^2) SBP and DBP

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Boerschmann *et al.*[86]	2010	Prospective cohort	Germany	*German Diabetes Association* – an OGTT with a 75-g glucose load. Women were considered to have GDM if two of three capillary blood glucose values exceeded the following limits: >5 mmol/l (fasting) before an OGTT, >10 mmol/l after 60 min, and >8.6 mmol/l after 120 min	232	Not reported	Not reported	11	BMI percentile
Krishnaveni *et al.*[18]	2010	Cohort study	India	*Carpenter and Coustan:* two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min)	Female (23), Male (12)/Control: female (191) male (190), Offspring of diabetic fathers male: (20), female: (19)	Not reported	Not reported	9.5 years after delivery	BMI (kg/m^2) BMI percentile SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) Lipids (mmol/l)
Lawlor *et al.*[30]	2010	Longitudinal cohort	England	GDM was defined as any record of a diagnosis of gestational diabetes at any time during the pregnancy in women without existing diabetes at the start of pregnancy. (At time of study recruitment: all pregnant women to have urine tested for glycosuria and proteinuria at every antenatal clinic visit. Glycosuria was defined as a record of at least ++ (equal to 13.9 mmol/l or 250 mg/100 ml) on at least two occasions at any time during the pregnancy.) GDM was tested further to these results, diagnosed in the medical records as GDM with no history of existing diabetes	53/control: (10,126) Existing diabetes (40) Glycosuria (372)	3711 (655)/control: 3416 (536), existing diabetes: 3248 (787), glycosuria: 3511 (534)	38.2 (1.9)/control: 39.5 (1.9), existing diabetes: 37.5 (2.6), glycosuria: 39.5 (1.8)	Average 9–11 years after delivery	BMI *z*-score
Pirkola *et al.*[41]	2010	Longitudinal cohort study	Finland	GDM risk factors; 40 years, BMI 25 kg/m^2, prior GDM, previous delivery of a macrosomia infant (birthweight 4500 g), glycosuria, and suspected fetal macrosomia in the current pregnancy. Glucose tolerance testing, performed after an overnight fast, conducted by administering a 2-h, 75-g OGTT: 5.5, 11.0, and 8.0 mmol/l at fasting and at 1 h and 2 h after the glucose load, respectively. Diagnosis of GDM was set after one abnormal value in the OGTT, according to prevailing national guidelines	Normal weight: (n = 49), Overweight: (n = 35)/Control total: (657) Normal weight: (503), Overweight (n = 154)	Overweight: 3700 (3490–3920) Normal 3670 (3530–3820)/ Overweight = 3780 (3680–3880), Normal weight: 3690 (3640–3740), Total: 3480 (3460–3500)	Overweight: 38.5 (37.8–39.1), Normal 39.0 (38.6–39.5)/ Overweight 39.4 (39.1–39.6), Normal weight 39.5 (39.4–39.7) Total 39.5 (39.4–39.5)	16 years after delivery	BMI (kg/m^2)
Tam *et al.*[15]	2010	Longitudinal cohort	Hong Kong	GDM defined based on *WHO criteria*: Gestational IGT (i.e., fasting PG level of 7.0 mmol/l and 2-h PG level of 7.8–11.1 mmol/l, and GDM (i.e., fasting PG level of 7.0 mmol/l and/or 2-h PG level of 11.1 mmol/l). WHO criteria states that "pregnant women who meet WHO criteria for diabetes mellitus of IGT are classified as having GDM"	42/87	3248 (351)/ 3273 (454)	Based on Tam *et al.*[21] with larger (n =): 39.6 ± 0.2/ 39.5 ± 0.2	15 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Glucose (mmol/l) Lipids (mmol/l)

Catalano *et al.*[11]	2009	Prospective cohort	USA	NDDG	25/38	3373 ± 532/ 3376 ± 496	38.7 ± 1.3/ 39.4 ± 1.2	Average 8.8 years after birth	BMI (kg/m^2) BMI *z*-score SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) HOMA-IR Lipids (mmol/l)
Vaarasmaki *et al.*[23]	2009	Prospective cohort study	England	Risk factors: glycosuria, prior gestational diabetes, suspected fetal macrosomia (birthweight 4500 g) in the current pregnancy, previous delivery of a macrosomic infant, BMI 25 kg/m^2 and age more than 40 years. A history of prior gestational diabetes or glycosuria in the current pregnancy warrants an earlier OGTT. Diagnosed with 2-h, 75-g OGTT usually at 26–28 week of gestation: one or more abnormal OGTT values (cutoff values for venous blood samples are 4.8 mmol/l at 0 min, 10.0 mmol/l at 60 min, and 8.7 mmol/l at 120 min)	96/3909	3727 (577)/ 3517 (471)	38.8 (1.7)/ 39.5 (1.5)	16 years after delivery	BMI SBP and DBP (mmHg) Glucose (mmol/l) Insulin (milliunits/l) Lipids (mmol/l)
Wright *et al.*[16]	2009	Cohort study	USA	Screening at 26–28 weeks with nonfasting 50-g 1-h oral glucose challenge. If test result was abnormal (i.e., blood glucose value of >140 mg/dl), then women were referred for fasting 3-h 100 OGTT. Two or more abnormal results were a diagnosis for GDM: a blood glucose >95 mg/dl at baseline, >180 mg/dl at 1 h, >155 mg/dl at 2 h, or >140 mg/dl at 3 h	51/control $n = 1035$, IGT $n = 152$	3510 (52)/ control = 3510/52, IGT 3600 (52)	Not reported	3 years after delivery	BMI (kg/m^2) BMI percentile BMI *z*-score SBP (mmHg)
Buzinaro *et al.*[10]	2008	Cohort study	Brazil	Based on OGTT values (cutoffs not specified)	23/Control (17) Hyperglycemia (23)	Not reported	Not reported	Average 12–16 years after birth	BMI (kg/m^2) SBP and DBP (mmHg) Glucose (mg/dl) Lipids (mg/dl)
Clausen *et al.*[56]	2008	Retrospective cohort study	Denmark	OGTT – GDM was based on risk indicators: family history of diabetes, overweight (20%) prepregnancy, prior GDM, delivery of macrosomic baby, glycosuria. Women with these risk indicators and two capillary blood glucose measurements > 4.1 mmol/l were offered a 3-h 50-g OGTT. OGTT was abnormal if more than two of seven values during the test exceeded mean 3 SDs for a reference group of normal weight nonpregnant women without family history of diabetes (Until September 1982 venous plasma used for OGTT, after then capillary whole blood)	168/128	3410 (530)/ 3474 (481)	273 (247–284)/ 280 (253–298)	18–27 years after delivery	Glucose (mmol/l)

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Pirkola *et al.*[17]	2008	Cohort study	Finland	Risk factors for diagnosis: glycosuria, prior gestational diabetes, suspected fetal macrosomia (birthweight 4500 g) in the current pregnancy, previous delivery of a macrosomic infant, BMI 25 kg/m^2 and age more than 40 years. A history of prior gestational diabetes or glycosuria in the current pregnancy warrants an earlier OGTT. Diagnosed with 2-h, 75-g OGTT usually at 26–28 week of gestation: one or more abnormal OGTT values (cutoff values for venous blood samples are 4.8 mmol/l at 0 min, 10.0 mmol/l at 60 min, and 8.7 mmol/l at 120 min)	22/T1D: 16, control: 25	3.708 (3.538–3.886)/ T1D: 3.818 (3.482–4.185), Control: 3.666 (3.452–3.893)	39.2 (38.7–39.7)/ T1D: 37.5 (36.8–38.2), 39.3 (38.8–39.8)	Mean 4.9 years after delivery	SBP and DBP (mmHg) Cord blood insulin (pmol/l)
Tam *et al.*[21]	2008	Longitudinal cohort study	Hong Kong	DM defined based on *WHO criteria*: Gestational IGT (i.e., fasting PG level of 7.0 mmol/l and 2-h PG level of 7.8–11.1 mmol/l, and GDM (i.e., fasting PG level of 7.0 mmol/l and/or 2-h PG level of 11.1 mmol/l). WHO criteria states that "pregnant women who meet WHO criteria for diabetes mellitus of IGT are classified as having GDM"	63/101	3292 ± 52/3245 ± 45	39.6 ± 0.2/ 39.5 ± 0.2	Average 7–8 years after delivery	BMI (kg/m^2) BMI percentile SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) Lipids (mmol/l)
Lee *et al.*[19]	2007	Cohort study	South Korea	*National Diabetes Data Group:* 50-g glucose challenge test was performed; if the 1-h plasma glucose value was 130 mg/dl (7.2 mmol/l), a 3-h OGTT was performed during 28–32 weeks of gestation	202/96	3344.6 ± 585.0/ 3286.6 ± 612.4	38.6 ± 1.5/ 38.7 ± 2.2	Average 4 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Lipids (mmol/l) Glucose (mmol/l) Insulin (mg/ml)
Boney *et al.*[87]	2005	Longitudinal cohort	USA	*National Diabetes Data Group* criteria described by *Carpenter and Coustain*	LGA: 42/43 AGA: 52/42	LGA: 4107 (386)/ 4132 (285) AGA: 3316 (310)/ 3370 (282)	Not reported	11 years after birth	BMI percentile BP >90th percentile (BP is either SBP or DBP) (mmHg) Glucose (mmol/l) Lipids (mmol/l)
Jaber *et al.*[34]	2006	Cohort study	Saudi Arabia	Venous fasting glucose concentration of >5.5 mol/l or of >8.0 mmol/l 2 h after a 75-g oral glucose load or both	26/Control (n = 32), FDM (n = 21)	3640 ± 690/CTRL: 3.30 ± 0.59, FDM: 3.18 ± 0.86	37.38 ± 0.64/CTRL: 37.28 ± 0.73, FDM: 37.48 ± 0.60	Approximately 2 weeks after delivery	BMI (kg/m^2) Glucose range (mmol/l) Insulin range (pmoL/l)
Krishnaveni *et al.*[38]	2005	Cohort study	India	*Carpenter and Coustan:* two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min)	41/Control: 588, Offspring of diabetic fathers: 41	3344 ± 421/CTRL: 2973 ± 408, ODF: 2869 ± 305	39.1 ± 1.2/CTRL 39.0 ± 1.8, ODF: 39.1 ± 1.2	1 and 5 years after delivery	Fasting plasma glucose (pmol/l)
Gillman *et al.*[88]	2003	Prospective Cohort	USA	Self-reported questionnaire	Female (246), male (219)/ female (n = 7735), male (n = 6681)	Female: 3.55 (0.56), male 3.68 (0.61)/ female 3.44 (0.48), male 3.58 (0.51)	Not reported	Average 9–14 years after delivery	BMI percentile

Vohr *et al.*[44]	1999	Prospective observational study	USA	24- to 28-week screening, GDM diagnosis made on initial 1-h 50-g glucose screen >130 mg/dl, followed by two abnormal values in a 100-g OGTT. *Criteria of O'Sullivan et al. modified by Carpenter and Coustan (recent 1999):* fasting plasma glucose >95 mg/dl and 1-h >180 mg/dl, 2-h >155 mg/dl, and 3-h >140 mg/dl	LGA: 47/46 AGA: 59/55	LGA: 4100 ± 3800/ 4200 ± 2900 AGA: 3300 ± 300/ 3400 ± 3000	LGA: 39.4 ± 1/ 40.0 ± 1, AGA: 39.4 ± 1/ 39.7 ± 1	4–7 years after delivery	BMI (kg/m^2)
Silverman *et al.*[42c]	1998	Long-term prospective cohort	USA	Unclear – from hospital records (From Silverman *et al.*[89])	Unclear	Not reported	Not reported	14–17 years after delivery	BMI (kg/m^2)
Whitaker *et al.*[28]	1998	Cohort study	USA	24- to 32-week screening, 1-h 50-g oral glucose load – glucose screening values >7.77mmol/l (140mg/dl) called back for 3-h 100-g OGTT. GDM diagnosed based on calculations *Carpenter and Coustan (recent 1998)*	63/Control: (257), Normal OGTT = 159, No OGTT = 45	Not reported	Not reported	5–10 years after delivery	BMI *z*-score BMI percentile
Plagemann *et al.*[55]	1997	Retrospective study	Germany	Diagnosed 26- to 28-week gestation by Furmann: a 50-g OGTT using the following criteria (two or more abnormal values): fasting venous blood glucose over 5.55 mmol/l, 1-h value over 8.88 mmol/l, 2-h value over 7.22 mmol/l	57/156	3500.8 ± 50.8 (117)/ 3443.5 ± 45.5 (200)	Not reported	Average 1–9 years delivery	Plasma insulin (mIU/ml)
Plagemann *et al.*[54]	1997	Cohort study	Germany	Diagnosed 26- to 28-week gestation by Furmann: a 50-g OGTT using the following criteria (two or more abnormal values): fasting venous blood glucose over 5.55 mmol/l, 1-h value over 8.88 mmol/l, 2-h value over 7.22 mmol/l	69/129	3460.1 ± 50.7/ 3411.2 ± 56.8	Not reported	Average 1–9 years after delivery	Glucose (mmol/l) Insulin (pmol/l)
Vohr *et al.*[43]	1995	Prospective cohort study	USA	Screening 24–28 weeks, GDM diagnosis made on initial 1-h 50-g glucose screen >130 mg/dl, followed by two abnormal values in a 100-g OGTT. *Criteria of O'Sullivan* et al. *modified by Carpenter and Coustan:* fasting plasma glucose >95 mg/dl and 1 h >180 mg/dl, 2 h >155 mg/dl, and 3 h >140 mg/dl	LGA: 57/74 AGA: 62/69	LGA: 4064 ± 305/ 4095 ± 267 AGA: 3301 ± 280/ 3282 ± 238	LGA: 39 ± 1/40 ± 1, AGA: 39 ± 1/39 ± 1	20 h after delivery	BMI (kg/m^2)
Teng *et al.*[48]	2017	Longitudinal cohort	India	*IADPSG criteria:* 75 g OGTT and if serum glucose level was over 1 mmol/l at 0 h, or 10.0 mmol/l at 1 h, or 8.5 mmol/l at 2 h, GDM was diagnosed	123/80	Not reported	Not reported	14 years after delivery	Glucose (mmol/l) Lipids (mmol/l)

IGT, impaired glucose tolerant; NDDG, National Diabetes Dat ` a Group; OGTT, oral glucose tolerance test; SDS, Standard Deviation Score; ADA, American Diabetes Association; BG, blood glucose; CTRL, control; LGA, large for gestational age; AGA, average for gestational age; SGA, small for gestational age; PGDM, previous gestational diabetes mellitus; PREGDM, previous GDM; NDM, nondiabetic mothers; PG, plasma glucose; HOMA-IR, homeostatic model assessment of insulin resistance; FDM, frank diabetic mothers; ODF, offspring of diabetic fathers.

[a]Birthweight centiles used rather than birthweight.

[b]Abstract only.

[c](*n*=) not known for GDM or non-GDM group.

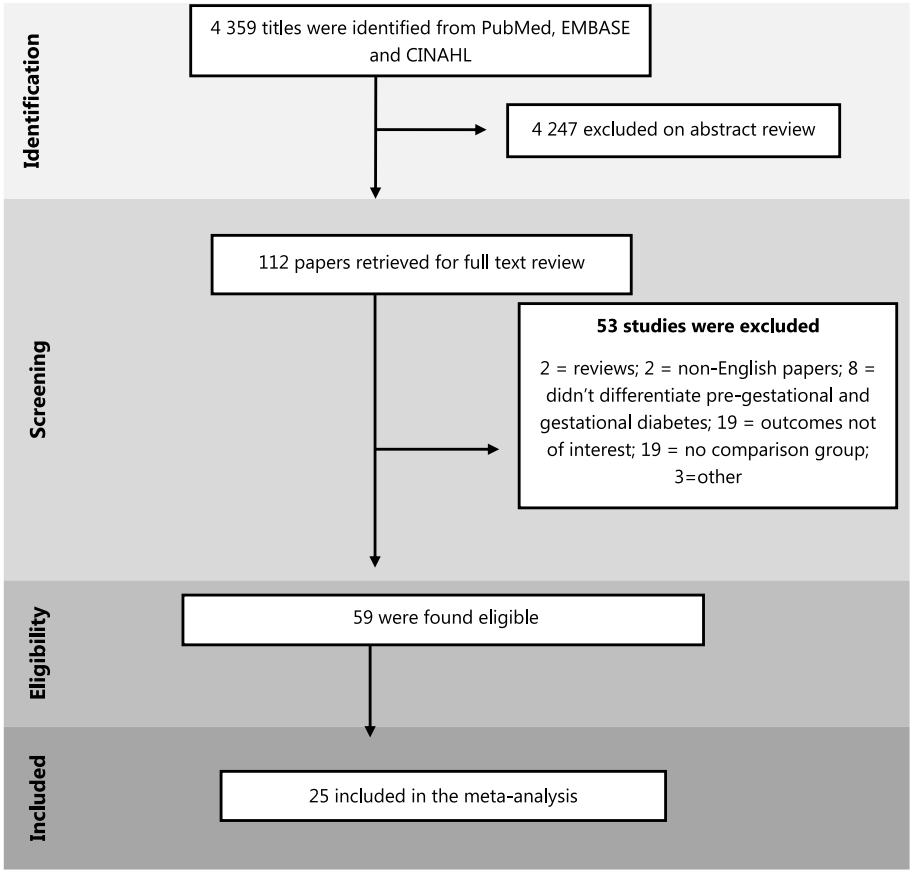


Fig. 1. PRISMA flow diagram of study selection.

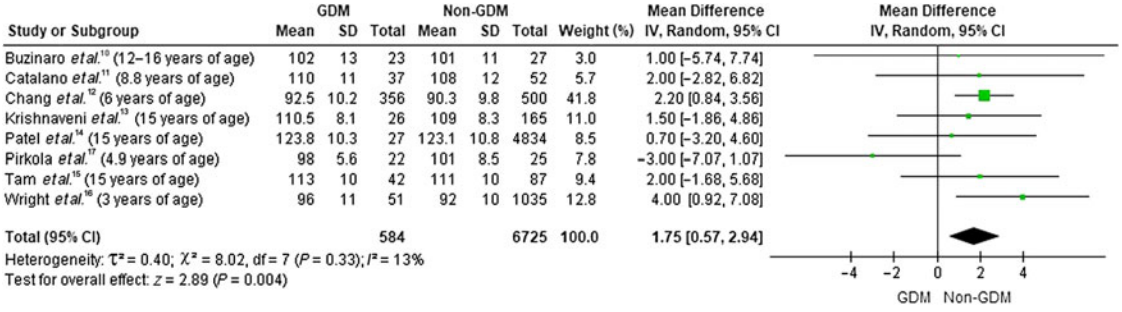


Fig. 2. Mean difference in systolic blood pressure (mmHg) in those exposed to GDM *in utero* and controls.

have 1.75 mmHg (95% CI 0.57–2.94) higher SBP compared to controls (n(total) = 7309, n(exposed to GDM) = 584; $P = 0.33$, $I^2 = 13\%$) (Fig. 2).[10–17] Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Of the seven studies not included in the meta-analysis,[5,18–23] four reported a significant increase in SBP among offspring exposed to GDM compared to controls (Supplementary Table S1).[5,18,21,22]

Diastolic blood pressure

DBP data were available from 13 studies of which 6 were included in the meta-analysis. The age at follow-up ranged between 8 and 16 years. The meta-analysis demonstrated no difference in DBP among GDM-exposed offspring and controls (MD −0.24, 95% CI −2.33 to 1.85; n(total) = 5367, n(exposed to GDM) = 177; $P = 0.08$, $I^2 = 50\%$[10,11,13–15]; Supplementary Fig. S1). Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Seven studies were not included in the meta-analysis,[5,17–23] of which two reported a significantly higher DBP in GDM offspring compared to controls (Supplementary Table S1).[21,22]

Body mass index

BMI data (i.e., BMI z-score, BMI (kg/m^2), and/or BMI percentile, BMI peak, BMI SD) were available from 48 studies. BMI z-score and BMI (kg/m^2) are reported in the meta-analysis, and other BMI data are reported in the nonmeta-analysis (Supplementary Table S1).

BMI z-score data were reported in 14 studies, of which 9 were included in the meta-analysis. The age at follow-up ranged from 3 to 15 years. Offspring exposed to GDM *in utero* showed an

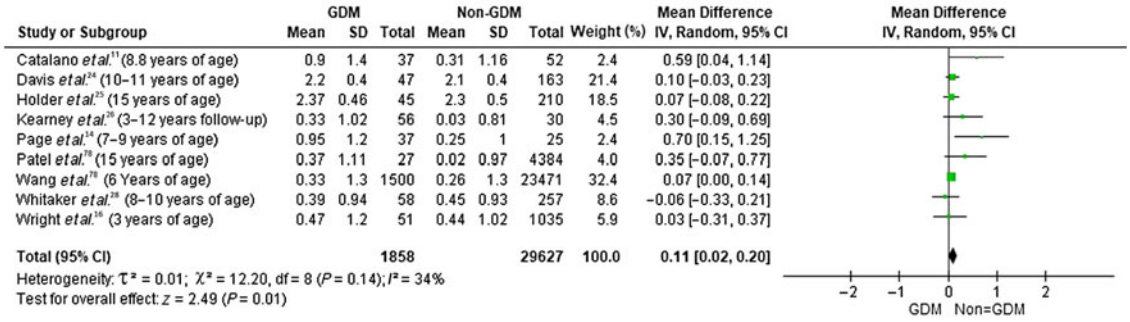


Fig. 3. Mean difference in BMI *z*-score in those exposed to GDM *in utero* and controls.

increase in BMI *z*-score compared to controls (MD 0.11, 95% CI 0.02–0.20; *n*(total) = 31,485, *n*(exposed to GDM) = 1858; $P = 0.14$, $I^2 = 34\%$)[11,14,16,24–28] (Fig. 3). Five studies were not included in the meta-analysis,[20,29–32] with two reporting significantly higher BMI *z*-scores in GDM-exposed offspring compared to controls[29,31] (Supplementary Table S1). Sensitivity analysis showed no difference in heterogeneity when removing low-quality studies (Supplementary Table S3A).

BMI (kg/m^2) data were available from 31 studies. Sixteen studies were included in the meta-analysis, with the age at follow-up ranging broadly from <48 h after birth to 25 years. Quantitative summary measures obtained through meta-analysis showed a 1.06-kg/m^2 increase in BMI among those exposed to GDM *in utero* compared to controls (95% CI 0.40–1.73; *n*(total) = 23,864, *n*(exposed to GDM) = 2154; $P < 0.00001$, $I^2 = 95\%$; Supplementary Fig. S2).[10–13,15,16,24–27,33–37] Sensitivity analysis showed no difference in heterogeneity when removing low-quality studies (Supplementary Table S3B). Fifteen studies were not included in the meta-analysis,[5,18,19,21,23,29,31,36,38–44] of which seven studies showed significantly higher BMI among offspring exposed to GDM compared to controls[18,22,29,31,36,38,42] (Supplementary Table S1). Krishnaveni *et al.* reported a significant association between females exposed to GDM *in utero* compared to female controls ($P < 0.001$).[18] One study that showed statistical significance did not report on the sample size for either GDM or control groups.[42]

BMI percentiles were reported in 21 studies. Of these, five reported a higher BMI within obese/overweight BMI percentiles among those exposed to GDM *in utero* compared to controls (i.e., ≥85th percentile)[5,29,45–47] (Supplementary Table S1).

Lipids

Studies on cord blood and serum lipids (i.e., total cholesterol, LDL, HDL, and triglycerides) were included.

Total cholesterol

Total cholesterol data were available from 12 studies (9 serum cholesterol and 3 cord blood cholesterol). Five studies on total serum cholesterol were included in the meta-analysis. The age of follow-up ranged from 8 to 16 years. There was no significant difference in total serum cholesterol between GDM and control groups (SMD −0.01, 95% CI −0.28 to 0.25; *n*(total) = 662, *n*(exposed to GDM) = 251; $P = 0.07$, $I^2 = 54\%$; Supplementary Fig. S3A).[10,11,13,15,48] The four studies that were not included in the meta-analysis showed no difference in total cholesterol between those exposed to GDM and controls (Supplementary Table S1).[5,19,21,23] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Three studies on cord blood total cholesterol were included in the meta-analysis. Quantitative summary measures did not show a significant difference in total cord blood cholesterol between GDM and control groups (SMD −0.90, 95% CI −2.41 to 0.61; *n*(total) = 374, *n*(exposed to GDM) = 164; $P < 0.00001$, $I^2 = 96\%$; Supplementary Fig. S3B).[33,49] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

LDL cholesterol

LDL cholesterol data were available from 10 studies (8 serum LDL cholesterol, 2 cord blood cholesterol).

Four studies on serum LDL cholesterol were included in the meta-analysis. The age of follow-up ranged from 8 to 16 years. There was no difference in serum LDL cholesterol between those exposed to GDM and controls (SMD −0.03, 95% CI −0.44 to 0.38; *n*(total) = 5129, *n*(exposed to GDM) = 129; $P = 0.01$, $I^2 = 73\%$; Supplementary Fig. S4A).[10,11,14,15] Four studies that were not included in the meta-analysis showed no difference in LDL between GDM and control groups[5,21,23,32] (Supplementary Table S1). Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Two studies on cord blood LDL were included in the meta-analysis. Quantitative summary measures did not show a significant difference in cord blood LDL between GDM and control groups (SMD −0.60, 95% CI −1.57 to 0.38; *n*(total) = 298, *n*(exposed to GDM) = 126; $P = 0.01$, $I^2 = 84\%$; Supplementary Fig. S4B).[49,50] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

HDL cholesterol

HDL cholesterol data were available from 15 studies (12 serum HDL cholesterol, 3 cord blood HDL cholesterol).

Six studies on serum HDL cholesterol were included in the meta-analysis. The age of follow-up ranged from 8 to 16 years. Quantitative summary measures showed no significant difference in serum HDL cholesterol between those exposed to GDM and controls (SMD 0.08, 95% CI −0.07 to 0.24; *n*(total) = 5073, *n*(exposed to GDM) = 278; $P = 0.77$, $I^2 = 0\%$; Supplementary Fig. S5A).[10,11,13–15,48] Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Six studies were not included in the meta-analysis.[5,18,19,21,23,32] Of these, one reported lower serum HDL cholesterol in the GDM group compared to controls (Supplementary Table S1).[21] Three studies on cord blood HDL were included in the meta-analysis. Quantitative summary measures showed no difference in cord blood HDL between GDM and controls groups (SMD −0.13, 95% CI −0.84 to 0.59; *n*(total) = 374, *n*(exposed to GDM) = 164; $P = 0.0006$, $I^2 = 87\%$; Supplementary Fig. S5B).[33,49,50] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

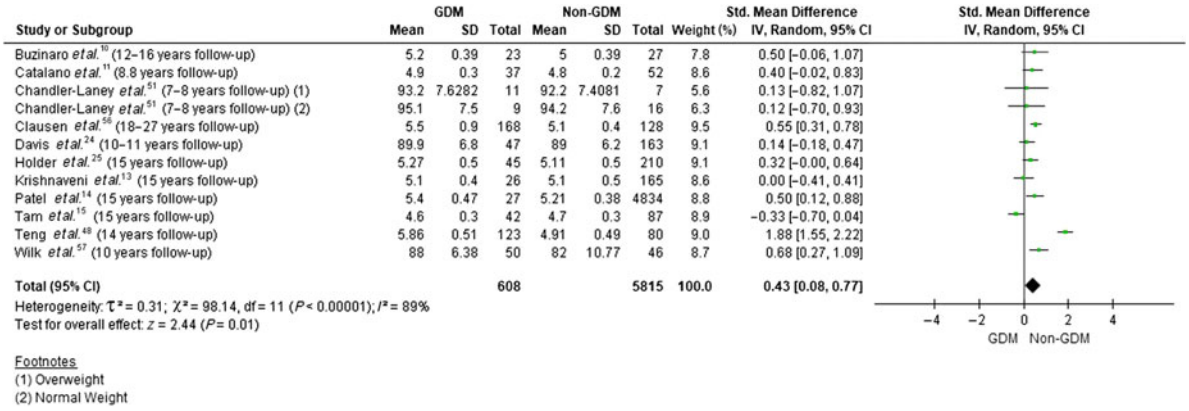


Fig. 4. Standard mean difference in fasting glucose in those exposed to GDM *in utero* and controls.

Triglycerides

Triglyceride data were available from 14 studies (11 serum triglycerides and 3 cord blood triglycerides). Six studies on serum triglycerides were included in the meta-analysis. The age at follow-up ranged from 7 to 16 years. Quantitative summary measures showed no difference in the level of serum triglycerides between GDM and control groups (SMD 0.50, 95% CI −0.14 to 1.14; n(total) = 5523, n(exposed to GDM) = 278; $P < 0.00001$, $I^2 = 93\%$; Supplementary Fig. S6A).[10,11,13–15,48] Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Five studies that were not included in the meta-analysis also showed no significant difference in serum triglycerides in GDM and control groups (Supplementary Table S1).[5,18,19,21,23] Three studies on cord blood triglycerides were included in the meta-analysis. There was no difference in cord blood triglycerides in the GDM group compared to controls (SMD 0.02, 95% CI −0.67 to −0.71; n(total) = 374, n(exposed to GDM) = 164; $P = 0.001$, $I^2 = 86\%$; Supplementary Fig. S6B).[33,49,50] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Insulin

Data for fasting serum insulin were collected for 20 studies (16 serum insulin and 4 cord blood insulin).

Four studies on serum insulin were included in the meta-analysis. The age at follow-up ranged from 8 to 15 years. The meta-analysis showed no difference in insulin between the two groups (SMD −0.02, 95% CI −0.70 to 0.67; n(total) = 5136, n(exposed to GDM) = 131; $P < 0.00001$, $I^2 = 89\%$; Supplementary Fig. S7A).[11,14,24,51] Sensitivity analyses showed no difference in heterogeneity when poor-quality studies were omitted (Supplementary Table S4)

Twelve studies were not included in the meta-analysis,[5,13,18–21,23,34,51–55] of which five reported significantly elevated insulin levels in the GDM group compared to controls[13,18,34,54,55] (Supplementary Table S1). Two of these studies showed a significant difference in fasting insulin between offspring exposed to pre-GDM (i.e., diabetes diagnosed before pregnancy) and GDM.[54,55] Two studies were included in a meta-analysis on cord blood insulin; however, there was no difference between the GDM and control groups (SMD −4.74 95%, CI −14.99 to 5.51; n(total) = 123, n(exposed to GDM) = 60; $P < 0.00001$, $I^2 = 99\%$; Supplementary Fig. S7B).[17,49] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Glucose

Glucose data were available from 25 studies (23 serum glucose and 2 cord blood glucose). Eleven studies on serum glucose were included in the meta-analysis, in which the age at follow-up ranged from 8 to 27 years. Based on quantitative summary measures, the meta-analysis showed an increase in glucose in offspring exposed to GDM *in utero* compared to controls, demonstrating a 0.43 SMD (95% CI 0.08–0.77; n(total) = 6423 n(exposed to GDM) = 608; $P = 0.00001$, $I^2 = 89\%$ (Fig. 4).[10,11,13–15,24,25,48,51,56,57] Sensitivity analysis showed no difference in heterogeneity when removing low-quality studies (Supplementary Table S5). Twelve studies were not included in the meta-analysis.[5,18–21,23,32,34,38,44,52] One study reported significantly higher serum glucose in the GDM group than controls.[20] One study reported a significantly lower serum glucose value in those exposed to GDM compared to controls.[34] Two studies assessed cord blood glucose with both newborn cohorts;[33,49] however, no difference was seen between the GDM and non-GDM groups (MD −2.69, 95% CI −5.80 to 0.42; n(total) = 346, n(exposed to GDM) = 149; $P = 0.19$, $I^2 = 42\%$; Supplementary Fig. S8).[33,49] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Discussion

This systematic review aimed to assess the prevalence of conventional cardiovascular risk factors in those exposed to GDM *in utero* compared to those not exposed to GDM. There is an established link between pregnancy complications and vascular outcomes such as elevated markers of inflammation and impaired fetal aortic intimal media thickness (aIMT).[58,59] Many reviews on GDM focus on cardiovascular endpoints including myocardial infarction and coronary heart disease. Identifying risk factors for CVD is vital in planning screening strategies to identify those at risk of future CVD with the aim of targeting preventive interventions. Hence, this review is a comprehensive synthesis of evidence from published studies comparing the main conventional cardiovascular risk factors in those born after pregnancies complicated by GDM compared to controls and includes outcomes that have not been recently reviewed in the literature such as serum and cord blood lipids.

Our meta-analysis showed that offspring exposed to GDM *in utero* have 1.75 mmHg higher SBP than controls (95% CI 0.57–2.94, $n = 7309$, eight studies). Aceti *et al.* showed a similar association for offspring of GDM pregnancies (1.39 mmHg, 95% CI 0.00–2.77); 10 studies, $P = 0.05$).[6] They also showed a smaller,

nonsignificant increase in DBP for GDM offspring (0.75 mmHg, 95% CI −0.47–1.97; nine studies, $P = 0.23$).[6]

This meta-analysis primarily consists of adolescent cohorts (i.e., 10–19 years) with one 3-year-old cohort. Therefore, the existing literature is not sufficient to show the trend in blood pressure throughout childhood and adolescence. These trends have been previously reported in a few large cohort studies. Krishnaveni *et al.* demonstrated that SBP remains elevated in those exposed to GDM compared to unexposed controls throughout ages 5, 9.5, and 13.5 years.[13,18,38] A similar association was seen in another cohort at ages 8 and 15.[15,21] Therefore, it is important to assess childhood cohorts to affirm any trends seen in long-term cohort studies.

Blood pressure that is elevated in childhood and adolescence is predictive of adult hypertension.[60] Raitakari *et al.* found a positive correlation between SBP at 12–16 years with carotid artery intima medial thickness (C-IMT), which is a predictive factor of future CVD.[61] The association was weaker in males at 3–9 years age, but not among females. In a study by Oikonen et al., two abnormal child or youth blood pressure observations were shown to predict risk for hypertension in adulthood.[62] While the effect size in our meta-analysis is small and blood pressure for all studies is generally within normal reference range, it is known that even a 2-mmHg increase in SBP is associated with 10% higher mortality from stroke, and 7% higher mortality from ischemic heart disease in middle age.[63] Therefore, offspring exposed to GDM may benefit from frequent blood pressure monitoring throughout childhood and adolescence. Dietary interventions during gestation, such as implication of a low glycemic index (GI) diet, may benefit offspring and reduce the risk of high blood pressure. It has been demonstrated that children at 12 months old born to mothers at risk of GDM with a low GI diet have significantly thinner aIMT than those children whose mothers had a standard high fiber diet.[64]

Among 31,485 participants, it was shown that BMI *z*-score is marginally higher in those exposed to GDM offspring compared to controls (MD 0.11, 95% CI 0.02–0.20, $n = 31{,}485$, nine studies). We also observed a higher BMI in those exposed to GDM compared to controls (Supplementary Fig. S2); however, BMI is not an accurate predictor of childhood obesity. As an indicator of adiposity, BMI varies greatly based on fat and muscle mass; hence, it may be accurate for fatter children but not those who are lean.[65] The findings of this meta-analysis on BMI *z*-scores are consistent with the findings reported in the review by Kawasaki *et al.* (pooled MD 0.14, 95% CI 0.04–0.24, seven studies).[66]

Higher BMI in youth is associated with dyslipidemia, hypertension, and reduced insulin sensitivity.[67] Jago *et al.* showed that a change in BMI *z*-score at ages 11–14 was associated in a change in cardiovascular risk factors including an increase in SBP and DBP, HDL-C, LDL-C, and triglycerides at the same age.[67] The results of this meta-analysis support previous findings of higher BMI in those exposed to GDM *in utero* compared to controls.[5,24,45] GDM is associated with newborn fat mass, indicative of the intrauterine environment in the final trimester of pregnancy.[68,69] Higher birthweight is associated with markers of subclinical atherosclerosis such as mean carotid IMT.[70] Therefore, those who are exposed to GDM *in utero* appear to have risk factors for CVD very early in life. We could not assess the age distribution in very young children as majority of published studies were in adolescence. Hence, more studies among young children are required to support the association between gestational diabetes and increasing BMI *z*-score in offspring.

Our meta-analysis demonstrated that those exposed to GDM *in utero* have marginally higher fasting blood glucose levels (SMD 0.43, 95% CI 0.08–0.77, $n = 6423$, 11 studies), but not fasting insulin compared to controls. Kawasaki *et al.* showed no difference in fasting plasma glucose among 7–10 and 15 year olds exposed to GDM compared to controls.[66] Plasma glucose was significantly higher at age 20 years among those exposed to GDM compared to controls (MD 0.4 mmol/l, 95% CI 0.25–0.55, seven studies).[66] Our meta-analysis showed a similar association in predominantly childhood–adolescent cohorts, with one cohort during adulthood. We can support an association between exposure to GDM *in utero* and impaired glucose tolerance in offspring; however, as the effect size is minimal, further studies are required to support this association.

Abnormal plasma glucose is a requisite for prediabetes, and if untreated and coupled with increasing obesity may lead to early onset T2DM, which progresses at a faster rate in children and adolescence than in adults.[71] Adolescents diagnosed with T2DM are predicted to lose 15 years from their life expectancy compared to those without T2DM.[72] Hence, frequent fasting blood glucose monitoring in those exposed to GDM *in utero* may reduce the risk of T2DM in the future. Also, interventions during pregnancy may be beneficial as evidenced by studies showing that infants born to mothers with diet or insulin controlled GDM have lower fasting blood glucose than controls.[34]

We acknowledge some limitations of our analyses. Both GDM and CVD are multifactorial diseases, influenced by genetic and environmental factors. Smoking during pregnancy is shown to have significant effects on childhood adiposity and elevated blood pressure.[73,74] High prepregnancy BMI is associated with elevated SBP and DBP in offspring.[75] GDM is shown to cluster in families, and variants of different genes are associated with increased risk of GDM.[76] We could not adjust for such important covariates due to limitations in the data that were available. We were unable to examine female and male subgroups due to lack of power; however, it may be of interest for future studies to consider this as Li *et al.* showed that male offspring of GDM pregnancy had higher BMI than male controls and an increased risk of obesity, while there was no significant association in the cohort of females exposed to GDM compared to female controls.[37]

We did not identify any studies that looked at microvascular function in offspring of GDM. West *et al.* found that offspring of diabetic pregnancies had increased levels of circulating cellular adhesion molecules such as E-selectin and VCAM1, even when adjusted for maternal prepregnancy BMI.[77] Therefore, further studies on this topic are required.

Most of the studies that we assessed in the meta-analysis are follow-up at adolescence, there were few studies that conducted follow-up during early childhood as well as in adulthood, therefore, we are unable to show age distributions in outcomes assessed.

Observational studies may be subject to publication bias, although visual analysis of funnel plots for BMI and glucose showed a low chance of publication bias (Supplementary Fig. S9). However, these outcomes showed high heterogeneity based on I^2, and hence need to be interpreted with caution. We performed sensitivity analysis for relevant outcomes; however, we observed no difference in heterogeneity for the outcomes assessed (Supplementary Tables S3–S5).

Conclusion

Offspring exposed to GDM *in utero* demonstrate risk factors for CVD in childhood and adolescence, including elevated SBP, BMI *z*-score, and fasting plasma glucose that are evident from early life. These outcomes at a young age, if not monitored, can lead to

adverse vascular and metabolic health parameters resulting in CVD in adulthood. Regular blood pressure monitoring and weight control from a young age may benefit offspring exposed to GDM. Further long-term cohort studies also need to be established, which can adjust for important covariates and allow for affirmation of effect sizes.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174419000850.

Acknowledgements. None.

Financial Support. Supported by the Faculty of Health Sciences Divisional Scholarship (MMP), NHMRC Australian Public Health and Health Services Fellowship (APP1141382) (ZSL), Lloyd Cox Professorial Research Fellowship (CTR), and NHMRC Peter Doherty Bio Medical Postdoctoral Fellowship (APP1090778).

Conflict of Interest. None.

References

1. Andraweera PH, Dekker GA, Arstall M, Bianco-Miotto T, Roberts CT. Complications of pregnancy and future cardiovascular risk. *Encycl Cardiovasc Res Med*. 2018; 1, 643–650.
2. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009; 373, 1773–1779.
3. Federation ID. *IDF Diabetes Atlas*, 2017. International Diabetes Federation, Brussels, Belgium.
4. Metzger BE, Lowe LP, Dyer AR, *et al.* Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008; 358: 1991–2002.
5. Tam WH, Ma RCW, Ozaki R, *et al. In utero* exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. *Diabetes Care* 2017; 40, 679–686.
6. Aceti A, Santhakumaran S, Logan KM, *et al.* The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. *Diabetologia* 2012; 55, 3114–3127.
7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009; 6, e1000097.
8. Drahota ABE. RevMan Calculator. Cochrane Handbook, Part 2. The Cochrane Collaboration.
9. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M. *Newcastle-Ottawa Quality Assessment Scale*, 2013. Ottawa Hospital Research Institute, Canada.
10. Buzinaro EF, Berchieri CB, Haddad AL, Padovani CR, Pimenta Wde P. Overweight in adolescent offspring of women with hyperglycemia during pregnancy. *Arq Bras Endocrinol Metabol*. 2008; 52, 85–92.
11. Catalano PM, Farrell K, Thomas A, *et al.* Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr*. 2009; 90, 1303–1313.
12. Chang Y, Chen X, Zhang ZK. Intrauterine exposure to maternal diabetes is associated with adiposity in children at 6 years of age in China. *Biomed Environ Sci*. 2015; 28, 140–142.
13. Krishnaveni GV, Veena SR, Jones A, *et al.* Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress in adolescent Indians. *J Clin Endocrinol Metab*. 2015; 100, 986–993.
14. Patel S, Fraser A, Smith GD, *et al.* Associations of gestational diabetes, existing diabetes, and glycosuria with offspring obesity and cardiometabolic outcomes. *Diabetes Care* 2012; 35, 63–71.
15. Tam WH, Ma RCW, Yang X, *et al.* Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: a 15-year follow-up study. *Diabetes Care* 2010; 33, 1382–1384.
16. Wright CS, Rifas-Shiman SL, Rich-Edwards JW, Taveras EM, Gillman MW, Oken E. Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure. *Am J Hypertens*. 2009; 22, 215–220.
17. Pirkola J, Vaarasmaki M, Leinonen E, *et al.* Maternal type 1 and gestational diabetes: postnatal differences in insulin secretion in offspring at preschool age. *Pediatr Diabetes* 2008; 9, 583–589.
18. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CH. Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. *Diabetes Care* 2010; 33, 402–404.
19. Lee H, Jang HC, Park HK, Cho NH. Early manifestation of cardiovascular disease risk factors in offspring of mothers with previous history of gestational diabetes mellitus. *Diabetes Res Clin Pract*. 2007; 78, 238–245.
20. Page KA, Romero A, Enriquez F, Xiang AH, Buchanan TA. Increased fasting glucose levels in children exposed to gestational diabetes *in utero*. *Diabetes* 2013; 62, A364.
21. Tam WH, Ma RCW, Yang X, *et al.* Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus *in utero*. *Pediatrics* 2008; 122, 1229–1234.
22. Tsadok MA, Friedlander Y, Paltiel O, *et al.* Obesity and blood pressure in 17-year-old offspring of mothers with gestational diabetes: insights from the Jerusalem Perinatal Study. *Exp Diabetes Res*. 2011; 2011, 906154.
23. Vääräsmäki M, Pouta A, Elliot P, *et al.* Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. *Am J Epidemiol*. 2009; 169, 1209–1215.
24. Davis JN, Gunderson EP, Gyllenhammer LE, Goran MI. Impact of gestational diabetes mellitus on pubertal changes in adiposity and metabolic profiles in Latino offspring. *J Pediatr*. 2013; 162, 741–745.
25. Holder T, Giannini C, Santoro N, *et al.* A low disposition index in adolescent offspring of mothers with gestational diabetes: a risk marker for the development of impaired glucose tolerance in youth. *Diabetologia* 2014; 57, 2413–2420.
26. Kearney M, Perron J, Marc I, Weisnagel JS, Tchernof A, Robitaille J. Association of prenatal exposure to gestational diabetes with offspring body composition and regional body-fat distribution. *Diabetes* 2017; 66, A368.
27. Page KA, Romero A, Buchanan TA, Xiang AH. Gestational diabetes mellitus, maternal obesity, and adiposity in offspring. *J Pediatr*. 2014; 164, 807–810.
28. Whitaker RC, Pepe MS, Seidel KD, Wright JA, Knopp RH. Gestational diabetes and the risk of offspring obesity. *Pediatrics* 1998; 101, E9.
29. Baptiste-Roberts K, Nicholson W, Wang N-Y, Brancati F. Gestational diabetes and subsequent growth patterns of offspring: The National Collaborative Perinatal Project . . . [corrected] [published erratum appears in MATERN CHILD HEALTH J 2012; 16(1):266]. *Matern Child Health J*. 2012; 16, 125–132.
30. Lawlor DA, Fraser A, Lindsay RS, *et al.* Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. *Diabetologia* 2010; 53, 89–97.
31. Page KA, Romero A, Enriquez I, Chirikian V, Buchanan TA, Xiang A. Increased central adiposity in hispanic children exposed to gestational diabetes *in utero*. *Diabetes* 2012; 61, A517.
32. Retnakaran R, Ye C, Hanley A, *et al.* Effect of maternal gestational diabetes on the cardiovascular risk factor profile of infants at 1 year of age. *Nutr Metab Cardiovasc Dis*. 2013; 23, 1175–1181.
33. Eslamian L, Akbari S, Marsoosi V, Jamal A. Association between fetal overgrowth and metabolic parameters in cord blood of newborns of women with GDM. *Minerva Med*. 2013; 104, 317–324.
34. Jaber SM. Metabolic hormones profile in 2 weeks old healthy infants of diabetic mothers. *Saudi Med J*. 2006; 27, 1338–1345.
35. König AB, Junginger S, Reusch J, Louwen F, Badenhoop K. Gestational diabetes outcome in a single center study: higher BMI in children after six months. *Horm Metab Res*. 2014; 46, 804–809.
36. Zhao P, Liu E, Qiao Y, *et al.* Maternal gestational diabetes and childhood obesity at age 9–11: results of a multinational study. *Diabetologia* 2016; 59, 2339–2348.
37. Li S, Zhu Y, Yeung E, *et al.* Offspring risk of obesity in childhood, adolescence and adulthood in relation to gestational diabetes mellitus: a sex-specific association. *Int J Epidemiol*. 2017; 46, 1533–1541.

38. Krishnaveni GV, Hill JC, Leary SD, *et al.* Anthropometry, glucose tolerance, and insulin concentrations in Indian children: relationships to maternal glucose and insulin concentrations during pregnancy. *Diabetes Care* 2005; 28, 2919–2925.
39. Nehring I, Chmitorz A, Reulen H, von Kries R, Ensenauer R. Gestational diabetes predicts the risk of childhood overweight and abdominal circumference independent of maternal obesity. *Diabet Med*. 2013; 30, 1449–1456.
40. Nielsen GL, Dethlefsen C, Lundbye-Christensen S, Pedersen JF, Molsted-Pedersen L, Gillman MW. Adiposity in 277 young adult male offspring of women with diabetes compared with controls: a Danish population-based cohort study. *Acta Obstet Gynecol Scand*. 2012; 91, 838–843.
41. Pirkola J, Pouta A, Bloigu A, *et al.* Risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal prepregnancy overweight and gestational diabetes mellitus. *Diabetes Care* 2010; 33, 1115–1121.
42. Silverman BL, Rizzo TA, Cho NH, Metzger BE. Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. *Diabetes Care* 1998; 21 (Suppl 2) B142–B149.
43. Vohr BR, McGarvey ST, Garcia Coll C. Effects of maternal gestational diabetes and adiposity on neonatal adiposity and blood pressure. *Diabetes Care* 1995; 18, 467–475.
44. Vohr BR, McGarvey ST, Tucker R. Effects of maternal gestational diabetes on offspring adiposity at 4–7 years of age. *Diabetes Care* 1999; 22: 1284–1291.
45. Farfel A, Rabinovitz R, Kampino G, *et al.* Children of mothers with pregestational and gestational diabetes tend to be overweight at age 17. *Horm Res Paediatr*. 2013; 80, 414.
46. Rutkowska J, Bandurska-Stankiewicz E, Wiatr-Bykowska D, Myszka-Podgórska K, Kuglarz E, Matuszewski W. The growth patterns in children born to mothers with gestational diabetes mellitus. *Diabetologia* 2015; 58, S488.
47. Le Moullec N, Fianu A, Maillard O, *et al.* Sexual dimorphism in the association between gestational diabetes mellitus and overweight in offspring at 5–7 years: the OBEGEST cohort study. *PLoS One* 2018; 13, e0195531.
48. Teng ZJ, Xia MJ, Qu CH, Yu HX. Long-term risk of metabolic disorders in gestational diabetes mellitus mothers and offspring. *Biomed Res (India)* 2017; 28, 4466–4470.
49. López Morales CM, Brito Zurita OR, González Heredia R, Cruz López M, Méndez Padrón A, Matute Briseño JA. Placental atherosclerosis and markers of endothelial dysfunction in infants born to mothers with gestational diabetes. *Medicina Clinica*. 2016; 147, 95–100.
50. Miettinen HE, Rono K, Koivusalo SB, Eriksson JG, Gylling H. Effect of gestational diabetes mellitus on newborn cholesterol metabolism. *Atherosclerosis* 2018; 275, 346–351.
51. Chandler-Laney PC, Bush NC, Granger WM, Rouse DJ, Mancuso MS, Gower BA. Overweight status and intrauterine exposure to gestational diabetes are associated with children's metabolic health. *Pediatr Obes*. 2012; 7, 44–52.
52. Borgoño CA, Hamilton JK, Ye C, *et al.* Determinants of insulin resistance in infants at age 1 year: impact of gestational diabetes mellitus. *Diabetes Care* 2012; 35, 1795–1797.
53. Bozkurt L, Göbl CS, Rami-Merhar B, *et al.* The cross-link between adipokines, insulin resistance and obesity in offspring of diabetic pregnancies. *Horm Res Paediatr*. 2016; 86, 300–308.
54. Plagemann A, Harder T, Kohlhoff R, Rohde W, Dorner G. Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. *Int J Obes Relat Metab Disord*. 1997; 21, 451–456.
55. Plagemann A, Harder T, Kohlhoff R, Rohde W, Dorner G. Glucose tolerance and insulin secretion in children of mothers with pregestational IDDM or gestational diabetes. *Diabetologia* 1997; 40, 1094–1100.
56. Clausen TD, Mathiesen ER, Hansen T, *et al.* High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care* 2008; 31, 340–346.
57. Wilk M, Horodnicka-Jozwa A, Moleda P, *et al.* Assessment of selected carbohydrate parameters in children exposed to gestational diabetes *in utero*. *Neuro Endocrinol Lett*. 2015; 36, 504–510.
58. Visentin S, Londero AP, Bellamio B, *et al.* Fetal endothelial remodeling in late-onset gestational hypertension. *Am J Hypertens*. 2016; 29, 273–279.
59. Visentin S, Lapolla A, Londero AP, *et al.* Adiponectin levels are reduced while markers of systemic inflammation and aortic remodelling are increased in intrauterine growth restricted mother-child couple. *Biomed Res Int*. 2014; 2014, 401595.
60. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation* 2008; 117, 3171–3180.
61. Raitakari OT, Juonala M, Kähönen M, *et al.* Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the cardiovascular risk in Young Finns Study. *JAMA* 2003; 290, 2277–2283.
62. Oikonen M, Nuotio J, Magnussen CG, *et al.* Repeated blood pressure measurements in childhood in prediction of hypertension in adulthood. *Hypertension* 2016; 67, 41–47.
63. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360, 1903–1913.
64. Kizirian NV, Kong Y, Muirhead R, *et al.* Effects of a low-glycemic index diet during pregnancy on offspring growth, body composition, and vascular health: a pilot randomized controlled trial. *Am J Clin Nutr*. 2016; 103, 1073–1082.
65. Freedman DS, Sherry B. The validity of BMI as an indicator of body fatness and risk among children. *Pediatrics* 2009; 124, Suppl 1, S23–34.
66. Kawasaki M, Arata N, Miyazaki C, *et al.* Obesity and abnormal glucose tolerance in offspring of diabetic mothers: a systematic review and meta-analysis. *PLoS One* 2018; 13, e0190676.
67. Jago R, Mendoza JA, Chen T, Baranowski T. Longitudinal associations between BMI, waist circumference, and cardiometabolic risk in US youth: monitoring implications. *Obesity (Silver Spring, Md)* 2013; 21, E271–E279.
68. Dissanayake HU, Anderson L, McMullan RL, *et al.* Influence of maternal and placental factors on newborn body composition. *J Paediatr Child Health* 2019. doi: 10.1111/jpc.14565. [Epub ahead of print].
69. Enzi G, Inelmen EM, Caretta F, Villani F, Zanardo V, DeBiasi F. Development of adipose tissue in newborns of gestational-diabetic and insulin-dependent diabetic mothers. *Diabetes* 1980; 29, 100–104.
70. Skilton MR, Siitonen N, Wurtz P, *et al.* High birth weight is associated with obesity and increased carotid wall thickness in young adults: the cardiovascular risk in young Finns study. *Arterioscler Thromb Vasc Biol*. 2014; 34, 1064–1068.
71. D'Adamo E, Caprio S. Type 2 diabetes in youth: epidemiology and pathophysiology. *Diabetes Care* 2011; 34, Suppl 2, S161–S165.
72. Rhodes ET, Prosser LA, Hoerger TJ, Lieu T, Ludwig DS, Laffel LM. Estimated morbidity and mortality in adolescents and young adults diagnosed with type 2 diabetes mellitus. (Report) (clinical report). *Diabetic Med*. 2012; 29, 453.
73. Li L, Peters H, Gama A, *et al.* Maternal smoking in pregnancy association with childhood adiposity and blood pressure. *Pediatr Obes*. 2016; 11, 202–209.
74. Riedel C, Fenske N, Muller MJ, *et al.* Differences in BMI z-scores between offspring of smoking and nonsmoking mothers: a longitudinal study of German children from birth through 14 years of age. *Environ Health Perspect*. 2014; 122, 761–767.
75. Gademan MG, van Eijsden M, Roseboom TJ, van der Post JA, Stronks K, Vrijkotte TG. Maternal prepregnancy body mass index and their children's blood pressure and resting cardiac autonomic balance at age 5 to 6 years. *Hypertension* 2013; 62, 641–647.
76. Shaat N, Groop L. Genetics of gestational diabetes mellitus. *Curr Med Chem*. 2007; 14, 569–83.

77. West NA, Crume TL, Maligie MA, Dabelea D. Cardiovascular risk factors in children exposed to maternal diabetes *in utero*. *Diabetologia* 2011; 54, 504–547.
78. Wang J, Pan L, Liu E, *et al.* Gestational diabetes and offspring's growth from birth to 6 years old. *Int J Obes*. 2019; 43, 663–672.
79. Kaseva N, Vaarasmaki M, Matinolli HM, *et al.* Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later: evidence from two birth cohort studies. *Int J Obes (Lond)*. 2018; 42, 872–879.
80. Hammoud NM, De Valk HW, Biesma DH, Visser GHA. Intrauterine adiposity and BMI in 4- to 5-year-old offspring from diabetic pregnancies. *Neonatology*. 2017; 111, 177–181.
81. Hakanen T, Saha MT, Salo MK, *et al.* Mothers with gestational diabetes are more likely to give birth to children who experience early weight problems. *Acta Paediatr Int J Paediatr*. 2016; 105, 1166–1172.
82. Page KA, Wang X, Romero A, Buchanan TA, Xiang AH. Insulin sensitivity and β-cell function are reduced in children exposed to gestational diabetes in utero. *Diabetes*. 2015; 64, A94.
83. Zhao YL, Ma RM, Lao TT, *et al.* Maternal gestational diabetes mellitus and overweight and obesity in offspring: a study in Chinese children. *J Dev Orig Health Dis*. 2015; 6, 479–484.
84. Pham MT, Brubaker K, Pruett K, Caughey AB. Risk of childhood obesity in the toddler offspring of mothers with gestational diabetes. *Obstet Gynecol*. 2013; 121, 976–982.
85. Jahan S, Ahmed CM, Zinnat R, *et al.* Influence of maternal diabetes on serum leptinemic and insulinemic status of the offspring: a case study of selected patients in a tertiary care hospital in Bangladesh. *Diabetes Metab Syndr*. 2011; 5, 33–37.
86. Boerschmann H, Pfluger M, Henneberger L, Ziegler AG, Hummel S. Prevalence and predictors of overweight and insulin resistance in offspring of mothers with gestational diabetes mellitus. *Diabetes Care*. 2010; 33, 1845–1849.
87. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics*. 2005; 115, e290–e296.
78. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics*. 2003; 111, e221–e226.
89. Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers. Relationship to fetal hyperinsulinism. *Diabetes Care*. 1995; 18, 611–617.

Appendix 3: Publication for Author response: Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero:* a systematic review and meta-analysis

Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

Commentary

Cite this article: Pathirana MM, Lassi ZS, Roberts CT, and Andraweera PH (2020) Author response: cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. *Journal of Developmental Origins of Health and Disease* **11**: 244–245. doi: 10.1017/S2040174420000185

Received: 26 February 2020
Accepted: 28 February 2020

Address for correspondence:
Prabha Andraweera, Adelaide Medical School, Robinson Research Institute, The University of Adelaide, South Australia, Adelaide 5005, Australia.
Email: prabha.andraweera@adelaide.edu.au

CAMBRIDGE UNIVERSITY PRESS

Author response: cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis

Maleesa M. Pathirana, Zohra S. Lassi, Claire T. Roberts and Prabha H. Andraweera

Adelaide Medical School, The Robinson Research Institute, The University of Adelaide, Adelaide 5005, Australia

Abstract

This commentary is an author response to Lu and Wang, regarding the manuscript entitled 'Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: Systematic review and meta-analysis'. We address their concern regarding duplication of studies in the meta-analysis and the quality of included studies.

Dear editor,

We thank Dr. Lu and Dr. Wang for their comments regarding our systematic review and meta-analysis on cardiovascular disease in offspring exposed to gestational diabetes mellitus *in utero*.[1] Their comments highlight important considerations regarding study quality in systematic review and meta-analyses and statistical methods put in place to address low-quality studies.

Although we have already specified our methodology regarding including publications of multiple cohorts in the meta-analysis, we appreciate the opportunity to provide further clarity. There has been the understanding that the cohort publications published by Krishnaveni *et al.*, Tam *et al.* and Vohr *et al.*, which we have included in our systematic review, have been doubly reported in the meta-analysis.[2-9] In our methods under the 'included studies' header, it states that 'when the same cohort was reported in multiple publications at different ages, the study reporting on the older age group was included in the meta-analysis'. We only used the publications of Krishnaveni *et al.*[4] and Tam *et al.* [7] in our meta-analysis as these studies have data on the most recent follow-up (i.e., 15 years of age for both cohorts).[3,7] The publications that have been mentioned in the previous commentary are only reported as supplementary data (Supplementary Table 1) but not in the meta-analyses. The Vohr *et al.* studies are also only reported in the supplementary data. We included 59 studies from 54 cohorts in our systematic review, and only 25 studies were used in the meta-analysis (Fig. 1). The reasons for not including 34 studies in the meta-analysis include but are not limited to: (1) reporting the cohort at an earlier follow-up and thus not being the most recent publication with the oldest follow-up age (in the case of Krishnaveni and Tam studies); (2) some studies not reporting a control group value (in the case of Vohr *et al.*[9]); (3) studies only including adjusted mean values that we could not incorporate in a meta-analysis due to limitation in the number of studies; (4) being unable to include median and interquartile range values in the analysis. While we endeavoured to contact authors for unadjusted and unknown values in the meta-analysis, we received a 44% response rate. It would be counter-intuitive to exclude these studies all together after trying to contact the authors for appropriate data; it seemed best to report these data in a supplementary table if it was not suitable for the analysis, thereby providing readers a more comprehensive review of the literature. Furthermore, in our protocol, we were interested in subgroup analyses stratified by childhood, adolescence and adulthood to determine if any of the cardiovascular risk factors appeared at certain points during the lifecourse in offspring exposed to Gestational diabetes mellitus *in utero*. However, we did not have sufficient number of studies to complete any subgroup analyses. We have addressed this in our discussion.

The second point mentioned by Lu and Wang regarding using only high-quality studies in a meta-analysis is an important one to address. While we have included studies of varying study quality, we must emphasise that our methods address how we handle low-quality studies. All 59 included studies have been verified by two authors and underwent quality assessment using the Newcastle–Ottawa Scale (NOS), which is a recommended quality assessment tool used for observational studies. The NOS broadly assesses study quality, including study selection, definition and comparability of cases and controls, assessment and reporting of outcome. We only found nine studies of low quality. We performed sensitivity analyses to omit all

low-quality studies from the meta-analysis, thereby assessing whether these studies would have influenced the effect size of the outcomes. Performing a quality assessment of studies and performing sensitivity analyses are common protocols for many meta-analyses.[10,11] Sensitivity analyses were done for only four outcomes, as these were the only outcomes that included low-quality studies. Our sensitivity analysis tables reported as supplementary data show that there was no significant difference between the effect estimates when removing the low-quality studies, based on I^2 and chi-square value. Therefore, the effect size of our meta-analysis is unaffected by these low-quality studies. Henceforth, the heterogeneity in these analyses needs to be explored in other avenues, including through visual analysis of funnel plots for heterogeneity (which in our analysis were all standard), through performing analyses with values adjusted for important covariates and subgroup analysis (both actions that we were unable to do).

Including all relevant studies and reporting them allow for an extensive scope of the literature, and it is important to assess and report which of this literature is high, moderate and low quality to ensure that clinical decision-making is based on the best-quality evidence.

References

1. Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. *J Dev Origins Health Dis*. 2020, 1–18. doi:10.1017/s2040174419000850.
2. Krishnaveni GV, Hill JC, Leary SD, *et al.* Anthropometry, glucose tolerance, and insulin concentrations in Indian children: relationships to maternal glucose and insulin concentrations during pregnancy. *Diabetes Care.* 2005; 28(12), 2919–2925.
3. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CH. Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. *Diabetes Care.* 2010; 33(2), 402–404.
4. Krishnaveni GV, Veena SR, Jones A, *et al.* Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress in adolescent Indians. *J Clin Endocrinol Metab.* 2015; 100(3), 986–993.
5. Tam WH, Ma RCW, Ozaki R, *et al.* In utero exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. *Diabetes Care.* 2017; 40(5), 679–686.
6. Tam WH, Ma RCW, Yang X, *et al.* Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus in utero. *Pediatrics.* 2008; 122(6), 1229–1234.
7. Tam WH, Ma RCW, Yang X, *et al.* Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: a15-year follow-up study. *Diabetes Care.* 2010; 33(6), 1382–1384.
8. Vohr BR, McGarvey ST, Garcia Coll C. Effects of maternal gestational diabetes and adiposity on neonatal adiposity and blood pressure. *Diabetes Care.* 1995; 18(4), 467–475.
9. Vohr BR, McGarvey ST, Tucker R. Effects of maternal gestational diabetes on offspring adiposity at 4-7 years of age. *Diabetes Care.* 1999; 22(8), 1284–1291.
10. Aceti A, Santhakumaran S, Logan KM, *et al.* The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-Analysis. *Diabetologia.* 2012; 55(11), 3114–3127.
11. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet.* 2009; 373(9677), 1773–1779.

Appendix 4: Publication for Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analyses

Endocrine (2021) 71:310–320
https://doi.org/10.1007/s12020-020-02492-1

META- ANALYSIS

Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis

Maleesa M. Pathirana[1,2] · Zohra S. Lassi[1,2] · Anna Ali[3,4] · Margaret A. Arstall[2,5] · Claire T. Roberts[1,6] · Prabha H. Andraweera[1,5]

Received: 10 July 2020 / Accepted: 3 September 2020 / Published online: 15 September 2020

Abstract

Purpose The primary aim of this systematic review and meta-analysis was to determine the association between gestational diabetes mellitus (GDM) and metabolic syndrome (MetS) in women and children. Our secondary aim was to assess the development of MetS with respect to the elapsed time postpartum at which MetS was diagnosed.

Methods This review is registered with PROSPERO (CRD42020173319). PubMed, CINHAL, SCOPUS, and EMBASE databases were searched. Studies reporting on the rate of MetS in pregnant women with GDM, the rate of MetS in women with a history of GDM, and the rate of MetS in offspring exposed to GDM in utero compared to healthy controls were selected.

Results We identified 588 articles from the literature search. Fifty-one studies were included in the review and of those 35 were included in the meta-analysis. Quantitative summary measures showed that women with a history of GDM had an increased risk of developing MetS compared to those without a history of GDM (RR 2.36, 95% CI 1.77–3.14, 29 studies, 13,390 participants; heterogeneity: χ^2 $p < 0.00001$; $I^2 = 93\%$). Offspring exposed to GDM in utero have an increased risk of developing MetS compared to those not exposed to GDM in utero. (RR 2.07, 95% CI 1.26–3.42, three studies, 4,421 participants; heterogeneity: χ^2 $p = 0.33$; $I^2 = 12\%$). Women diagnosed with GDM have an increased risk of developing MetS during pregnancy (RR 20.51, 95% CI 5.04–83.55; three studies, 406 participants; heterogeneity: χ^2 $p = 0.96$; $I^2 = 0\%$). Subgroup analysis revealed that MetS is diagnosed as early as <1 year postpartum in women with a history of GDM.

Conclusions/interpretation Women with GDM have an increased risk of developing MetS during pregnancy. Women with a history of GDM and offspring exposed to GDM in utero have higher risks of developing MetS compared to those with no history of GDM. Metabolic syndrome in women with a history of GDM is seen as early as <1 year postpartum.

Keywords Gestational diabetes · Women's health · Metabolic syndrome · Childhood obesity

Supplementary information The online version of this article (https://doi.org/10.1007/s12020-020-02492-1) contains supplementary material, which is available to authorized users.

✉ Prabha H. Andraweera
prabha.andraweera@adelaide.edu.au

[1] Adelaide Medical School and Robinson Research Institute, The University of Adelaide, Adelaide, SA 5005, Australia

[2] Faculty of Health and Medical Sciences, Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia

[3] Health Performance and Policy Research Unit, Basil Hetzel Institute, The University of Adelaide, Adelaide, SA, Australia

[4] Adelaide G-TRAC Centre and CRE Frailty and Healthy Ageing Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia

[5] Department of Cardiology, Lyell McEwin Hospital, Elizabeth Vale, SA, Australia

[6] Flinders Health and Medical Research Institute, Flinders University, Bedford Park, SA 5042, Australia

Abbreviations

MetS	metabolic syndrome
CVD	cardiovascular disease
GDM	gestational diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is impairment of glucose that is first diagnosed during pregnancy, hence different from both type I and II diabetes mellitus. GDM is estimated to affect one in seven pregnancies [1]. Women with a history of GDM are more likely to be obese, have dyslipidaemia and hypertension during the postpartum period [2]. These women also have an approximately sevenfold increased risk of developing type II diabetes mellitus (T2DM) later in life [3]. The diagnostic criteria for GDM have changed as of recent, being defined as fasting glycaemia ≥5.1 mmol/l, or 1-h plasma glucose ≥10.0 mmol/l and 2-h plasma glucose: ≥8.5 mmol/l with a 75 g oral glucose tolerance test [4].

Metabolic syndrome (MetS) is defined as a cluster of metabolic disorders, conventionally defined as three or more of the following: central obesity, reduced high-density lipoprotein cholesterol, hypertriglyceridemia, hyperglycemia, and hypertension. However, the cut-offs for these individual components of MetS are different between definitions [5, 6]. Both GDM and MetS share a similar etiology and both increase the risk of chronic diseases such as T2DM and cardiovascular disease (CVD) [3, 7–9].

GDM is promoted by an inability of β-cells to undergo expansion. Therefore, β-cells are unable to compensate for the highly insulin resistant state leading to the subsequent elevation of glucose during pregnancy [10]. Development of pregnancy complications, such as GDM, is influenced by prepregnancy lifestyle and metabolic characteristics [11]. Women with MetS are already in a state of pro-inflammation and insulin resistance [12], therefore it is possible that when they become pregnant, they are more susceptible to developing GDM [13]. This association has not been explored in a systematic review and meta-analysis. Furthermore, GDM increases the risk of developing CVD in later life and ~50% of women who develop GDM go on to develop T2DM later in life [14]. Therefore, women who may not have MetS in pregnancy or only present with one or two components of MetS may be at risk of developing MetS postpartum. A meta-analysis in 2014 showed that women who experience GDM have a higher risk of developing MetS than women with a normal pregnancy [15]. However, the studies included in the above meta-analysis were conducted before the implementation of the new International Association of Diabetes in Pregnancy Study Group (IADPSG) guidelines that recommended a lowering of the glucose threshold for the diagnosis of GDM [16]. As the new guidelines are known to increase the number of women diagnosed with GDM, it is possible that the number of metabolic risk factors in women who had GDM will also increase. Children exposed to GDM in utero may also be more susceptible to developing MetS, as it has been shown that they have higher systolic blood pressure (SBP), body mass index (BMI), and blood glucose than those not exposed to GDM in utero [17]. To our knowledge, no systematic review has assessed the risk for MetS among children born to pregnancies complicated by GDM. Even small improvements in the components of MetS such as hypertension and dyslipidaemia can significantly reduce the risk of ischemic heart disease in young and middle age adults [18–20] and reducing childhood adiposity can reduce the risk of CVD later in life [21].

Therefore, the objective of our systematic review and meta-analysis was to evaluate the association between GDM and MetS by determining (1) the risk of MetS in pregnancy among women who are diagnosed with GDM, (2) the risk for postpartum MetS among women who experienced GDM, and (3) the risk of developing MetS in children born to pregnancies complicated by GDM.

Methods

The review protocol is registered in PROSPERO (CRD42020173319). The review was undertaken with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [22].

Search strategy

All studies describing the association between GDM and MetS were identified by searching the following electronic databases: PubMed, CINAHL, SCOPUS, and EMBASE with an end search date of February 18, 2020. The search was conducted by Z.S.L. The search strategy included the terms ("gestational diabetes*" OR "pregnancy induced diabetes") AND ("metabolic syndrome" OR "insulin resistance syndrome" OR "syndrome X") and is detailed in Appendix S1. We included observational studies (case-control, cross-sectional, and cohort). Bibliographies of previously conducted systematic reviews and meta-analyses on closely related topics, and eligible studies were checked for additional studies. All identified studies were independently assessed for relevance by two authors (M.M.P. and A.A.). Two authors (M.M.P. and A.A.) independently extracted data, and discrepancies were resolved by discussion with Z.S.L. and P.H.A.

Studies were eligible for inclusion if they reported the number of cases of MetS in (1) pregnant women diagnosed

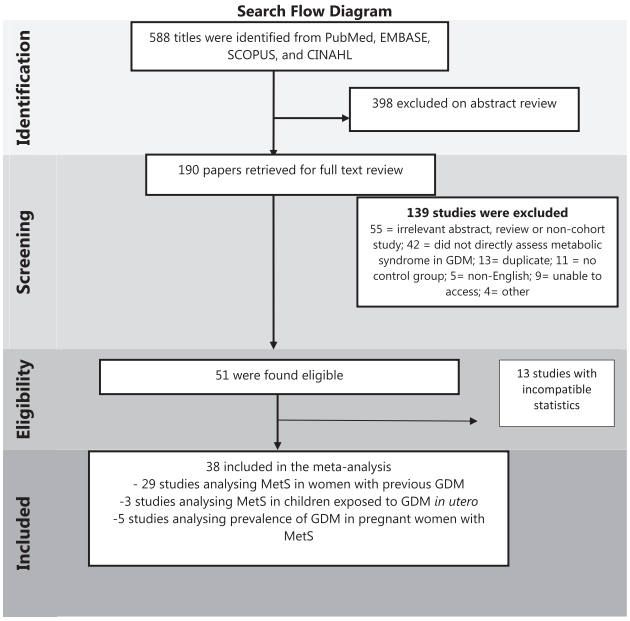


Fig. 1 Flow chart showing selection of eligable studies

with GDM, (2) women with a history of GDM, compared to women who did not experience/have a history of GDM, and (3) those exposed to GDM in utero compared to those not exposed to GDM in utero. We included studies that defined GDM based on the IADPSG guidelines [23]. However, since the diagnostic criteria have been revised recently, we included studies that used prior recommended diagnostic criteria of GDM including the 1999 World Health Organization (WHO) definition [5], and other regional and study-specific definitions as detailed in Table S1 [5, 24–31]. MetS was defined based on the definitions of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP-III) [6], International Diabetes Federation (IDF) [32], the WHO [5], or the American Heart Association [33]. Because there is no validated definition of MetS in children and pregnant women, we accepted variations of current guidelines and study-specific definitions. The definitions of GDM and MetS of included studies are detailed in Table S1. Studies that did not include a definition of GDM or MetS, those that did not define the case and control groups, and those that compared women with GDM in pregnancy/postpartum, and those exposed to GDM in utero to another risk group were excluded.

Statistical analysis

Data were extracted independently and in duplicate for the number of MetS cases. We analyzed all studies collectively as an overall analysis, and subsequently stratified into subgroups based on the time of follow up postpartum as: <1 year, 1–5 years, 5–10 years, and 10+ years from the index pregnancy. Some studies analyzed the rate of MetS based on the multiple definitions. Therefore, when assessing data from those studies, the NCEP-ATP-III definition was used in the overall analysis as the majority of studies used this definition. However, we conducted subgroup analyses based on the rate of MetS defined according to the NCEP-ATP-III, IDF, and WHO guidelines. We performed an ad hoc analysis based on ethnicity, but only for Asian and Caucasian ethnicities, as these were the most commonly reported ethnicities. When the same cohort was assessed multiple times during the postpartum period, the study with the largest sample size was used in the overall analysis. For the analysis on offspring exposed to GDM in utero, the oldest cohort was used in the meta-analysis. We considered studies published in English. We did not need to contact any authors for additional information, as only one dichotomous outcome was evaluated, and only studies reporting on the outcome were eligible.

The following data were collected from each included study: definition of GDM, definition of MetS, time of postpartum follow up (number of years since index pregnancy for both women and children), or gestational age (week) at which MetS and GDM were diagnosed during pregnancy, number of cases (those who experienced GDM) and controls (those who did not experience GDM), birthweight of offspring and gestational age at delivery for both cases and controls.

The meta-analysis was performed using RevMan software (Review Manager Version 5.3) based on an inverse variance method. As per protocol, the random effects model was selected to account for the differences in diagnostic criteria of GDM. For each outcome measure, the number of events and the total number of participants were used in the meta-analysis to analyze the risk difference. If the number was only reported as a percentage, then the number of participants/events was calculated based on the total sample size for each group. The analysis was cross-checked and discrepancies were resolved by discussion (P.H.A. and M.M.P.).

Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the Chi² p value was <0.1. Data from eligible studies that could not be included in the meta-analysis are included in Table S2. To assess publication bias, funnel plots were used for the primary outcome. The methodological quality was assessed using the National Heart, Lung and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and are presented in the Supplementary data (Table S3) [34]. Sensitivity analysis was performed to evaluate heterogeneity for outcomes after excluding low-moderate quality studies (i.e., studies that were considered of low-moderate quality in the NHLBI Quality assessment tool after discussion with authors).

Results

The literature search identified 588 articles. One hundred and ninety articles were eligible for full text review. Of these, 51 were included in the review and 35 were included in the meta-analyses (Table S1). The reasons for excluding 139 studies are detailed in Fig. 1. The quality assessment showed that all studies were of moderate to high quality (Table S3).

Risk of MetS in pregnancy among women diagnosed with GDM

Eight studies were included in the assessment of this outcome [13, 35–41], of which three studies were included in the meta-analysis [35–37]. All three studies assessed GDM and MetS at the same time (i.e., ~24–32 weeks gestation). Pooled analysis showed that women diagnosed with GDM had an increased risk of MetS in pregnancy (RR 20.51, 95% CI 5.04–83.55; three studies, 406 participants; heterogeneity: χ^2 $p = 0.96$; $I^2 = 0\%$) (Fig. 2a). Five studies were not included in the meta-analysis [13, 38–41], with four showing an increased risk of developing GDM in women who are diagnosed with MetS during pregnancy [39, 40, 42, 43] (Table S2).

Risk of MetS in women with a history of GDM

Thirty-five studies were included in the assessment of this outcome [42, 44–78], of which 29 studies were included in the meta-analysis [30, 42, 44–71]. Pooled analysis showed that women with a history of GDM had a significantly increased risk of developing MetS (RR 2.36, 95% CI 1.77–3.14; 29 studies, 13,390 participants; heterogeneity: χ^2 $p < 0.00001$; $I^2 = 93\%$) (Fig. 2b). Of the six studies that were not included in the meta-analysis [72–78], one showed an increase in prevalence of MetS among women with a history of GDM compared to controls [51] (Table S2). Sensitivity analysis after excluding the studies of moderate quality resulted in a slight reduction in heterogeneity (χ^2 $p < 0.00001$; $I^2 = 78\%$) (Fig. S1). Assessment of the funnel plot of the meta-analysis revealed moderate publication bias (Fig. S2).

Risk of MetS in offspring exposed to GDM in utero

Four studies were included in the assessment of this outcome [79–82], of which three studies were included in the meta-analysis [79–81]. Pooled analysis showed that offspring exposed to GDM in utero had a significantly increased risk of developing MetS (RR 2.07, 95% CI 1.26–3.42; three studies, 4421 participants; heterogeneity: χ^2 p 0.33; $I^2 = 12\%$) (Fig. 2c). The study that was not included in the meta-analysis showed an increased MetS severity Z-score in those exposed to GDM in utero compared to controls [82] (Table S2).

Subgroup analyses

We conducted subgroup analyses based on the time of postpartum follow up among women with a history of GDM. The results are shown in Table S4. The risk of developing MetS was significantly increased in women with a history of GDM at <1 year postpartum (RR 1.95, 95% CI 1.15–3.28, three studies, 850 participants; heterogeneity χ^2 $p = 0.09$; $I^2 = 59\%$), 1–5 years postpartum (RR 2.99, 95% CI 2.14–4.18, 18 studies, 7.328 participants; heterogeneity χ^2 $p < 0.00001$; $I^2 = 70\%$), 5–10 years postpartum (RR 2.29, 95% CI 1.62–3.25, nine studies, 4518 participants; heterogeneity χ^2 $p < 0.0001$; $I^2 = 79\%$), and >10 years postpartum (RR 2.07 95% CI 1.22–3.50, six studies, 3037 participants; heterogeneity χ^2 $p < 0.00001$; $I^2 = 94\%$).

We conducted a subgroup analysis to evaluate the risk of developing MetS in women with a history of GDM based on the three most common definitions of MetS (i.e., NCEP-ATP-III, IDF, and WHO). A significantly increased risk of MetS was demonstrated for women with a history of GDM compared to women without a history of GDM, irrespective of the definition used to diagnose MetS (NCEP-ATP-III: RR 2.58 95% CI 1.72–3.87, 20 studies, 8768 participants; heterogeneity χ^2 $p < 0.00001$; $I^2 = 94\%$; IDF: RR 2.15 95% CI 1.60–2.90, 11 studies, 5615 participants; heterogeneity χ^2 $p < 0.00001$; $I^2 = 79\%$; WHO: RR 2.99 95% CI 2.51–3.57, five studies, 3433 participants; heterogeneity χ^2 $p = 0.69$; $I^2 = 0\%$) (Table S5). We performed an ad hoc analysis based on ethnicity (Asian and Caucasian) and found that there was a similar increased risk of MetS for women with a history of GDM for both ethnicities (Table S6).

Discussion

Main findings

Our meta-analysis revealed that women with a history of GDM are at a significantly increased risk of developing MetS later in life, and that this risk is seen as early as <1 year postpartum. Our results also demonstrate that the risk for MetS in pregnancy is higher among women diagnosed with GDM and that children born to women who experience GDM have an increased risk of developing MetS in later life.

Strengths and limitations

This systematic review and meta-analysis was a comprehensive review of the literature on the association between

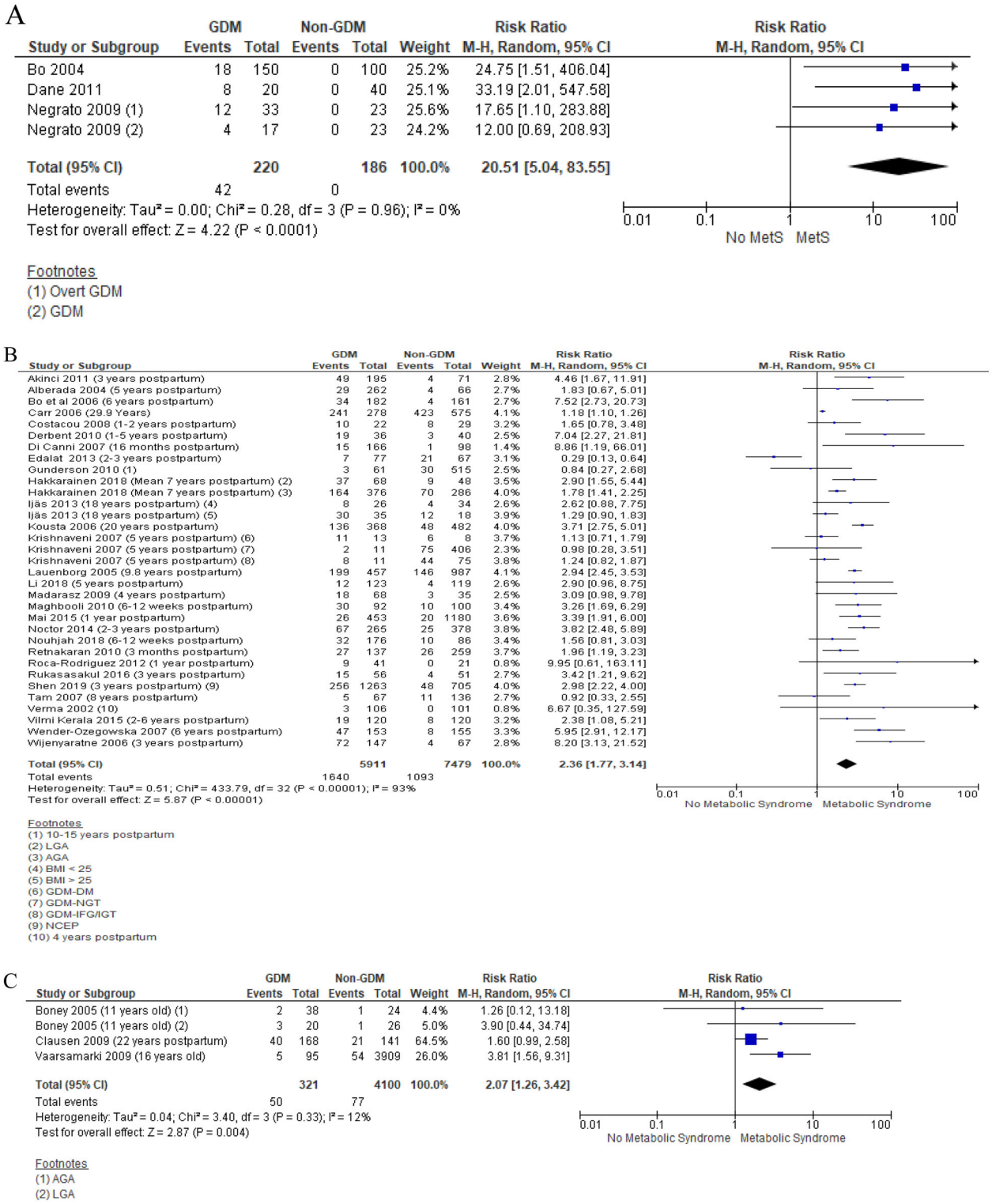


Fig. 2 **a** Meta-analysis showing the risk of developing MetS during pregnancy in women with GDM. **b** Meta-analysis showing the risk of developing metabolic syndrome in women with previous GDM. **c** Meta-analysis showing the risk of developing GDM in those born to women with GDM

GDM and MetS, among women and their offspring. There has not been a systematic review and meta-analysis that investigated the association between GDM and MetS in pregnant women and offspring, and no review has evaluated the association between GDM and MetS in women with a history of GDM after the change of guidelines in 2013 [15].

Many environmental and genetic factors contribute to the risk for GDM. There are certain candidate genes that are associated with T2DM and GDM that mainly influence insulin secretion [83]. Obesity and GDM share the same causal pathway, through elevation of free fatty acids and dysregulation of cytokines to promote insulin resistance [84, 85]. Common risk factors such as advanced maternal age, familial history of T2DM or GDM in a first-degree relative (either mother or sister) also contribute to a higher risk for GDM [86]. Therefore, it is unclear whether MetS in overweight/obese women with a history of GDM is due to the disease phenotype, or due to a preexisting predisposition. Asian ethnicity is a significant risk factor for GDM [86] and diagnosis of MetS can also vary based on ethnicity. Therefore, we assessed the influence of ethnicity through an ad hoc analysis and found that both Caucasian and Asian ethnicities conferred similar increased risks for MetS in women with a history of GDM (Table S6). Women and men have different CVD risks, particularly with regard to obesity, as men generally have greater muscle mass and women have higher fat mass. Research into a modified female definition of MetS may be important, considering the differences in body composition and conventional risk factors between males and females and the higher risk of CVD among women who experience major pregnancy complications [87].

Our results on the risk for MetS among women with a history of GDM showed substantial heterogeneity. However, when we performed subgroup analyses based on the time of diagnosis of MetS, definition of MetS and ethnicity, heterogeneity was substantially reduced (Tables S4 and S5). Sensitivity analysis also showed a reduction in heterogeneity after removing studies of moderate quality. Funnel plot assessment revealed a moderate degree of publication bias (Fig. S2). It is difficult to elucidate the reason for heterogeneity in aggregate data, but it is typically due to differences in study design, differences in definitions (i.e., MetS and GDM definitions), years of postpartum follow-up, and study populations. The heterogeneity that was observed in our analysis could also be attributed to genetic and environmental factors. Large, well-characterized longitudinal cohort studies will contribute to further evidence and help reduce overall heterogeneity.

Interpretation in light of other evidence

Our meta-analysis revealed that women with a history of GDM are at significantly increased risk for developing MetS later in life (RR 2.48). Women who experience GDM have a reduction in insulin sensitivity in the third trimester, to support an increase in glucose transfer to the fetus. This is promoted by an increase in fetal and placental factors [84, 88]. However, if women are insulin resistant prior to pregnancy and fail to increase β-cell capacity during pregnancy, maternal glucose levels are unlikely to return to normal after pregnancy [89]. Considering the increased risk for cardiovascular risk factors and T2DM in women with a history of GDM [3, 11], it is not surprising that these women are at a higher risk for developing MetS later in life. Intervention trials to reduce the development of T2DM are known to be successful during the early period after pregnancy, but compliance in exercise and weight loss are shown to decrease over time [90–92]. This is likely due to the difficulty in changing behavioral patterns and individual circumstances. It may be more beneficial to intervene before a diagnosis of GDM, as both diet and physical activity changes have been shown to result in an 18% reduction in the risk for GDM among women with a prepregnancy BMI $<25\ kgm^2$ as well as $\geq 25\ kgm^2$; and this intervention was shown to be most effective before 15 weeks' gestation [93]. The prevalence of obesity in women of reproductive age is around 15–18% in Australian women [94]. Therefore, it is necessary to identify women who are at increased risk of developing GDM and implement interventions as soon as practical (either during preconception planning or in early pregnancy) with the aim of reducing the risk of development of GDM. This is especially important, as our results showed that women who experience GDM are at increased risk of being diagnosed with MetS, as early as <1 year postpartum.

Our study also demonstrated that offspring exposed to GDM in utero have a twofold increased risk of developing MetS. GDM promotes a hyperinsulinemic environment to allow increased nutrient delivery to the fetus, thereby increasing fetal growth and body mass resulting in macrosomia which may persist as obesity throughout childhood and adolescence [88]. This idea pertains to "The Barker Hypothesis" which states that adverse nutrition in early life increases the likelihood of developing metabolic risk factors [95]. We have recently shown in a meta-analysis that those exposed to GDM in utero have higher SBP, BMI z-score, and blood glucose compared to those not exposed to GDM in utero [17]. Previous studies have also shown that juvenile T2DM is significantly associated with exposure to GDM in utero [96, 97], therefore highlighting the need for weight management and lifestyle guidance throughout childhood and adolescence for this group. It is important to note that there were only four eligible studies for the meta-analysis on offspring of pregnancies complicated by GDM. We believe this is influenced by the lack of consensus on a definition of MetS in childhood. An IDF recommended definition for the diagnosis of MetS in children older than 6 years of age does exist, but this definition is not universally used [98]. Furthermore, obesity as measured by BMI is not an accurate measure, as BMI varies greatly based on the muscle mass and fat mass, hence it is accurate

for fatter children but not for those who are lean. BMI *z*-score is a more appropriate measure as it adjusts for age and gender [99]. Only one study assessed the MetS *z*-score, which adjusts for age and gender [82]. Considering the increasing rate of childhood obesity, a clear definition of MetS is required that can accurately account for childhood adiposity and adjust for important factors such as age, gender, weight distribution, and puberty.

We also observed that the risk for MetS in pregnancy was increased among women who were diagnosed with GDM compared to normoglycaemic women (RR 20.51). There are studies that have investigated the association between individual components of MetS including dyslipidaemia and obesity and the risk of developing GDM [100–102]. Gunderson et al. showed that BMI and waist circumference were associated with increased risks for GDM after adjusting for lipids, fasting glucose, and insulin [102]. Studies by Grieger and Chatzi showed a threefold increased risk of GDM for women diagnosed with MetS in early pregnancy [13, 39]. It is difficult to diagnose MetS in pregnancy due to hemodynamic and inflammatory changes that occur during the first trimester of pregnancy, as SBP and maternal lipids decrease during this time [43, 103]. Furthermore, placental and maternal hormones during pregnancy promote weight gain and also result in altered fat distribution in both healthy pregnancies and those complicated by GDM [104]. Therefore, these results signify a need for further research in large pregnancy cohorts.

Conclusion

Pregnant women with GDM are at a higher risk of developing MetS during pregnancy. Furthermore, women who experience GDM have an increased risk of developing MetS later in life. They may develop MetS as early as <1 year postpartum. Children born to pregnancies complicated by GDM are also at increased risk of developing MetS in later life. This review signifies the importance of considering GDM in CVD risk stratification, thus allowing an opportunity for primordial prevention. Based on our findings, pre-conceptional management of cardiometabolic risk factors may be useful to reduce the risk of both GDM and MetS. Furthermore, it will be beneficial to screen women who experience GDM and children born to pregnancies complicated by GDM to detect modifiable CVD risk factors.

Funding M.M.P. is funded by Faculty of Health and Medical Sciences Divisional Scholarship from the University of Adelaide. Z.S.L. is supported by an NHMRC Public Health Early Career Fellowship (GNT1141382).

Author contributions M.M.P., Z.S.L., M.A.A., C.T.R., and P.H.A. designed and conceptualized this particular study. Z.S.L. designed and performed the literature search. M.M.P., Z.S.L., A.A., and P.H.A. were involved in screening and selecting the included studies. M.M.P. performed the meta-analysis with expert advice from Z.S.L. The original manuscript was drafted by M.M.P. All authors critically reviewed and revised the manuscript and approved the final version. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. International Diabetes Federation, *IDF Diabetes Atlas* (International Diabetes Federation, Belgium, 2017)
2. P.H. Andraweera, G.A. Dekker, M. Arstall, T. Bianco-Miotto, C. T. Roberts, Complications of pregnancy and future cardiovascular risk. in *Encylopedia of Cardiovascular Research and Medicine*, (eds D.B. Sawyer, R.S. Vasan) vol. 1 (Oxford, The Netherlands, 2018), pp. 643–650
3. L. Bellamy, J.P. Casas, A.D. Hingorani, D. Williams, Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet **373**(9677), 1773–1779 (2009). https://doi.org/10.1016/s0140-6736(09)60731-5
4. A. Lorenzo-Almorós, T. Hang, C. Peiró, L. Soriano-Guillén, J. Egido, J. Tuñón, Ó. Lorenzo, Predictive and diagnostic biomarkers for gestational diabetes and its associated metabolic and cardiovascular diseases. Cardiovasc. Diabetol. **18**(1), 140 (2019). https://doi.org/10.1186/s12933-019-0935-9
5. K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet. Med. **15**(7), 539–553 (1998). https://doi.org/10.1002/(sici)1096-9136(199807)15:7<539::Aid-dia668>3.0.Co;2-s
6. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP), Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA **285**(19), 2486–2497 (2001). https://doi.org/10.1001/jama.285.19.2486
7. C.K. Kramer, S. Campbell, R. Retnakaran, Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia **62**(6), 905–914 (2019). https://doi.org/10.1007/s00125-019-4840-2
8. J. Fan, Y. Song, Y. Chen, R. Hui, W. Zhang, Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies. Int. J. Cardiol. **168**(5), 4761–4768 (2013). https://doi.org/10.1016/j.ijcard.2013.07.230
9. P.W. Wilson, W.B. Kannel, H. Silbershatz, R.B. D'Agostino, Clustering of metabolic factors and coronary heart disease. Arch. Intern. Med. **159**(10), 1104–1109 (1999). https://doi.org/10.1001/archinte.159.10.1104
10. J.F. Plows, J.L. Stanley, P.N. Baker, C.M. Reynolds, M.H. Vickers, The pathophysiology of gestational diabetes mellitus. Int. J. Mol. Sci. **19**(11) (2018). https://doi.org/10.3390/ijms19113342
11. P. Andraweera, G. Dekker, M. Arstall, T. Bianco-Miotto, C. Roberts, Complications of pregnancy and future cardiovascular risk. in *Encyclopedia of Cardiovascular Research and Medicine*,

(eds D.B. Sawyer, R.S. Vasan) vol. 1 (Elsevier, Oxford The Netherlands, 2018)
12. F.K. Welty, A. Alfaddagh, T.K. Elajami, Targeting inflammation in metabolic syndrome. Transl. Res. **167**(1), 257–280 (2016). https://doi.org/10.1016/j.trsl.2015.06.017
13. J.A. Grieger, T. Bianco-Miotto, L.E. Grzeskowiak, S.Y. Leemaqz, L. Poston, L.M. McCowan, L.C. Kenny, J.E. Myers, J.J. Walker, G.A. Dekker, C.T. Roberts, Metabolic syndrome in pregnancy and risk for adverse pregnancy outcomes: a prospective cohort of nulliparous women. PLoS Med. **15**(12), e1002710 (2018). https://doi.org/10.1371/journal.pmed.1002710
14. S.L. Kjos, R.K. Peters, A. Xiang, O.A. Henry, M. Montoro, T.A. Buchanan, Predicting future diabetes in Latino women with gestational diabetes. Utility of early postpartum glucose tolerance testing. Diabetes **44**(5), 586–591 (1995). https://doi.org/10.2337/diab.44.5.586
15. Y. Xu, S. Shen, L. Sun, H. Yang, B. Jin, X. Cao, Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. PLoS ONE **9**(1), e87863 (2014). https://doi.org/10.1371/journal.pone.0087863
16. D.R. Coustan, L.P. Lowe, B.E. Metzger, A.R. Dyer; International Association of Diabetes and Pregnancy Study Groups, The hyperglycemia and adverse pregnancy outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Am. J. Obst. Gynecol. **202**(6), 654.e651–654.e6546 (2010). https://doi.org/10.1016/j.ajog.2010.04.006
17. M.M. Pathirana, Z.S. Lassi, C.T. Roberts, P.H. Andraweera, Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. J. Dev. Orig. Health Dis. 1–18 (2020). https://doi.org/10.1017/s2040174419000850
18. E. Di Angelantonio, N. Sarwar, P. Perry, S. Kaptoge, K.K. Ray, A. Thompson, A.M. Wood, S. Lewington, N. Sattar, C.J. Packard, R. Collins, S.G. Thompson, J. Danesh, Major lipids, apolipoproteins, and risk of vascular disease. JAMA **302**(18), 1993–2000 (2009). https://doi.org/10.1001/jama.2009.1619
19. Y. Yano, J. Stamler, D.B. Garside, M.L. Daviglus, S.S. Franklin, M.R. Carnethon, K. Liu, P. Greenland, D.M. Lloyd-Jones, Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. J. Am. Coll. Cardiol. **65**(4), 327–335 (2015). https://doi.org/10.1016/j.jacc.2014.10.060
20. J.S. Son, S. Choi, K. Kim, S.M. Kim, D. Choi, G. Lee, S.M. Jeong, S.Y. Park, Y.Y. Kim, J.M. Yun, S.M. Park, Association of Blood Pressure Classification in Korean Young Adults According to the 2017 American College of Cardiology/American Heart Association Guidelines With Subsequent Cardiovascular Disease Events. JAMA **320**(17), 1783–1792 (2018). https://doi.org/10.1001/jama.2018.16501
21. A. Umer, G.A. Kelley, L.E. Cottrell, P. Giacobbi Jr., K.E. Innes, C. L. Lilly, Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health **17**(1), 683 (2017). https://doi.org/10.1186/s12889-017-4691-z
22. D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ **339**, b2535 (2009). https://doi.org/10.1136/bmj.b2535
23. B.E. Metzger, S.G. Gabbe, B. Persson, T.A. Buchanan, P.A. Catalano, P. Damm, A.R. Dyer, Ad. Leiva, M. Hod, J.L. Kitzmiler, L.P. Lowe, H.D. McIntyre, J.J.N. Oats, Y. Omori, M.I. Schmidt, International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 33(3), 676 (2010). https://doi.org/10.2337/dc09-1848
24. National Diabetes Data Group, Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes **28**(12), 1039–1057 (1979). https://doi.org/10.2337/diab.28.12.1039
25. M.W. Carpenter, D.R. Coustan, Criteria for screening tests for gestational diabetes. Am. J. Obstet. Gynecol. **144**(7), 768–773 (1982). https://doi.org/10.1016/0002-9378(82)90349-0
26. American Diabetes Association, Standards of medical care in diabetes-2007. Diabetes Care **30**(Suppl 1), S4–S41 (2007). https://doi.org/10.2337/dc07-S004
27. P.R. Rani, J. Begum, Screening and diagnosis of gestational diabetes mellitus, where do we stand. J. Clin. Diagn. Res. **10**(4), QE01–QE04 (2016). https://doi.org/10.7860/jcdr/2016/17588.7689
28. J.B. O'Sullivan, C.M. Mahan, Criteria for the oral glucose tolerance test in pregnancy. Diabetes **13**, 278–285 (1964)
29. Current Care Guidelines, Working group set up by the Finnish Medical Society Duodecim, the Medical Advisory Board of the Finnish Diabetes Association and the Finnish Gynecological Association. 2013. www.kaypahoito.fi
30. E. Wender-Ozegowska, M. Sporna, A. Sporna, J. Brazert, A. Zawiejska, Components of metabolic syndrome (MS) in women after gestational diabetes (GDM). J. Diabetes **1**, A286–A287 (2009). https://doi.org/10.1111/j.1753-0407.2009.00020.x
31. T. Hansen, H. Vestergaard, Increasing incidence of diabetes after gestational diabetes. Diabetes Care **27**(5), 1194–1199 (2004). https://doi.org/10.2337/diacare.27.5.1194
32. K.G.M.M. Alberti, P. Zimmet, J. Shaw, The metabolic syndrome—a new worldwide definition. The Lancet **366**(9491), 1059–1062 (2005). https://doi.org/10.1016/S0140-6736(05)67402-8
33. S.M. Grundy, J.I. Cleeman, S.R. Daniels, K.A. Donato, R.H. Eckel, B.A. Franklin, D.J. Gordon, R.M. Krauss, P.J. Savage, S. C. Smith Jr., J.A. Spertus, F. Costa, Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation **112**(17), 2735–2752 (2005). https://doi.org/10.1161/circulationaha.105.169404
34. National Institutes of Health, Quality assessment tool for observational cohort and cross-sectional studies (2014), https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort. Accessed 14 Apr 2020
35. S. Bo, G. Menato, M.L. Gallo, C. Bardelli, A. Lezo, A. Signorile, R. Gambino, M. Cassader, M. Massobrio, G. Pagano, Mild gestational hyperglycemia, the metabolic syndrome and adverse neonatal outcomes. Acta Obstet. Gynecol. Scand. **83**(4), 335–340 (2004). https://doi.org/10.1111/j.0001-6349.2004.00314.x
36. B. Dane, F. Ustaoğlu, Y. Yildirim, Y. Döventaş, C. Dane, A. Çetin, M. Yenigün, Are the criteria of metabolic syndrome associated with pregnancy complications? Turk Jinekoloji ve Obstetrik Dernegi Dergisi **8**(2), 100–106 (2011)
37. C.A. Negrato, L. Jovanovic, A. Rafacho, M.A. Tambascia, B. Geloneze, A. Dias, M.V. Rudge, Association between different levels of dysglycemia and metabolic syndrome in pregnancy. Diabetol. Metab. Syndr. **1**(1), 3–3 (2009). https://doi.org/10.1186/1758-5996-1-3
38. F. Zaman, S. Nouhjah, H. Shahbazian, N. Shahbazian, S.M. Latifi, A. Jahanshahi, Risk factors of gestational diabetes mellitus using results of a prospective population-based study in Iranian pregnant women. Diabetes Metab. Syndr. **12**(5), 721–725 (2018). https://doi.org/10.1016/j.dsx.2018.04.014
39. L. Chatzi, E. Plana, A. Pappas, D. Alegkakis, P. Karakosta, V. Daraki, C. Tsatsanis, A. Kafatos, A. Koutis, M. Kogevinas, Metabolic syndrome in early pregnancy and risk of gestational diabetes mellitus. Diabetologia **52**(S1), S457 (2009). https://doi.org/10.1007/s00125-009-1445-1

40. M. Migda, M.S. Migda, B. Migda, P. Krzyżanowska, E. Wender-Ożegowska, Components of metabolic syndrome in the first trimester of pregnancy as predictors of adverse perinatal outcome. Ginekol. Pol. **87**(9), 644–650 (2016). https://doi.org/10.5603/GP.2016.0060
41. R. Retnakaran, S.W. Wen, H. Tan, C. Ye, M. Shen, G.N. Smith, M.C. Walker, Pregravid metabolic syndrome and risk of adverse outcomes in pregnancy: a preconception cohort study. Diabetes **68** (2019). https://doi.org/10.2337/db19-1419-P
42. T. Costacou, Z. Bosnyak, G.F. Harger, N. Markovic, N. Silvers, T.J. Orchard, Postpartum adiponectin concentration, insulin resistance and metabolic abnormalities among women with pregnancy-induced disturbances. Prev. Cardiol. **11**(2), 106–115 (2008). https://doi.org/10.1111/j.1751-7141.2008.07512.x
43. P. Soma-Pillay, C. Nelson-Piercy, H. Tolppanen, A. Mebazaa, Physiological changes in pregnancy. Cardiovasc. J. Afr. **27**(2), 89–94 (2016). https://doi.org/10.5830/CVJA-2016-021
44. B. Akinci, A. Celtik, S. Genc, S. Yener, T. Demir, M. Secil, L. Kebapcilar, S. Yesil, Evaluation of postpartum carbohydrate intolerance and cardiovascular risk factors in women with gestational diabetes. Gynecol. Endocrinol. **27**(5), 361–367 (2011). https://doi.org/10.3109/09513590.2010.492885
45. M. Albareda, A. Caballero, G. Badell, J. Rodríguez-Espinosa, J. Ordóñez-Llanos, A. de Leiva, R. Corcoy, Metabolic syndrome at follow-up in women with and without gestational diabetes mellitus in index pregnancy. Metabolism **54**(8), 1115–1121 (2005). https://doi.org/10.1016/j.metabol.2005.03.017
46. B. Edalat, F. Sharifi, Z. Badamchizadeh, A. Hossein-Nezhad, B. Larijani, M. Mirarefin, H. Fakhrzadeh, Association of metabolic syndrome with inflammatory mediators in women with previous gestational diabetes mellitus. J. Diabetes Metab. Disord. **12**(1), 8 (2013). https://doi.org/10.1186/2251-6581-12-8
47. S. Bo, G. Menato, C. Botto, I. Cotrino, C. Bardelli, R. Gambino, M. Cassader, M. Durazzo, A. Signorile, M. Massobrio, G. Pagano, Mild gestational hyperglycemia and the metabolic syndrome in later life. Metab. Syndr. Relat. Disord. **4**(2), 113–121 (2006). https://doi.org/10.1089/met.2006.4.113
48. D.B. Carr, K.M. Utzschneider, R.L. Hull, J. Tong, T.M. Wallace, K. Kodama, J.B. Shofer, S.R. Heckbert, E.J. Boyko, W.Y. Fujimoto, S.E. Kahn, Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care **29**(9), 2078–2083 (2006)
49. A. Derbent, A. Kargili, C. Koca, I.I. Gümüş, S. Sevgili, S. Smavli, F. Karakurt, N.O. Turhan, Serum platelet-activating factor acetylhydrolase activity: relationship with metabolic syndrome in women with history of gestational diabetes mellitus. Gynecol. Endocrinol. **27**(2), 128–133 (2011). https://doi.org/10.3109/09513590.2010.487612
50. G. Di Cianni, C. Lencioni, L. Volpe, A. Ghio, I. Cuccuru, G. Pellegrini, L. Benzi, R. Miccoli, S. Del Prato, C-reactive protein and metabolic syndrome in women with previous gestational diabetes. Diabetes Metab. Res. Rev. **23**(2), 135–140 (2007). https://doi.org/10.1002/dmrr.661
51. E.P. Gunderson, D.R. Jacobs Jr, V. Chiang, C.E. Lewis, J. Feng, C.P. Quesenberry Jr, S. Sidney, Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). Diabetes **59**(2), 495–504 (2010). https://doi.org/10.2337/db09-1197
52. H. Hakkarainen, H. Huopio, H. Cederberg, R. Voutilainen, S. Heinonen, Future risk of metabolic syndrome in women with a previous LGA delivery stratified by gestational glucose tolerance: a prospective cohort study. BMC Pregnancy Childbirth **18** (1), N.PAG (2018). https://doi.org/10.1186/s12884-018-1958-z
53. H. Ijäs, L. Morin-Papunen, A.K. Keränen, R. Bloigu, A. Ruokonen, K. Puukka, T. Ebeling, T. Raudaskoski, M. Vääräsmäki, Pre-pregnancy overweight overtakes gestational diabetes as a risk factor for subsequent metabolic syndrome. Eur. J. Endocrinol. **169**(5), 605–611 (2013). https://doi.org/10.1530/EJE-13-0412
54. E. Kousta, Z. Efstathiadou, N.J. Lawrence, J.A.R. Jeffs, I.F. Godsland, S.C. Barrett, C.J. Doré, A. Penny, V. Anyaoku, B.A. Millauer, E. Cela, S. Robinson, M.I. McCarthy, D.G. Johnston, The impact of ethnicity on glucose regulation and the metabolic syndrome following gestational diabetes. Diabetologia **49**(1), 36–40 (2006). https://doi.org/10.1007/s00125-005-0058-6
55. G.V. Krishnaveni, J.C. Hill, S.R. Veena, S. Geetha, M.N. Jayakumar, C.L.S. Karat, C.H.D. Fall, Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. Diabetes Res. Clin. Pract. **78**(3), 398–404 (2007). https://doi.org/10.1016/j.diabres.2007.06.002
56. J. Lauenborg, E. Mathiesen, T. Hansen, C. Glümer, T. Jørgensen, K. Borch-Johnsen, P. Hornnes, O. Pedersen, P. Damm, The prevalence of the metabolic syndrome in a Danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. J. Clin. Endocrinol. Metab. **90**(7), 4004–4010 (2005). https://doi.org/10.1210/jc.2004-1713
57. L.J. Li, I.M. Aris, L.L. Su, Y.S. Chong, T.Y. Wong, K.H. Tan, J. J. Wang, Effect of gestational diabetes and hypertensive disorders of pregnancy on postpartum cardiometabolic risk. Endocr. Connect. **7**(3), 433–442 (2018). https://doi.org/10.1530/EC-17-0359
58. E. Madarász, G. Tamás, A.G. Tabák, Z. Kerényi, Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. Diabetes Res. Clin. Pract. **85**(2), 197–202 (2009). https://doi.org/10.1016/j.diabres.2009.05.001
59. Z. Maghbooli, A. Hossein-Nezhad, K. Mirzaei, F. Karimi, A. Besharati, K. Omidfar, B. Larijani, Association between retinol-binding protein 4 concentrations and gestational diabetes mellitus and risk of developing metabolic syndrome after pregnancy. Reprod. Sci. **17**(2), 196–201 (2010). https://doi.org/10.1177/1933719109351097
60. C. Mai, M. Hou, R. Chen, D. Duan, H. Xu, X. Lin, J. Wen, L. Lv, Q. Lei, J. Niu, Cardiovascular risk factors in Chinese women with a history of gestational diabetes mellitus. Int. J. Clin. Exp. Med. **8**(11), 21694–21698 (2015)
61. E. Noctor, C. Crowe, L.A. Carmody, B. Kirwan, A. O'Dea, L.G. Glynn, B.E. McGuire, P.M. O'Shea, F.P. Dunne, ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. Acta Diabetol. (2014). https://doi.org/10.1007/s00592-014-0621-z
62. S. Nouhjah, H. Shahbazian, N. Shahbazian, S. Jahanfar, A. Jahanshahi, B. Cheraghian, Z.D. Mohammadi, N. Ghodrati, S. Houshmandi, Early postpartum metabolic syndrome in women with or without gestational diabetes: results from Life after Gestational Diabetes Ahvaz cohort study. Diabetes Metab. Syndr. **12**(3), 317–323 (2018). https://doi.org/10.1016/j.dsx.2017.12.027
63. R. Retnakaran, Y. Qi, P.W. Connelly, M. Sermer, B. Zinman, A. J.G. Hanley, Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. J. Clin. Endocrinol. Metab. **95**(2), 670–677 (2010). https://doi.org/10.1210/jc.2009-1990
64. M.M. Roca-Rodríguez, C. López-Tinoco, A. Fernández-Deudero, M. Murri, M.V. García-Palacios, M.A. García-Valero, F.J. Tinahones-Madueño, M. Aguilar-Diosdado, Adipokines and metabolic syndrome risk factors in women with previous

gestational diabetes mellitus. Diabetes Metab. Res. Rev. **28**(6), 542–548 (2012). https://doi.org/10.1002/dmrr.2313
65. R. Ruksasakul, T. Tharavanij, P. Sritipsukho, Metabolic syndrome in Thai women previously diagnosed with gestational diabetes. J. Med. Assoc. Thai. **99**(Suppl 4), S195–S202 (2016)
66. Y. Shen, W. Li, J. Leng, S. Zhang, H. Liu, W. Li, L. Wang, H. Tian, J. Chen, L. Qi, X. Yang, Z. Yu, J. Tuomilehto, G. Hu, High risk of metabolic syndrome after delivery in pregnancies complicated by gestational diabetes. Diabetes Res. Clin. Pract. **150**, 219–226 (2019). https://doi.org/10.1016/j.diabres.2019.03.030
67. W.H. Tam, X.L. Yang, J.C. Chan, G.T. Ko, P.C. Tong, R.C. Ma, C.S. Cockram, D. Sahota, M.S. Rogers, Progression to impaired glucose regulation, diabetes and metabolic syndrome in Chinese women with a past history of gestational diabetes. Diabetes Metab. Res. Rev. **23**(6), 485–489 (2007)
68. A. Verma, C.M. Boney, R. Tucker, B.R. Vohr, Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. J. Clin. Endocrinol. Metab. **87**(7), 3227–3235 (2002). https://doi.org/10.1210/jcem.87.7.8684
69. T. Vilmi-Kerälä, O. Palomäki, M. Vainio, J. Uotila, A. Palomäki, The risk of metabolic syndrome after gestational diabetes mellitus—a hospital-based cohort study. Diabetol Metab. Syndr. **7**, 43–43 (2015). https://doi.org/10.1186/s13098-015-0038-z
70. A. Zawiejska, E. Wender-Ozegowska, J. Brazert, K. Sodowski, Components of metabolic syndrome and their impact on fetal growth in women with gestational diabetes mellitus. J. Physiol. Pharmacol. **59**(Suppl 4), 5–18 (2008)
71. C.N. Wijeyaratne, R. Waduge, D. Arandara, A. Arasalingam, A. Sivasuriam, S.H. Dodampahala, A.H. Balen, Metabolic and polycystic ovary syndromes in indigenous South Asian women with previous gestational diabetes mellitus. BJOG **113**(10), 1182–1187 (2006). https://doi.org/10.1111/j.1471-0528.2006.01046.x
72. B. Akinci, A. Celtik, S. Yener, S. Yesil, Prediction of developing metabolic syndrome after gestational diabetes mellitus. Fertil. Steril. **93**(4), 1248–1254 (2010). https://doi.org/10.1016/j.fertnstert.2008.12.007
73. B. Akinci, A. Celtik, F. Yuksel, S. Genc, S. Yener, M. Secil, M. A. Ozcan, S. Yesil, Increased osteoprotegerin levels in women with previous gestational diabetes developing metabolic syndrome. Diabetes Res. Clin. Pract. **91**(1), 26–31 (2011). https://doi.org/10.1016/j.diabres.2010.09.028
74. E.W. Dehmer, M.A. Phadnis, E.P. Gunderson, C.E. Lewis, K. Bibbins-Domingo, S.M. Engel, M. Jonsson Funk, H. Kramer, A. V. Kshirsagar, G. Heiss, Association between gestational diabetes and incident maternal CKD: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am. J. Kidney Dis. **71**(1), 112–122 (2018). https://doi.org/10.1053/j.ajkd.2017.08.015
75. T.B. Ferraz, R.S. Motta, C.L. Ferraz, D.M. Capibaribe, A.C. Forti, A.R. Chacra, C-reactive protein and features of metabolic syndrome in Brazilian women with previous gestational diabetes. Diabetes Res. Clin. Pract. **78**(1), 23–29 (2007). https://doi.org/10.1016/j.diabres.2007.01.025
76. E.P. Gunderson, D.R. Jacobs, V. Chiang, C.E. Lewis, J. Feng, C. P. Quesenberry, S. Sidney, Lactation and lower incidence of the metabolic syndrome in women of reproductive age by gestational diabetes mellitus: a 20-year prospective study of CARDIA women. Diabetes **58**, 495–504 (2009)
77. C. Mai, B. Wang, J. Wen, X. Lin, J. Niu, Lipoprotein-associated phospholipase A2 and AGEs are associated with cardiovascular risk factors in women with history of gestational diabetes mellitus. Gynecol. Endocrinol. **30**(3), 241–244 (2014). https://doi.org/10.3109/09513590.2013.871522
78. W.H. Tam, R.C.W. Ma, X. Yang, G.T.C. Ko, T.T.H. Lao, M.H. M. Chan, C.W.K. Lam, C.S. Cockram, J.C.N. Chan, Cardiometabolic risk in Chinese women with prior gestational diabetes: a 15-year follow-up study. Gynecol. Obstet. Invest. **73**(2), 168–176 (2012). https://doi.org/10.1159/000329339
79. C.M. Boney, A. Verma, R. Tucker, B.R. Vohr, Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics **115**(3), e290–e296 (2005). https://doi.org/10.1542/peds.2004-1808
80. T.D. Clausen, E.R. Mathiesen, T. Hansen, O. Pedersen, D.M. Jensen, J. Lauenborg, L. Schmidt, P. Damm, Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. J. Clin. Endocrinol. Metab. **94**(7), 2464–2470 (2009). https://doi.org/10.1210/jc.2009-0305
81. M. Vääräsmäki, A. Pouta, P. Elliot, P. Tapanainen, U. Sovio, A. Ruokonen, A.-L. Hartikainen, M. McCarthy, M.-R. Järvelin, Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. Am. J. Epidemiol. **169**(10), 1209–1215 (2009). https://doi.org/10.1093/aje/kwp020
82. E. Maslova, S. Hansen, L.G. Grunnet, M. Strøm, A.A. Bjerregaard, L. Hjort, F.B. Kampmann, C.M. Madsen, A.C.B. Thuesen, B.H. Bech, T.I. Halldorsson, A.A. Vaag, C. Zhang, S.F. Olsen, Maternal glycemic index and glycemic load in pregnancy and offspring metabolic health in childhood and adolescence—a cohort study of 68,471 mother–offspring dyads from the Danish National Birth Cohort. Eur. J. Clin. Nutr. **73**(7), 1049–1062 (2019). https://doi.org/10.1038/s41430-018-0316-6
83. L. Wu, L. Cui, W.H. Tam, R.C. Ma, C.C. Wang, Genetic variants associated with gestational diabetes mellitus: a meta-analysis and subgroup analysis. Sci. Rep. **6**, 30539 (2016). https://doi.org/10.1038/srep30539
84. S.K. Abell, B. De Courten, J.A. Boyle, H.J. Teede, Inflammatory and other biomarkers: role in pathophysiology and prediction of gestational diabetes mellitus. Int. J. Mol. Sci. **16**(6), 13442–13473 (2015). https://doi.org/10.3390/ijms160613442
85. J.F. Plows, J.L. Stanley, P.N. Baker, C.M. Reynolds, M.H. Vickers, The pathophysiology of gestational diabetes mellitus. Int. J. Mol. Sci. **19**(11), 3342 (2018). https://doi.org/10.3390/ijms19113342
86. R.S. Pons, F.C. Rockett, B. de Almeida Rubin, M.L.R. Oppermann, V.L: Bosa, Risk factors for gestational diabetes mellitus in a sample of pregnant women diagnosed with the disease. Diabetol. Metab. Syndr. **7**(1), A80 (2015). https://doi.org/10.1186/1758-5996-7-S1-A80
87. E. Jarosz, Lifestyle behaviours or socioeconomic characteristics? Gender differences in covariates of BMI in Hungary. Obes. Sci. Pract. **4**(6), 591–599 (2018). https://doi.org/10.1002/osp4.316
88. D. Mitanchez, C. Yzydorczyk, B. Siddeek, F. Boubred, M. Benahmed, U. Simeoni, The offspring of the diabetic mother-short- and long-term implications. Best Pract. Res. Clin. Obstet. Gynaecol. **29**(2), 256–269 (2015). https://doi.org/10.1016/j.bpobgyn.2014.08.004
89. T.A. Buchanan, A.H. Xiang, R.K. Peters, S.L. Kjos, K. Berkowitz, A. Marroquin, J. Goico, C. Ochoa, S.P. Azen, Response of pancreatic beta-cells to improved insulin sensitivity in women at high risk for type 2 diabetes. Diabetes **49**(5), 782–788 (2000). https://doi.org/10.2337/diabetes.49.5.782
90. N.W. Shek, C.S. Ngai, C.P. Lee, J.Y. Chan, T.T. Lao, Lifestyle modifications in the development of diabetes mellitus and metabolic syndrome in Chinese women who had gestational diabetes mellitus: a randomized interventional trial. Arch. Gynecol. Obstet. **289**(2), 319–327 (2014). https://doi.org/10.1007/s00404-013-2971-0
91. A. Ferrara, M.M. Hedderson, C.L. Albright, S.F. Ehrlich, C.P. Quesenberry Jr, T. Peng, J. Feng, J. Ching, Y. Crites, A pregnancy and postpartum lifestyle intervention in women with

gestational diabetes mellitus reduces diabetes risk factors: a feasibility randomized control trial. Diabetes Care **34**(7), 1519–1525 (2011). https://doi.org/10.2337/dc10-2221
92. R.E. Ratner, C.A. Christophi, B.E. Metzger, D. Dabelea, P.H. Bennett, X. Pi-Sunyer, S. Fowler, S.E. Kahn, Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J. Clin. Endocrinol. Metab. **93**(12), 4774–4779 (2008). https://doi.org/10.1210/jc.2008-0772
93. C. Song, J. Li, J. Leng, R.C. Ma, X. Yang, Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials. Obes. Rev. **17**(10), 960–969 (2016). https://doi.org/10.1111/obr.12442
94. AIHW, A picture of overweight and obesity in Australia (2017)
95. D.J. Barker, The developmental origins of adult disease. J. Am. Coll. Nutr. **23**(6 Suppl), 588S–595S (2004). https://doi.org/10.1080/07315724.2004.10719428
96. A.L. Blotsky, E. Rahme, M. Dahhou, M. Nakhla, K. Dasgupta, Gestational diabetes associated with incident diabetes in childhood and youth: a retrospective cohort study. CMAJ **191**(15), E410–E417 (2019). https://doi.org/10.1503/cmaj.181001
97. J. Halipchuk, B. Temple, A. Dart, D. Martin, E.A.C. Sellers, Prenatal, obstetric and perinatal factors associated with the development of childhood-onset type 2 diabetes. Can. J. Diabetes **42**(1), 71–77 (2018). https://doi.org/10.1016/j.jcjd.2017.04.003
98. International Diabetes Federation, The IDF consensus definition of the metabolic syndrome in children and adolescents (2007). Accessed 5 May 2020
99. D.S. Freedman, B. Sherry, The validity of BMI as an indicator of body fatness and risk among children. Pediatrics **124**(Suppl 1), S23–S34 (2009). https://doi.org/10.1542/peds.2008-3586E
100. E.S. Han, R.M. Krauss, F. Xu, S.B. Sridhar, A. Ferrara, C.P. Quesenberry, M.M. Hedderson, Prepregnancy adverse lipid profile and subsequent risk of gestational diabetes. J. Clin. Endocrinol. Metab. **101**(7), 2721–2727 (2016). https://doi.org/10.1210/jc.2015-3904
101. Y.M. Wei, H.X. Yang, W.W. Zhu, X.Y. Liu, W.Y. Meng, Y.Q. Wang, L.X. Shang, Z.Y. Cai, L.P. Ji, Y.F. Wang, Y. Sun, J.X. Liu, L. Wei, Y.F. Sun, X.Y. Zhang, T.X. Luo, H.X. Chen, L.J. Yu, Risk of adverse pregnancy outcomes stratified for pre-pregnancy body mass index. J. Matern. Fetal. Neonatal. Med. **29** (13), 2205–2209 (2016). https://doi.org/10.3109/14767058.2015.1081167
102. E.P. Gunderson, C.P. Quesenberry Jr., D.R. Jacobs Jr, J. Feng, C.E. Lewis, S. Sidney, Longitudinal study of prepregnancy cardiometabolic risk factors and subsequent risk of gestational diabetes mellitus: the CARDIA study. Am. J. Epidemiol. **172** (10), 1131–1143 (2010). https://doi.org/10.1093/aje/kwq267
103. N.F. Butte, Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am. J. Clin. Nutr. **71**(5 Suppl), 1256S–1261S (2000). https://doi.org/10.1093/ajcn/71.5.1256s
104. D.E. Smith, C.E. Lewis, J.L. Caveny, L.L. Perkins, G.L. Burke, D. E. Bild, Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. JAMA **271**(22), 1747–1751 (1994)

Appendix 5: Publication for Protective effect of breastfeeding on cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: a systematic review and meta-analysis

Review

international lactation consultant association®

Journal of Human Lactation
1–15

DOI: 10.1177/0890334421034779
journals.sagepub.com/home/jhl
SAGE

Protective Influence of Breastfeeding on Cardiovascular Risk Factors in Women With Previous Gestational Diabetes Mellitus and Their Children: A Systematic Review and Meta-Analysis

Maleesa M. Pathirana, B. Med Sci (Hons)[1,2], Anna Ali, MSc, BDS[1,2,3,4], Zohra S Lassi, PhD[1,2], Margaret A. Arstall, MBBS, PhD, FRACP, FCSANZ[1,5], Claire T. Roberts, PhD[1,6], and Prabha H. Andraweera, MBBS, PhD[1,2,6]

Abstract

Background: There is evidence that breastfeeding may provide protection against cardiovascular risk factors in mothers with a history of gestational diabetes mellitus and their children who were exposed in utero.

Research Aim: To perform a systematic review and meta-analysis of observational studies to ascertain the effects of breastfeeding on cardiovascular risk factors in women with previous gestational diabetes mellitus and their children exposed in utero.

Methods: Studies assessing conventional cardiovascular risk factors in women with previous gestational diabetes mellitus and children exposed in utero stratified by breastfeeding/no breastfeeding or breastfed/not breastfed were included. Gestational diabetes mellitus was defined based on the International Association of Diabetes in Pregnancy Study Group definition or previous accepted definitions. Breastfeeding was defined as reported in each study.

Results: The literature search yielded 260 titles, of which 17 studies were selected to be in the review. Women with previous gestational diabetes mellitus who did not breastfeed had higher blood glucose (*SMD*: 0.32, 95% CI [0.12, 0.53]) and a greater risk of developing Type 2 diabetes mellitus (*RR*: 2.08 95% CI [1.44, 3.00]) compared to women with no history. There were not enough studies to conduct a meta-analysis on the effects of breastfeeding on risk factors for cardiovascular disease among children exposed to gestational diabetes mellitus in utero.

Conclusion: Breastfeeding appears to be protective against cardiovascular risk factors among women who experience gestational diabetes mellitus.

Keywords

breastfeeding, breastfeeding benefits, cardiovascular risk, gestational diabetes mellitus, maternal health, meta-analysis

Background

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is initially diagnosed during pregnancy and affects 1 in 7 pregnancies globally (International Diabetes Federation [IDF], 2007). Women with previous GDM have an approximately 7-fold increased risk of developing Type 2 diabetes mellitus (T2DM) later in life (Bellamy et al., 2009). Furthermore, women with previous GDM are more likely to be hypertensive, obese, and have dyslipidaemia postpartum (Pathirana et al., 2021). These metabolic and vascular morbidities promote the development of metabolic syndrome, which is a significant global concern and important risk factor for CVD (Ranasinghe et al., 2017). It has been reported in a previous systematic review and meta-analysis, that women with a history of GDM are at a higher risk of developing metabolic syndrome later in life (Pathirana et al., 2020b). Furthermore, women with a GDM history have a 2-fold increased risk of developing cardiovascular disease (CVD), irrespective of disease progression to T2DM (Andraweera, 2018). It has also been reported that children exposed to GDM in utero also exhibit higher systolic blood pressure, obesity, and higher blood glucose throughout life compared to children born to non-GDM pregnancies, thereby significantly increasing their risk of T2DM and CVD at an earlier age (Pathirana et al., 2020). Therefore, preventative

strategies are necessary to reduce CVD risk in both mothers and children exposed to GDM.

Human milk is "the gold standard for infant feeding," with lactation being mutually beneficial for both mother and child (Lessen & Kavanagh, 2015). Breastfeeding over 12 months promotes a significant reduction in both chronic hypertension and T2DM in women (Rameez et al., 2019). Furthermore, children who are breastfed are less likely to develop obesity and T2DM compared to those who are not breastfed (Yan et al., 2014). Breastfeeding for 6 months exclusively, and for up to 2 years as complementary to other nutritional sources is encouraged in women (Lessen & Kavanagh, 2015). Two reviews have assessed breastfeeding and metabolic risk factor reduction in women with previous GDM (Feng et al., 2018; Ma et al., 2019) but these studies have not reported on all conventional cardiovascular risk factors, such as blood pressure and lipids. Having a comprehensive assessment of the effects of breastfeeding on all major cardiovascular risk factors can aid treatment strategies and disease mitigation. These reviews also did not assess the effects of breastfeeding on all major CVD risk factors in children exposed to GDM in utero. Therefore, our aim was to perform a systematic review and meta-analysis to determine the effects of breastfeeding on cardiovascular risk factors in women with previous GDM and their exposed children.

Key Messages

- Gestational diabetes mellitus increases the risk of cardiovascular disease in both mothers and children. Evidence has suggested that breastfeeding promotes good cardiovascular health in both mothers and children.
- Our meta-analysis revealed that breastfeeding for any length of time reduced diastolic blood pressure, serum triglycerides, blood glucose, and the risk of Type 2 diabetes mellitus in participants with a history of gestational diabetes mellitus.
- Our research demonstrated that participants with previous gestational diabetes mellitus should be encouraged to breastfeed to reduce their risk of cardiovascular disease later in life.

Methods

Design: We undertook a systematic review of the literature and meta-analysis of observational studies in order to assess the effects of breastfeeding on cardiovascular risk factors in mothers with previous GDM and children exposed to GDM in utero. The review was undertaken with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al., 2009). The protocol of this review is registered in PROSPERO (CRD42020190529)

Sample: Studies eligible for the meta-analyses included women who had a history of GDM/those exposed to GDM in utero, the intervention assessed was breastfeeding/being breastfed compared to not breastfeeding/not being breastfed, and the outcomes of interest were conventional cardiovascular risk factors. Observational studies (i.e., cross-sectional, case-control, and cohort) were included. Studies that did not include a definition of GDM, those that did not define the breastfeeding and non-breastfeeding groups, or did not include participants with GDM, were excluded. We assessed the following in our review (1) CVD risk factors in women with previous GDM who breastfed compared to women with previous GDM who did not breastfeed; (2) CVD risk factors in those exposed to GDM in utero who were breastfed compared to those exposed to GDM in utero who were not breastfed. We included studies of CVD risk assessment at any point in the postpartum period. Key search terms included (gestational diabetes OR pregnancy-induced diabetes) AND (breast feeding OR breastfeeding OR breastmilk OR human milk OR lactat*) AND (formula fed OR infant formula) AND (blood pressure OR hypertension OR cholesterol OR lipids OR body mass index OR glucose OR diabetes OR metabolic syndrome).

As different definitions of breastfeeding were used among studies, breastfeeding was considered as exposure to human milk (either exclusive or mostly breastfed), as defined in the study or feeding at hospital discharge, and not breastfeeding was considered as feeding predominantly or exclusively using other sources (i.e., formula, animal milk, solids, and other liquids) that were not human milk, as well as those reporting on "not breastfeeding at hospital

[1]Adelaide Medical School and Robinson Research Institute, University of Adelaide, Adelaide, SA, Australia
[2]Faculty of Health and Medical Sciences, Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia
[3]Health Performance and Policy Research Unit, Basil Hetzel Institute, University of Adelaide, Woodville South, SA, Australia
[4]Adelaide G-TRAC Centre & CRE Frailty & Healthy Ageing Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia
[5]Department of Cardiology, Lyell McEwin Hospital, Elizabeth Vale, SA, Australia
[6]Flinders Health and Medical Research Institute, Flinders University, Bedford Park, SA, Australia

Date submitted: November 9, 2020; Date accepted: June 30, 2021.

Corresponding Author:
Dr. Prabha H Andraweera, MBBS, PhD, The Robinson Research Institute, and The Adelaide Medical School, The University of Adelaide, South Australia, Australia.
Email: prabha.andraweera@adelaide.edu.au

discharge." The definitions of breastfeeding that were reported in the studies are specified in Table 1. GDM is currently defined based on the International Association of Diabetes in Pregnancy Study Group (IADPSG) guidelines (Metzger et al., 2010). However, since GDM diagnosis has been revised recently, we included studies defining GDM based on prior recommended diagnostic criteria such as the 1999 World Health Organization (WHO) definition (Alberti & Zimmet, 1998), and other regional and study specific definitions. All GDM definitions reported for each study are detailed in Table 1. The literature search generated 260 titles, of which 233 were identified through electronic search and 27 were found through bibliographic search of similar reviews (Feng et al., 2018; Ma et al., 2019). Of these, 39 papers were assessed in full text and 18 were found to be eligible. Figure 1 describes the reasons for excluding studies. Overall, nine studies were included in the meta-analysis. The 10 studies that were not included in the meta-analysis are reported in Table 1.

Data Collection: All studies describing the effects of breastfeeding on conventional CVD risk factors in women with previous GDM and those exposed to GDM in utero were identified by searching electronic databases PubMed Medical Subject Headings (Ormesher et al., 2018), CINAHL, and EMBASE, including all studies up until May 26, 2020. MP conducted the search. The complete search strategy is included in Appendix 1. Bibliographic search of previous observational studies, and systematic reviews and meta-analyses on similar topics were cross-checked for additional studies. All identified studies were independently assessed for relevance by two authors (MP, AA). Data was independently extracted by two authors (MP, AA) and discrepancies were resolved by discussion with ZL and PA.

For each study, the following data were extracted: author's last name, study year, country, study design, definition of GDM, assessment of breastfeeding (i.e., how breastfeeding was assessed and how breastfeeding and not breastfeeding were defined), number of women breastfeeding/non-breastfeeding or children who were breastfed/not breastfed, years of postpartum follow-up/age at assessment, outcome measures, and significant findings.

Measurement: Data extraction was completed independently and in duplicate for the following cardiovascular outcomes: systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI), serum lipid levels (low density lipoprotein [LDL] high density lipoprotein [HDL], total cholesterol, and triglycerides), blood glucose, fasting insulin and incidence of T2DM. If the same cohort was assessed in different studies, the meta-analysis would include the study with the largest sample size. The oldest cohort was used for the analysis of children born to pregnancies complicated by GDM. We considered studies published in English. Authors of studies were contacted for data clarification (i.e., any missing data) and additional data, when required. If missing or unclear data could be not clarified, these studies were included in the review and reported in Table 1 but not the meta-analysis.

The National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to assess the methodological quality of each study (NHLBI, 2020). Studies were assessed for internal validity and study quality was decided between authors. Two authors (MP and AA) assessed all eligible studies based on this criteria. Study quality (i.e., high, medium, and low quality) was ascertained based on the authors' scoring and after discussion. The quality assessment is graphically illustrated in the supplementary data (Supplementary Table 1).

Data Analysis: All conventional cardiovascular risk factors were assessed including blood pressure, serum lipids, blood glucose, insulin, and Type 2 diabetes mellitus. The random-effects model was selected as per protocol, in order to account for variability in GDM diagnosis, and differences in breastfeeding practices. For continuous outcomes, mean and standard deviation (*SD*) were reported in the meta-analyses. Standard Error of Mean (*SEM*) was converted to *SD* on RevMan software if Mean and *SD* were not reported. The Standardized Mean Difference (*SMD*) was used when individual studies reported outcome in different units, and Mean Difference (*MD*) was used when units were consistent. For dichotomous outcomes, the *n* of events and *n* of participants were used in the meta-analysis to analyze the Risk Ratio (RR) and the associated 95% CI. The number of participants/events were calculated based on the total sample size for breastfeeding and not breastfeeding groups, if the numbers were only reported as a percentage. All analyses were cross-checked and discrepancies were resolved by discussion (ZL, MP). The significant differences of breastfeeding compared to not breastfeeding for all outcomes was a p of $< .05$. All test values were two-tailed.

When the I^2 statistic exceeded 50%, and the X^2 p value was less than 0.1, substantial heterogeneity was considered. Data that were unable to be reported in the meta-analyses, but still reported an association between breastfeeding and CVD risk in women with GDM history and exposed children were included in Table 1 under significant findings. The meta-analysis was performed using Review Manager Version 5.3, based on inverse variance. Sensitivity analyses were conducted to ascertain heterogeneity for each outcome after excluding studies classified as of low to moderate quality in the NHLBI Quality assessment, as determined after author discussion. Five authors were contacted for additional data, of whom one responded (20% author response rate). Assessment of publication bias by funnel plot analysis was not required for any of the meta-analysis, as there was an inadequate number of studies in the meta-analysis to perform a sufficient assessment.

Table 1. Summary of Reviewed Studies ($N = 17$).

1st Author (date) Country	Design	Definition of GDM	Assessment and definition of BF	n = BF /not breastfed	F/U assessment time or age at f/u	Outcomes	Significant Findings
Studies assessing offspring of mothers with previous GDM							
Hui* (2018) Hong Kong	Prospective cohort	Self-reported (WHO 1999)	Self-administered questionnaire: FF, mix feeding or BF only	464/4,143	0-3 months	BMI Z-Score, Glucose	BF GDM *in utero* = lower BMI > not breastfed at 3 mos. only. Infant glucose levels = lower in BF > not BF infants > *M* blood glucose FF first feed
Martens* (2016) Canada	Retrospective databases	Hospital diagnosis at 21 wks. GA	Medical records	42,332/208,060	24 years	Type II DM	BF initiation was associated > 17% reduced risk of youth onset type 2 DM
Studies assessing mothers with previous GDM							
Chamberlain (2015) Australia	Retrospective database	ADIPS	Discharge medical records	Fully BF = 217 (75%) Partial BF = 51 (18%) Never BF = 17 (6%)	3, 5, 8 years PP	Type II DM	Increased rate of progression to type 2 DM partially BF compared to those who fully Bf at discharge
Corrado (2019) Italy	Retrospective cohort	Italian Institute of Health	Interviewed at OGTT frequency of BF	81/16	3 months	BMI Lipids Glucose Insulin	HOMA-IR is associated with BF
Chouinard-Castonguay (2013) Canada	Retrospective follow-up	Medical records	Self-reported questionnaires. Sum of months of lactation, either exclusive or mixed.	116/28	4 years	BMI Glucose Insulin	BF Higher HOMA-IS than none. Lactation duration was an independent predictor of insulin sensitivity.
Dijigow (2015) Brazil	Retrospective cohort	IADPSG	Medical records BF =yes/no	114/18	40 days PP	Glucose	BF was a protective factor > PP glucose intolerance
Gunderson* (2011) USA	Prospective Observational Cohort	Carpenter & Coustan	Self-reported at 6-9 wks. PP telephone & monthly questionnaires. EBF; Mostly BF; Mixed; EFF	EBF = 211 Mostly BF = 99 Mixed = 77 EFF = 135	6-9 weeks	BMI Glucose	EBF > lower plasma glucose & insulin than FF
Gunderson (2015) USA	Prospective Observational Cohort	Carpenter & Coustan	Same as 2011	EBF = 205 Mostly BF = 387 Mixed = 214 EFF = 153	Same as 2011	Same as 2011	Higher lactation intensity and longer duration is associated with lower adjusted rates of incident DM.
Kim* (2011) South Korea	Prospective Observational	Carpenter & Coustan	Self-reported	BF GDM-NGT = 52% Mixed = 32.3% Not BF GDM = 15.6% prediabetes BF = 47% mixed = 44% No BF GDM-T2DM = 8.3%	6-12 weeks	Type II DM	Lactation and duration of lactation have no significant effect on PP glucose status
Kjos (1993) USA	Prospective Observational	NDDG	Self-reported 4-12 wks. after delivery "Are you nursing your infant?" (Yes or no)	404/405	44-45 days PP	BMI, Lipids Glucose Type II DM	HDL-C was lower in history of GDM in non-lactating compared lactating BF with either diet or insulin therapy had significantly lower fasting serum glucose and higher HDL cholesterol

(continued)

Table 1. (continued)

1st Author (date) Country	Design	Definition of GDM	Assessment and definition of BF	*n* = BF /not breastfed	F/U assessment time or age at f/u	Outcomes	Significant Findings
Martens* (2016) Canada	Retrospective database	Hospital diagnosis at 21 wks. GA	Medical records	7,510/3,040	5, 10, 15, 20, 24 yrs.	Type II DM	Initiating BF inversely related to PP T2DM with & without GDM
McManus (2011) Canada	Prospective Observational	ADA	Not specified	BF 3 mos. = 14 Did not BF past discharge = 12	3 months	Blood pressure BMI Lipids Glucose Insulin	Previous GDM BF = lower systolic BP compared to non-BF DBP = was lower with previous GDM BF Women with a history of GDM BF = higher β-cell function for the degree of insulin resistance based on disposition index
Nelson* (2008) USA	Retrospective cohort	Not specified	Self-reported	BF 1 yr. = 36%	1 year PP	Blood glucose	Normal GTT PP = more likely to BF BF did not protect women from deteriorating GTT
Saucedo (2014) Mexico	Prospective Observational	ADA	Not specified	BF < 6 wks. BF >6 wks. - 6 mos.	6 mos. PP	Lipids Glucose Insulin	BF > 6 wks. = > weight loss PP and lower leptin levels, after wgt. adjustment
Shub* (2019) Australia	Secondary analysis of cohort study	ADIPS	EBF, EFF or mixed	GDM group: EBF = 106 Non-BF = 53 Controls: BF = 65 Non-BF = 19	6-10 wks. PP	Lipids Glucose	Adjusting BMI, age and ethnicity, women with GDM BF = lower fasting glucose No difference > fasting lipids GDM BF and non-BF
Yashui (2017) Japan	Retrospective	Japan Society of Obstetrics & Gynaecology	Questionnaire or telephone interview BF practices at 6-8 wks., 6 mos. & 12 mos. PP. High intensity BF = infants fed by BF alone or roughly 80% at 6-8 wks. & 6 mos. PP	High intensity = 70, non-high = 18	6-8 wks. 6-8 mos. 12-14 mos.	BMI Glucose Insulin	High intensity BF associated with abnormal glucose tolerance HOMA-IR lower in high intensity BF
Ziegler* (2012) Germany	Prospective Observational	German Diabetes Association	Questionnaire BF (yes/no) duration full BF at 9 mos. PP	BF = 201 >3 mo. BF =109 Full BF = 62%	15 years PP	Type II DM	BF associated with a marked delay in DM BF Duration BF inversely associated with PP DM risk and longer DM free duration.

Note. Bf = breastfeeding; EBF = exclusive breastfeeding; FF = formula feeding; EFF = exclusive formula feeding; F/U = follow-up; BMI-Z = Body Mass Index z-score; GA = gestational age; DM = diabetes mellitus; ADIPS = Australian Diabetes in Pregnancy Society; OGTT = Oral Glucose Tolerance Test; HOMA-IR = Homeostatic Model of Insulin Resistance; HOMA-IS = Homeostatic Model of Insulin Sensitivity; IADPSG = International Association of Diabetes in Pregnancy Study Group; NDDG = National Diabetes Data Group 1979; HDL-C = High-density lipoprotein – cholesterol; ADA = American Diabetes Association. Articles not included in the meta-analysis are noted with *.

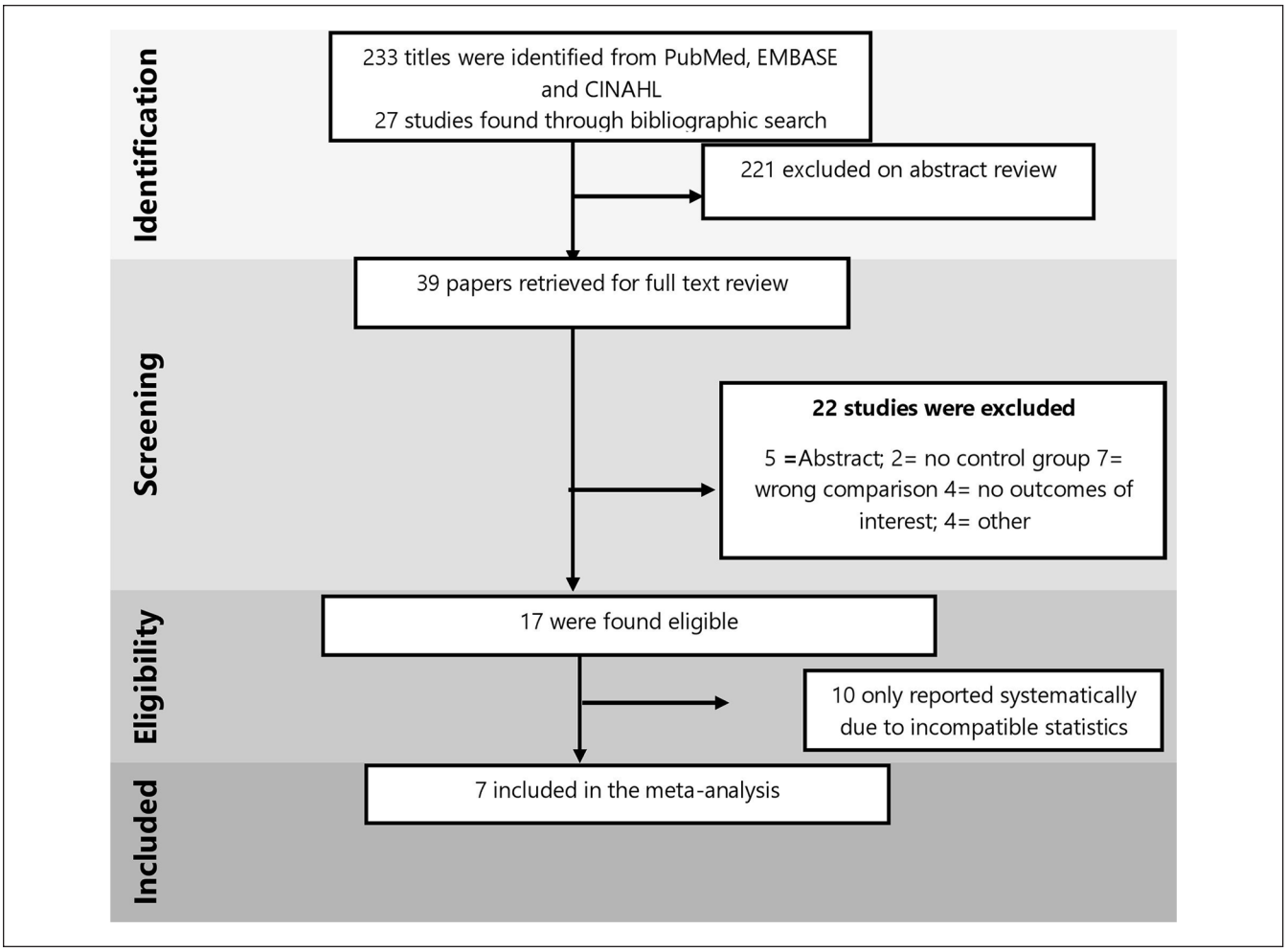


Figure 1. Flow Chart.

Results

Effects of Breastfeeding on Cardiovascular Risk Factors in Women With Previous GDM

Characteristics of the Sample: Table 1 highlights the details of each study. Overall, the majority of studies defined GDM based on the previous criteria; only three studies in the review defined GDM based on definitions influenced by IADPSG guidelines. Most studies were conducted in Caucasian populations, with two studies conducted in Asian populations. The age range of participants across studies was wide, with participants as young as < 25 to > 40 years of age. Follow-up assessment varied between less than 1 month postpartum to 24 years postpartum.

Quality Assessment of Studies: Quality assessment of studies based on the NHLBI tool revealed that nine studies were of high quality, 10 studies were of moderate quality, and none of the studies were of poor quality (Supplementary Table 1).

Blood Pressure: Blood pressure data was reported in one study (McManus et al., 2001). The study showed that systolic and diastolic blood pressure was lower in women with a history of GDM who breastfed compared to those who did not (Table 1).

Body Mass Index: Body Mass Index (BMI) data were reported in five studies (Chouinard-Castonguay et al., 2013; Corrado et al., 2019; Gunderson et al., 2012; Kjos et al., 1993; McManus et al., 2001; Yasuhi et al., 2017). BMI was not different in women with previous GDM who did not breastfeed compared to those who breastfed based on quantitative summary measures (Supplementary Figure 1).

Total Cholesterol: Total cholesterol data was reported in five studies (Corrado et al., 2019; Kjos et al., 1993; McManus et al., 2001; Saucedo, 2014). Total cholesterol levels were not different between women with previous GDM who did not breastfeed in comparison to those who did breastfed (Supplementary Figure 2).

Triglycerides: Serum triglyceride data were available from five studies (Corrado et al., 2019; Kjos et al., 1993; McManus et al., 2001; Saucedo, 2014; Shub et al., 2019). Four studies were reported in the meta-analysis (Corrado

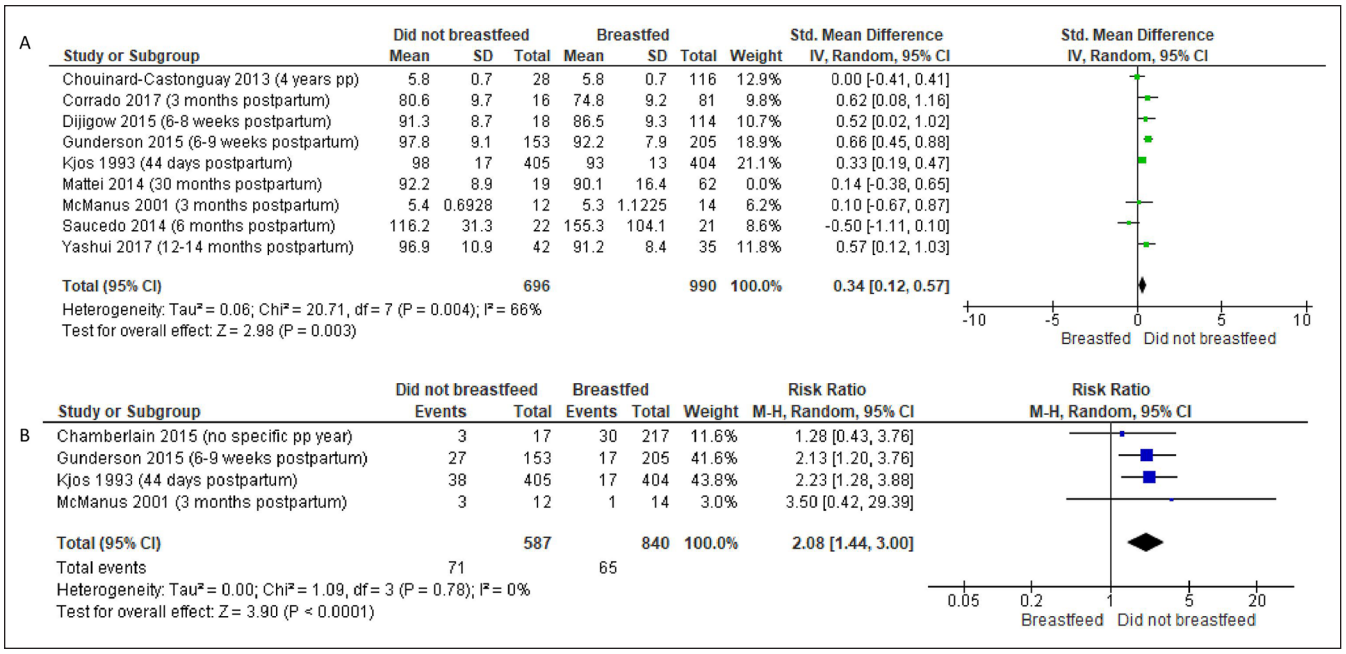


Figure 2. (A) Meta-Analysis of Blood Glucose; (B) Meta-Analysis of T2DM.

et al., 2019; Kjos et al., 1993; McManus et al., 2001; Saucedo, 2014). Serum triglycerides were not different between women who had a history of GDM who did not breastfeed compared to those who did breastfeed (*SMD* = 0.23; 95% CI [-0.01, 0.47]; $p = .06$; $I^2 = 26\%$; Supplementary Figure 3). The authors of the one study not reported in the meta-analysis found that serum triglycerides were not significantly different between women who had a history of GDM who breastfed compared to women with previous GDM who did not breastfeed (Shub et al., 2019).

HDL and LDL Cholesterol: Two studies reported on LDL and HDL cholesterol (Kjos et al., 1993; Shub et al., 2019). Both studies showed that serum LDL-C levels were not different between women who had a history of GDM who did not breastfeed compared to those who breastfed. However the study by Kjos et al. 1993 demonstrated that HDL-C was lower in those with a history of GDM who were non-lactating compared to those who were lactating (Table 1).

Insulin: Fasting insulin data were available from five studies (Chouinard-Castonguay et al., 2013; Corrado et al., 2019; McManus et al., 2001; Saucedo, 2014; Yasuhi et al., 2017). There was no significant difference in fasting insulin between women with previous GDM who did not breastfeed compared to those who breastfed, based on quantitative summary measures (Supplementary Figure 4).

Glucose: Serum glucose data were available from 11 studies (Chouinard-Castonguay et al., 2013; Corrado et al., 2019; Dijigow et al., 2015; Gunderson et al., 2012; 2015; Kjos et al., 1993; McManus et al., 2001; Nelson et al., 2008; Saucedo, 2014; Shub et al., 2019; Yasuhi et al., 2017), of which eight were included in the meta-analysis (Chouinard-Castonguay et al., 2013; Corrado et al., 2019; Dijigow et al., 2015; Gunderson et al., 2015; Kjos et al., 1993; McManus et al., 2001; Saucedo, 2014; Yasuhi et al., 2017). Based on quantitative summary measures, there was a 0.34 *SMD* higher serum glucose level among women with previous GDM who did not breastfeed compared to those who breastfed (*SMD* 0.32; 95% CI [0.12, 0.57]; $p = .003$; $I^2 = 66\%$; Figure 2A). The authors of two studies that were not included in the meta-analysis reported that women with previous GDM who breastfed had significantly lower blood glucose compared to those who did not breastfeed in both unadjusted and adjusted models (Gunderson et al., 2012; Shub et al., 2019). However, Nelson et al. (2008) reported that breastfeeding was not protective against deteriorating glucose tolerance in women with previous GDM.

Incidence of Type 2 diabetes mellitus: Type 2 diabetes mellitus incidence was reported in seven studies (Chamberlain et al., 2016; Gunderson et al., 2015; Kim et al., 2011; Kjos et al., 1993; Martens et al., 2016; McManus et al., 2001; Ziegler et al., 2012), of which four were reported in the meta-analysis (Chamberlain et al., 2016; Gunderson et al., 2015; Kjos et al., 1993; McManus et al., 2001). Based on quantitative summary measures, women with previous GDM who did not breastfeed were at a significantly higher risk of developing T2DM compared to women who breastfed (*RR* 2.21; 95% CI [1.50, 3.27]; $p < .0001$; $I^2 = 0\%$; Figure 2B). From the results of the three studies that were not reported in the meta-analysis, authors of two studies reported that breastfeeding was associated with a reduction in T2DM (Chamberlain et al., 2016; Martens et al., 2016; Ziegler et al., 2012). However, Kim et al. (2011) reported that lactation and

duration of lactation had no significant effect on postpartum glucose status, including progression to T2DM.

Sensitivity Analyses: The results of sensitivity analyses including moderate quality studies showed a significant decrease in heterogeneity for outcomes BMI, triglycerides, and total cholesterol. However, there was an increase in heterogeneity for outcomes blood glucose and insulin. (Supplementary Table 2).

Effect of Breastfeeding on Cardiovascular Risk Factors Among Children Exposed to GDM in Utero

Two studies were eligible for inclusion (Hui et al., 2018; Martens et al., 2016). The details for both studies are included in Table 1.

BMI: One study reported on BMI z-score. Hui et al., in a prospective birth cohort, reported that breastfeeding does not attenuate the association between GDM exposure in utero and BMI in the offspring at 3 months of age (Table 1; Hui et al., 2018).

Type 2 diabetes mellitus: Martens et al. (2016) reported that breastfeeding initiation before hospital discharge was associated with a reduced risk of T2DM at a 24-year follow up in those who were exposed to GDM in utero, (overall HR = 0.83; 95% CI [0.69, 0.99]; $p = .038$).

Discussion

This systematic review comprehensively assessed the influences of breastfeeding on all conventional risk factors for CVD in women with previous GDM, and among children born to pregnancies complicated by GDM. The results of the meta-analysis demonstrated that participants with previous GDM, who breastfed their infants at any stage, had a decrease in some cardiovascular risk factors compared to those who did not breastfeed. There were not enough studies to conduct meta-analyses on the effects of breastfeeding on cardiovascular risk factors in children exposed to GDM in utero. Longitudinal studies with sufficient power are required to ascertain the effects of breastfeeding on cardiovascular risk factors in children exposed to GDM in utero.

Pregnancy complications, including GDM, may confer risk for the development of CVD in women with a predisposition to poor life-long cardiovascular health, due to either genetics or poor lifestyle (or both) Andraweera, 2018. GDM occurs when β-cells fail to undergo sufficient expansion resulting in inadequate compensation for placental induction of a hyperinsulinemic state, which promotes elevation of blood glucose (Abell et al., 2015). This may lead to long-lasting β-cell damage following pregnancy. The growing fetus is also affected as GDM causes an excess of nutrient transport from the maternal to fetal circulation via the placenta. The fetus adapts epigenetically in response to this adverse intrauterine environment and is said to be programmed, which affects growth and long term metabolic health (Hales & Barker, 2001). Therefore, mothers and their children are at higher risk of metabolic and cardiovascular diseases later in life. Preventive strategies and treatments to reduce development of obesity are required to significantly reduce development of CVD in women with a history of GDM and their offspring.

Evidence strongly suggests that changes in body adipose tissue content and reducing hyperglycaemia can promote disease mitigation (Kim et al., 2011). While lifestyle changes can promote a significant risk reduction, compliance drops after 1 year postpartum (Ratner et al., 2008). Physiological preparation for breastfeeding occurs during pregnancy and initiation of breastfeeding after birth aids maternal recovery and is mutually beneficial for both mother and baby (Stuebe & Rich-Edwards, 2009). Authors of various studies have reported that mothers who breastfeed for a period of 6–12 months are leaner with a lower BMI than those who do not (Jiang et al., 2018). Those who are breastfed are also less likely to be overweight or obese than those who are formula fed (Harder et al., 2005; Yan et al., 2014). Therefore, good quality evidence on the effects of breastfeeding on women with a history of GDM and their children is necessary to support updates to guidelines regarding breastfeeding in women with previous GDM and the benefits for long-term cardiovascular health.

Overall, study participants with previous GDM had a higher cumulative incidence of hypertension and ischemic heart disease compared with controls (Daly et al., 2018). Breastfeeding may mitigate the risk of hypertension in all mothers, as it has been reported that women who breastfed are less likely to be hypertensive in comparison to those who did not (Rameez et al., 2019). It is thought that the increase in oxytocin and prolactin in breastfeeding mothers influences blood pressure regulation and furthermore promotes positive changes to vascular remodeling (Burgess et al., 2019). This concept supports the hypothesis that breastfeeding may cause a physiological reset to the adverse effects that occur due to pregnancy (Lessen & Kavanagh, 2015). There were not enough studies to complete a meta-analysis on systolic and diastolic blood pressure in those with a history of GDM who breastfed. Therefore, further research is required to understand the effects of breastfeeding on systolic and diastolic blood pressure in women with a history of GDM.

Women who breastfeed have a higher metabolic expenditure and increased rate of lipolysis than those who do not breastfeed (Gunderson et al., 2007). Previously researchers have reported that breastfeeding duration was associated with a reduction of dyslipidaemia in young women, including a reduction in the level of serum triglycerides. Furthermore, triglycerides made up the majority of fats in human milk (Martin et al., 2016). We were unable to show a difference in serum triglycerides between those with a history of GDM who breastfed compared to those who did not breastfeed. Therefore, more research may be needed to

investigate an association between breastfeeding and the reduction in serum triglycerides in mothers.

There is strong evidence to suggest that breastfeeding reduces the risk of T2DM (Horta et al., 2015; Rameez et al., 2019). It has been reported that women who have never breastfed have a 50% higher risk for developing T2DM than women who breastfed for as little as 1–3 months postpartum (Schwarz et al., 2010). Our results support an association between breastfeeding and a reduced risk of T2DM in women with previous GDM. Considering the significantly higher risk of developing T2DM among women with previous GDM, many of whom also exhibit a pre-diabetic phenotype (Buchanan et al., 2012), breastfeeding should be highly encouraged in this population to reduce the risk of T2DM later in life.

Researchers have suggested that breastfeeding can reduce the risk of non-communicable disease in children. Human milk is composed of long-chain polyunsaturated fatty acids, which can promote blood pressure reduction, and changes in skeletal muscle allowing for protection against insulin resistance and development of T2DM (Horta et al., 2015). Whereas, formula fed or mixed fed infants have been reported to present with higher levels of insulin resistance and atherosclerotic markers, and exhibit poor β-cell function (Lucas et al., 1980; Shoji & Shimizu, 2019). Breastfeeding may also promote a healthier diet, as those who are breastfed are more likely to have a higher intake of fruits and vegetables than those who are not (Moss et al., 2020). This may also be influenced by the fact that women who choose to breastfeed may be more likely to have a high quality diet and promote this lifestyle in their children. As obesity and metabolic risk factors manifest as young as 3 years old in offspring exposed to GDM in utero (Pathirana et al., 2020), breastfeeding may be protective against early life obesity. Only two studies in the review assessed cardiovascular risk factors in those exposed to GDM in utero who were and were not breastfed. Based on current literature, longitudinal studies that assess long-term cardiovascular benefits of breastfeeding among children exposed to GDM in utero are warranted.

Limitations: Based on the qualitative assessment, many of the studies were of high to moderate quality. Due to the observational and retrospective design of the studies included in the review, it was not possible for the majority of authors of studies to assess the frequency and volume of human milk fed to infants exposed to GDM in utero. A qualitative study design renders it difficult to assess outcomes continuously; rather, a randomized control trial design would be more effective to account for variables in a controlled manner. However, studies by Gunderson et al. (2015) and Yashui et al. (2017) utilized a design in which participants were contacted via telephone over the study period and interviewed about their current breastfeeding routine, therefore enabling less change of recall bias.

Some outcomes in the meta-analysis exhibited higher heterogeneity. However, sensitivity analysis resulted in reduced heterogeneity on outcomes of BMI, total cholesterol, and triglycerides (Supplementary Table 2) but a moderate increase in heterogeneity for the other outcomes. Funnel plot analysis was not required, as the number of studies for each outcome did not exceed 10. Heterogeneity in aggregate data is hard to ascertain. It can be due to study specific differences, such as diversity in population, age of assessment, definition of disease, and so forth. We attribute some heterogeneity in these analyses to the different definitions of breastfeeding, particularly as lactation was defined in some studies as $> = 6$ months of exclusive breastfeeding, and in others as breastfeeding at hospital discharge. The majority of the studies used definitions of GDM that were prior to the new IADPSG definition, which has a lower cut-off for GDM diagnosis, and is therefore thought to increase the number of women being diagnosed with GDM. Therefore, this may affect the assessment of cardiovascular outcomes and representation of women with GDM as studies with the old definition were used primarily in the meta-analysis. Presentation of CVD risk factors in these women may be affected by the time of postpartum assessment. We were unable to complete subgroup analyses stratified by time of risk factor assessment due to the low number of available studies. However, previous reviews we have completed have demonstrated that cardiovascular risk factors are seen as early as < 1 year postpartum in women with previous GDM (Pathirana et al., 2020a; 2020b).

Conclusion

Women with previous GDM should be encouraged to breastfeed to reduce their risk of CVD later in life. More research in this area is required in order to integrate it fully for clinical use and disease mitigation strategies. Lactation specialists should promote breastfeeding in women with previous GDM through integrating what is known about the benefits of breastfeeding on cardiovascular disease risk factors. More research is needed to determine the effects of breastfeeding on cardiovascular risk factors in children exposed to GDM in utero, but the limited literature reports protective effects.

Appendix 1

P – Women with history of GDM, children who are exposed to GDM *in utero*

I – Breastfeeding

C – Formula fed

O – Conventional Cardiovascular risk factors (BP, BMI/BMI z-score, Glucose, Lipids, Insulin), T2DM, metabolic syndrome

I had a look on PubMed again – I don't think there will be many studies for this review except for studies looking at T2DM. I think it'll be pretty similar to the MetS review

GDM	Breastfeeding	Formula milk	Outcomes	Population
"Diabetes, Gestational"[MeSH] OR "gestational diabetes*" [tiab] OR "pregnancy induced diabetes" [tiab]	Breast Feeding [MeSH] OR milk, human [MeSH] OR "breastfeeding" [tiab] OR "breast milk" [tiab] OR "breastfeed" [tiab] OR "lactat*" [tiab] OR "breastfed" [tiab]	"infant formula" [MeSH] OR "animal milk" [tiab] OR "cow milk" [tiab] OR "cow's milk" [tiab] OR "goat milk" [tiab] OR "goat's milk" [tiab] ~~OR "animal colostrum" [tiab]~~ OR "infant formula" [tiab] OR "formula milk" OR "baby formula" [tiab]	"metabolic syndrome"[MeSH] ~~OR "Diabetes, Gestational"[MESH]~~ OR "Blood Pressure"[MESH] OR "hypertension"[MESH] OR "cholesterol"[MESH] OR "lipids"[MESH] OR "triglyceride"[MESH] OR "body mass index"[MESH] OR "insulin"[MESH] OR "glucose"[MESH] OR "diabetes mellitus, type 2"[MeSH] OR "blood pressure"[tiab] OR "diabetes" [tiab] OR "BMI" [tiab] OR "cardiovascular" [tiab] OR "metabolic"[tiab] OR "lipid"[tiab] OR "hypertension"[tiab] OR "body mass index"[tiab] OR "obesity"[tiab] OR "overweight"[tiab] OR lipid*[tiab] OR "cholesterol"[tiab] OR "triglyceride*"[tiab] OR "glucose"[tiab] OR "insulin"[tiab] OR "vascular"[tiab] OR "type 2 diabetes mellitus"[tiab] OR "T2DM"[tiab] OR "metabolic syndrome"[tiab] OR "insulin resistance syndrome"[tiab] OR "syndrome X"[tiab]	"pregnan*"[tiab] OR "mother"[tiab] OR "women"[tiab] OR "woman"[tiab] OR "kid"[tiab] OR "adult"[tiab] OR "child*"[tiab] OR "offspring"[tiab] OR "neonate"[tiab] OR "infant"[tiab] OR "adult"[tiab]

PUBMED = 35 on PUBMED

("Diabetes, Gestational"[MeSH] OR "gestational diabetes*" [tiab] OR "pregnancy induced diabetes" [tiab]) AND (Breast Feeding [MeSH] OR milk, human [MeSH] OR "breastfeeding" [tiab] OR "breast milk" [tiab] OR "breastfeed" [tiab] OR "lactat*" [tiab] OR "breastfed" [tiab]) AND ("infant formula" [MeSH] OR "animal milk" [tiab] OR "formula fed" OR "cow milk" [tiab] OR "cow's milk" [tiab] OR "goat milk" [tiab] OR "goat's milk" [tiab] OR "colostrum" [tiab] OR "infant formula" [tiab] OR "formula milk" OR "baby formula" [tiab]) AND ("metabolic syndrome"[MeSH] OR "Diabetes, Gestational"[MESH] OR "Blood Pressure"[MESH] OR "hypertension"[MESH] OR "cholesterol"[MESH] OR "lipids"[MESH] OR "triglyceride"[MESH] OR "body mass index"[MESH] OR "insulin"[MESH] OR "glucose"[MESH] OR "diabetes mellitus, type 2"[MeSH] OR "blood pressure"[tiab] OR "diabetes" [tiab] OR "BMI" [tiab] OR "cardiovascular" [tiab] OR "metabolic"[tiab] OR "lipid"[tiab] OR "hypertension"[tiab] OR "body mass index"[tiab] OR "obesity"[tiab] OR "overweight"[tiab] OR lipid*[tiab] OR "cholesterol"[tiab] OR "triglyceride*"[tiab] OR "glucose"[tiab] OR "insulin"[tiab] OR "vascular"[tiab] OR "type 2 diabetes mellitus"[tiab] OR "T2DM"[tiab] OR "metabolic syndrome"[tiab] OR "insulin resistance syndrome"[tiab] OR "syndrome X"[tiab]) AND ("pregnan*"[tiab] OR "mother"[tiab] OR "women"[tiab] OR "woman"[tiab] OR "kid"[tiab] OR "adult"[tiab] OR "child*"[tiab] OR "offspring"[tiab] OR "neonate"[tiab] OR "infant"[tiab] OR "adult"[tiab])

EMBASE

GDM	Breastfeeding	Formula milk	Outcomes	Population
"Diabetes, Gestational"/ Ex OR "gestational diabetes*":ti,ab OR "pregnancy induced diabetes" :ti,ab	Breast Feeding/ex OR milk, human/ex OR "breastfeeding" :ti,ab OR "breast milk" :ti,ab OR "breastfeed" :ti,ab OR "lactat*":ti,ab OR "breastfed" :ti,ab	"infant formula"/ex OR "animal milk" :ti,ab OR "cow milk" :ti,ab OR "cow's milk" :ti,ab OR "goat milk" :ti,ab OR "goat's milk" :ti,ab ~~OR colostrum"~~ :ti,ab OR "infant formula" :ti,ab OR "formula milk" :ti,ab OR "baby formula" :ti,ab	"metabolic syndrome"/ ex OR "Diabetes, Gestational"/ex OR "Blood Pressure"/ex OR "hypertension"/ ex OR "cholesterol"/ ex OR "lipids"/ex OR "triglyceride"/ex OR "body mass index"/ ex OR "insulin"/ex OR "glucose"/ex OR "diabetes mellitus, type 2"/ex OR "blood pressure":ti,ab OR "diabetes":ti,ab OR "BMI" :ti,ab OR "cardiovascular":ti,ab OR "metabolic":ti,ab OR "lipid":ti,ab OR "hypertension" :ti,ab OR "body mass index" :ti,ab OR "obesity" :ti,ab OR "overweight" :ti,ab OR lipid*:ti,ab OR "cholesterol" :ti,ab OR "triglyceride*":ti,ab OR "glucose" :ti,ab OR "insulin" :ti,ab OR "vascular":ti,ab OR "type 2 diabetes mellitus":ti,ab OR "T2DM":ti,ab OR "metabolic syndrome":ti,ab OR "insulin resistance syndrome":ti,ab OR "syndrome X":ti,ab	"pregnan*":ti,ab OR "mother" :ti,ab OR "women":ti,ab OR "woman":ti,ab OR "kid" :ti,ab OR "adult" :ti,ab OR "child*":ti,ab OR "offspring" :ti,ab OR "neonate" :ti,ab OR "infant" :ti,ab OR "adult" :ti,ab

EMBASE = 133

'diabetes, gestational'/exp OR 'gestational diabetes*':ti,ab OR 'pregnancy induced diabetes':ti,ab AND breast AND 'feeding'/exp OR milk, AND 'human'/exp OR 'breastfeeding':ti,ab OR 'breast milk':ti,ab OR 'breastfeed':ti,ab OR 'lactat*':ti,ab OR 'breastfed':ti,ab AND 'infant formula'/exp OR 'animal milk':ti,ab OR 'cow milk':ti,ab OR 'cows milk':ti,ab OR 'goat milk':ti,ab OR 'colostrum':ti,ab OR 'infant formula':ti,ab OR 'formula milk':ti,ab OR 'baby formula':ti,ab AND 'metabolic syndrome'/exp OR 'diabetes, gestational'/exp OR 'blood pressure'/exp OR 'hypertension'/exp OR 'cholesterol'/exp OR 'lipids'/exp OR 'triglyceride'/exp OR 'body mass index'/exp OR 'insulin'/exp OR 'glucose'/exp OR 'diabetes mellitus, type 2'/exp OR 'blood pressure':ti,ab OR 'diabetes':ti,ab OR 'bmi':ti,ab OR 'cardiovascular':ti,ab OR 'metabolic':ti,ab OR 'lipid':ti,ab OR 'hypertension':ti,ab OR 'body mass index':ti,ab OR 'obesity':ti,ab OR 'overweight':ti,ab OR lipid*:ti,ab OR 'cholesterol':ti,ab OR 'triglyceride*':ti,ab OR 'glucose':ti,ab OR 'insulin':ti,ab OR 'vascular':ti,ab OR 'type 2 diabetes mellitus':ti,ab OR 't2dm':ti,ab OR 'metabolic syndrome':ti,ab OR 'insulin resistance syndrome':ti,ab OR 'syndrome x':ti,ab AND 'pregnan*':ti,ab OR 'mother':ti,ab OR 'women':ti,ab OR 'woman':ti,ab OR 'kid':ti,ab OR 'child*':ti,ab OR 'offspring':ti,ab OR 'neonate':ti,ab OR 'infant':ti,ab OR 'adult':ti,ab

CINHAL

GDM	Breastfeeding	Formula milk	Outcomes	Population
MH "Diabetes, Gestational" + OR "gestational diabetes*" OR "pregnancy induced diabetes"	Breast Feeding [MeSH] "breastfeeding" OR "breast milk" OR "breastfeed" OR "lactat*" OR "breastfed"	"infant formula" +OR "animal milk" OR "cow milk" OR "cow's milk" OR "goat milk" OR "goat's milk" OR "animal colostrum" OR "infant formula" OR "formula milk" OR "baby formula"	"metabolic syndrome" + OR "Diabetes, Gestational" + OR "Blood Pressure" + OR "hypertension"+ OR "cholesterol" + OR "lipids" + OR "triglycerides" + OR "body mass index" + OR "insulin" + OR "glucose" +OR "diabetes mellitus, type 2" + OR "blood pressure" OR "diabetes" OR "BMI" OR "cardiovascular" OR "metabolic" OR "lipid" OR "hypertension" OR "body mass index" OR "obesity" OR "overweight" OR lipid* OR "cholesterol" OR "triglyceride*" OR "glucose" OR "insulin" OR "vascular" OR "type 2 diabetes mellitus" OR "T2DM" OR "metabolic syndrome" OR "insulin resistance syndrome" OR "syndrome X"	"pregnan*"OR "mother" OR "women" OR "woman" OR "kid" OR "adult" OR "child*" OR "offspring" OR "neonate" OR "infant" OR "adult"

CINHAL -65

MH "Diabetes, Gestational" + OR TX ("gestational diabetes*" OR "pregnancy induced diabetes" AND

MH Breast Feeding+ OR TX ("breastfeeding" OR "breast milk" OR "breastfeed" OR "lactat*" OR "breastfed" AND

MH "infant formula" + OR TX ("animal milk" OR "cow milk" OR "cow's milk" OR "goat milk" OR "goat's milk" OR "animal colostrum" OR "infant formula" OR "formula milk" OR "baby formula") AND MH ("metabolic syndrome" + OR "Diabetes, Gestational" + OR "Blood Pressure" + OR "hypertension"+ OR "cholesterol" + OR "lipids" + OR "triglycerides" + OR "body mass index" + OR "insulin" + OR "glucose" +OR "diabetes mellitus, type 2") OR TX ("blood pressure" OR "diabetes" OR "BMI" OR "cardiovascular" OR "metabolic" OR "lipid" OR "hypertension" OR "body mass index" OR "obesity" OR "overweight" OR lipid* OR "cholesterol" OR "triglyceride*" OR "glucose" OR "insulin" OR "vascular" OR "type 2 diabetes mellitus" OR "T2DM" OR "metabolic syndrome" OR "insulin resistance syndrome" OR "syndrome X") OR "blood pressure" OR "diabetes" OR "BMI" OR "cardiovascular" OR "metabolic" OR "lipid" OR "hypertension" OR "body mass index" OR "obesity" OR "overweight" OR lipid* OR "cholesterol" OR "triglyceride*" OR "glucose" OR "insulin" OR "vascular" OR "type 2 diabetes mellitus" OR "T2DM" OR "metabolic syndrome" OR "insulin resistance syndrome" OR "syndrome X" "pregnan*"OR "mother" OR "women" OR "woman" OR "kid" OR "adult" OR "child*" OR "offspring" OR "neonate" OR "infant" OR "adult"

Disclosures and Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Claire T. Roberts https://orcid.org/0000-0002-9250-2192
Prabha H. Andraweera https://orcid.org/0000-0003-2434-8370

Supplemental Material

Supplementary Material may be found in the "Supplemental material" tab in the online version of this article.

References

Abell, S. K., De Courten, B., Boyle, J. A., & Teede, H. J. (2015). Inflammatory and other biomarkers: Role in pathophysiology and prediction of gestational diabetes mellitus. *International Journal of Molecular Sciences*, *16*(6), 13442–13473. https://doi.org/10.3390/ijms160613442

Alberti, K. G., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine*, *15*(7), 539–553. https://doi.org/10.1002/(sici)1096-9136(199807)15:7<539::Aid-dia668>3.0.Co;2-s

Andraweera, P., Dekker, G., Arstall, M., Bianco-Miotto, T., & Roberts, C. (2018). Complications of pregnancy and future cardiovascular risk. In D. Sawyer & R. Vasan (Ed.), *Encyclopedia of cardiovascular research and medicine* (Vol. 1). Elsevier Inc.

Bellamy, L., Casas, J. P., Hingorani, A. D., & Williams, D. (2009). Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. *Lancet*, *373*(9677), 1773–1779. https://doi.org/10.1016/s0140-6736(09)60731-5

Buchanan, T. A., Xiang, A. H., & Page, K. A. (2012). Gestational diabetes mellitus: Risks and management during and after pregnancy. *Nature Reviews Endocrinology*, *8*(11), 639–649. https://doi.org/10.1038/nrendo.2012.96

Burgess, A., McDowell, W., & Ebersold, S. (2019). Association between lactation and postpartum blood pressure in women with preeclampsia. *The American Journal of Maternal Child Nursing*, *44*(2), 86–93. https://doi.org/10.1097/nmc.0000000000000502

Chamberlain, C. R., Oldenburg, B., Wilson, A. N., Eades, S. J., O'Dea, K., Oats, J. J., & Wolfe, R. (2016). Type 2 diabetes after gestational diabetes: greater than fourfold risk among indigenous compared with non-indigenous Australian women. *Diabetes/Metabolism Research and Reviews*, *32*(2), 217–227. https://doi.org/10.1002/dmrr.2715

Chouinard-Castonguay, S., Weisnagel, S. J., Tchernof, A., & Robitaille, J. (2013). Relationship between lactation duration and insulin and glucose response among women with prior gestational diabetes. *European Journal of Endocrinology*, *168*(4), 515–523. https://doi.org/10.1530/eje-12-0939

Corrado, F., Giunta, L., Granese, R., Corrado, S., Micali, M., Santamaria, A., D'Anna, R., & Di Benedetto, A. (2019). Metabolic effects of breastfeeding in women with previous gestational diabetes diagnosed according to the IADPSG criteria. *Journal of Maternal–Fetal and Neonatal Medicine*, *32*(2), 225–228. https://doi.org/10.1080/14767058.2017.1377175

Daly, B., Toulis, K. A., Thomas, N., Gokhale, K., Martin, J., Webber, J., Keerthy, D., Jolly, K., Saravanan, P., & Nirantharakumar, K. (2018). Increased risk of ischemic heart disease, hypertension, and Type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study. *PLoS Medicine*, *15*(1), e1002488. https://doi.org/10.1371/journal.pmed.1002488

Dijigow, F. B., Paganoti Cde, F., Costa, R. A., Francisco, R. P., & Zugaib, M. (2015). Influência da amamentação nos resultados do teste oral de tolerância à glicose pós-parto de mulheres com diabetes mellitusgestacional [The influence of breastfeeding in postpartum oral glucose tolerance test in women with recent gestational diabetes mellitus]. *Revista Brasileira de Ginecologia e Obstetrícia*, *37*(12), 565–570. https://doi.org/10.1590/so100-720320150005488

Feng, L., Xu, Q., Hu, Z., & Pan, H. (2018). Lactation and progression to Type 2 diabetes in patients with gestational diabetes mellitus: A systematic review and meta-analysis of cohort studies. *Journal of Diabetes Investigation*, *9*(6), 1360–1369. https://doi.org/10.1111/jdi.12838

Gunderson, E. P., Hedderson, M. M., Chiang, V., Crites, Y., Walton, D., Azevedo, R. A., Fox, G., Elmasian, C., Young, S., Salvador, N., Lum, M., Quesenberry, C. P., Lo, J. C., Sternfeld, B., Ferrara, A., & Selby, J. V. (2012). Lactation intensity and postpartum maternal glucose tolerance and insulin resistance in women with recent GDM: The SWIFT cohort. *Diabetes Care*, *35*(1), 50–56. https://doi.org/10.2337/dc11-1409

Gunderson, E. P., Hurston, S. R., Ning, X., Lo, J. C., Crites, Y., Walton, D., Dewey, K. G., Azevedo, R. A., Young, S., Fox, G., Elmasian, C. C., Salvador, N., Lum, M., Sternfeld, B., Quesenberry, C. P., Selby, J., Ferrara, A., & Chiang, V. (2015). Lactation and progression to Type 2 diabetes mellitus after gestational diabetes mellitus a prospective cohort study. *Annals of Internal Medicine*, *163*(12), 889–898. https://doi.org/10.7326/M15-0807

Gunderson, E. P., Lewis, C. E., Wei, G. S., Whitmer, R. A., Quesenberry, C. P., & Sidney, S. (2007). Lactation and changes in maternal metabolic risk factors. *Obstetrics and Gynecology*, *109*(3), 729–738. https://doi.org/10.1097/01.Aog.0000252831.06695.03

Hales, C. N., & Barker, D. J. (2001). The thrifty phenotype hypothesis. *British Medical Bulletin*, *60*, 5–20. https://doi.org/10.1093/bmb/60.1.5

Harder, T., Bergmann, R., Kallischnigg, G., & Plagemann, A. (2005). Duration of breastfeeding and risk of overweight: A meta-analysis. *American Journal of Epidemiology*, *162*(5), 397–403. https://doi.org/10.1093/aje/kwi222

Horta, B. L., Loret de Mola, C., & Victora, C. G. (2015). Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and Type 2 diabetes: A systematic review and meta-analysis. *Acta Paediatrica*, *104*(467), 30–37. https://doi.org/10.1111/apa.13133

Hui, L. L., Li, A. M., Nelson, E. A. S., Leung, G. M., Lee, S. L., & Schooling, C. M. (2018). In utero exposure to gestational diabetes and adiposity: does breastfeeding make a difference? *International Journal of Obesity*, *42*(7), 1317–1325. https://doi.org/10.1038/s41366-018-0077-2

International Diabetes Federation. (2007). *The IDF consensus definition of the metabolic syndrome in children and adolescents*. International Diabetes Federation. https://www.idf.org/e-library/consensus-statements/61-idf-consensus-definition-of-metabolic-syndrome-in-children-and-adolescents.html

Jiang, M., Gao, H., Vinyes-Pares, G., Yu, K., Ma, D., Qin, X., & Wang, P. (2018). Association between breastfeeding duration and postpartum weight retention of lactating mothers: A meta-analysis of cohort studies. *Clinical Nutrition*, *37*(4), 1224–1231. https://doi.org/10.1016/j.clnu.2017.05.014

Kim, S. H., Kim, M. Y., Yang, J. H., Park, S. Y., Yim, C. H., Han, K. O., Yoon, H. K., & Park, S. (2011). Nutritional risk factors of early development of postpartum prediabetes and diabetes in

women with gestational diabetes mellitus. *Nutrition*, *27*(7–8), 782–788. https://doi.org/10.1016/j.nut.2010.08.019

Kjos, S. L., Henry, O., Lee, R. M., Buchanan, T. A., & Mishell, D. R., Jr. (1993). The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. *Obstetrics and Gynecology*, *82*(3), 451–455.

Lessen, R., & Kavanagh, K. (2015). Position of the academy of nutrition and dietetics: Promoting and supporting breastfeeding. *Journal of the Academy of Nutrition and Dietetics*, *115*(3), 444–449. https://doi.org/10.1016/j.jand.2014.12.014

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., & Collins, R. (2002). Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*, *360*(9349), 1903–1913. https://doi.org/10.1016/s0140-6736(02)11911-8

Lucas, A., Sarson, D. L., Blackburn, A. M., Adrian, T. E., Aynsley-Green, A., & Bloom, S. R. (1980). Breast vs bottle: Endocrine responses are different with formula feeding. *Lancet*, *1*(8181), 1267–1269. https://doi.org/10.1016/s0140-6736(80)91731-6

Ma, S., Hu, S., Liang, H., Xiao, Y., & Tan, H. (2019). Metabolic effects of breastfeed in women with prior gestational diabetes mellitus: A systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews*, *35*(3), e3108. https://doi.org/10.1002/dmrr.3108

Martens, P. J., Shafer, L. A., Dean, H. J., Sellers, E. A., Yamamoto, J., Ludwig, S., Heaman, M., Phillips-Beck, W., Prior, H. J., Morris, M., McGavock, J., Dart, A. B., & Shen, G. X. (2016). Breastfeeding initiation associated with reduced incidence of diabetes in mothers and offspring. *Obstetrics and Gynecology*, *128*(5), 1095–1104. https://doi.org/10.1097/aog.0000000000001689

Martin, C. R., Ling, P. R., & Blackburn, G. L. (2016). Review of infant feeding: Key features of breast milk and infant formula. *Nutrients*, *8*(5). https://doi.org/10.3390/nu8050279

McManus, R. M., Cunningham, I., Watson, A., Harker, L., & Finegood, D. T. (2001). Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. *Metabolism*, *50*(6), 715–719. https://doi.org/10.1053/meta.2001.23304

Metzger, B. E., Gabbe, S. G., Persson, B., Buchanan, T. A., Catalano, P. A., Damm, P., Dyer, A. R., Leiva, A., Hod, M., Kitzmiler, J. L., Lowe, L. P., McIntyre, H. D., Oats, J. J., Omori, Y., & Schmidt, M. I. (2010). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*, *33*(3), 676–682. https://doi.org/10.2337/dc09-1848

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*, *339*, b2535. https://doi.org/10.1136/bmj.b2535

Moss, K. M., Dobson, A. J., Tooth, L., & Mishra, G. D. (2020). Associations between feeding practices in infancy and fruit and vegetable consumption in childhood. *British Journal of Nutrition*, 1–9. https://doi.org/10.1017/s000711452000238x

Nelson, A. L., Le, M. H., Musherraf, Z., & Vanberckelaer, A. (2008). Intermediate-term glucose tolerance in women with a history of gestational diabetes: natural history and potential associations with breastfeeding and contraception. *American Journal of Obstetrics and Gynecology*, *198*(6), 699, e691–697; discussion 699, e697–698. https://doi.org/10.1016/j.ajog.2008.03.029

National Heart, Lung, and Blood Institute. (2020). *Study quality assessment tools*. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Ormesher, L., Johnstone, E. D., Shawkat, E., Dempsey, A., Chmiel, C., Ingram, E., Higgins, L. E., & Myers, J. E. (2018). A clinical evaluation of placental growth factor in routine practice in high-risk women presenting with suspected pre-eclampsia and/or fetal growth restriction. *Pregnancy Hypertension*, *14*, 234–239. https://doi.org/10.1016/j.preghy.2018.03.007

Pathirana, M. M., Lassi, Z., Ali, A., Arstall, M., Roberts, C. T., & Andraweera, P. H. (2020a). Cardiovascular risk factors in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. *Reviews in Endocrine and Metabolic Disorders*. https://doi.org/10.1007/s11154-020-09587-0

Pathirana, M. M., Lassi, Z. S., Ali, A., Arstall, M. A., Roberts, C. T., & Andraweera, P. H. (2020b). Association between metabolic syndrome and gestational diabetes mellitus in women and their children: A systematic review and meta-analysis. *Endocrine*. https://doi.org/10.1007/s12020-020-02492-1

Pathirana, M. M., Lassi, Z. S., Ali, A., Arstall, M. A., Roberts, C. T., & Andraweera, P. H. (2021). Association between metabolic syndrome and gestational diabetes mellitus in women and their children: A systematic review and meta-analysis. *Endocrine*, *71*(2), 310–320. https://doi.org/10.1007/s12020-020-02492-1

Pathirana, M. M., Lassi, Z. S., Roberts, C. T., & Andraweera, P. H. (2020). Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: Systematic review and meta-analysis. *Journal of Developmental Origins of Health and Disease*, 1–18. https://doi.org/10.1017/s2040174419000850

Rameez, R. M., Sadana, D., Kaur, S., Ahmed, T., Patel, J., Khan, M. S., Misbah, S., Simonson, M. T., Riaz, H., & Ahmed, H. M. (2019). Association of maternal lactation with diabetes and hypertension: A systematic review and meta-analysis. *JAMA Network Open*, *2*(10), e1913401. https://doi.org/10.1001/jamanetworkopen.2019.13401

Ranasinghe, P., Mathangasinghe, Y., Jayawardena, R., Hills, A. P., & Misra, A. (2017). Prevalence and trends of metabolic syndrome among adults in the asia-pacific region: a systematic review. *BMC Public Health*, *17*(1), 101. https://doi.org/10.1186/s12889-017-4041-1

Ratner, R. E., Christophi, C. A., Metzger, B. E., Dabelea, D., Bennett, P. H., Pi-Sunyer, X., Fowler, S., & Kahn, S. E. (2008). Prevention of diabetes in women with a history of gestational diabetes: Effects of metformin and lifestyle interventions. *The Journal of Clinica Endocrinology & Metabolism*, *93*(12), 4774–4779. https://doi.org/10.1210/jc.2008-0772

Saucedo, R., B. L., Galvan, R., Sanchez, J., Hernadez, M., Puello, E., & Zarate, A. (2014). Duration of lactation is associated with lower leptin levels in patients with gestational diabetes mellitus. *Instituto Mexican del Suguro Social, 06720*. https://doi.org/10.1530/EJE-12-0939

Schwarz, E. B., Brown, J. S., Creasman, J. M., Stuebe, A., McClure, C. K., Van Den Eeden, S. K., & Thom, D. (2010). Lactation and maternal risk of Type 2 diabetes: A population-based study. *American Journal of Medicine*, *123*(9), 863 e861–866. https://doi.org/10.1016/j.amjmed.2010.03.016

Shoji, H., & Shimizu, T. (2019). Effect of human breast milk on biological metabolism in infants. *Pediatrics International*, *61*(1), 6–15. https://doi.org/10.1111/ped.13693

Shub, A., Miranda, M., Georgiou, H. M., McCarthy, E. A., & Lappas, M. (2019). The effect of breastfeeding on postpartum glucose tolerance and lipid profiles in women with gestational diabetes mellitus. *International Breastfeeding Journal*, *14*, 46. https://doi.org/10.1186/s13006-019-0238-5

Stuebe, A. M., & Rich-Edwards, J. W. (2009). The reset hypothesis: Lactation and maternal metabolism. *American Journal of Perinatology*, *26*(01), 081–088. https://doi.org/10.1055/s-0028-1103034

Yan, J., Liu, L., Zhu, Y., Huang, G., & Wang, P. P. (2014). The association between breastfeeding and childhood obesity: A meta-analysis. *BMC Public Health*, *14*, 1267. https://doi.org/10.1186/1471-2458-14-1267

Yasuhi, I., Soda, T., Yamashita, H., Urakawa, A., Izumi, M., Kugishima, Y., & Umezaki, Y. (2017). The effect of high-intensity breastfeeding on postpartum glucose tolerance in women with recent gestational diabetes. *International Breastfeeding Journal*, *12*, 32. https://doi.org/10.1186/s13006-017-0123-z

Ziegler, A. G., Wallner, M., Kaiser, I., Rossbauer, M., Harsunen, M. H., Lachmann, L., Maier, J., Winkler, C., & Hummel, S. (2012). Long-term protective effect of lactation on the development of Type 2 diabetes in women with recent gestational diabetes mellitus. *Diabetes*, *61*(12), 3167–3171. https://doi.org/10.2337/db12-0393