Obstetrical interventions during labour and birth: an examination of effects on breastfeeding, neonatal mortality and children's educational outcomes

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Declaration

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed: …… ………………………………………………….

Engida Yisma Derbie (Candidate)

Date: 4-Dec-2020

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List of abbreviations and acronyms

ACOG	American College of Obstetricians and Gynaecologists
AIPW	Augmented Inverse Probability Weighting
aPR	Adjusted Prevalence Ratio
ATE	Average Treatment Effect
CI	Confidence Interval
DAG	Directed Acyclic Graph
DHS	Demographic and Health Surveys
GPS	Global Positioning System
HIV	The human immunodeficiency virus
IQ	Intelligence quotient
IRB	Institutional Review Board
IRSAD	Index of Relative Socio-economic Advantage and Disadvantage
IUGR	Intrauterine Growth Restriction
LMICs	Low and Middle Income Countries
NAPLAN	National Assessment Program – Literacy and Numeracy
NICE	National Institute for Health and Clinical Excellence
NICU	Neonatal Intensive Care Unit
NMS	National Minimal Standard
OR	Odds Ratio
PGE1	Prostaglandin E1
PGE2	Prostaglandin E2
PROM	Pre-labour rupture of membranes
PSU	Primary Sampling Unit

RR	Relative Risk
SAECDP	South Australian Early Childhood Data Project
SD	Standard deviations
SEP	Socioeconomic position
SOGC	Society of Obstetricians and Gynaecologists of Canada
UNICEF	United Nations International Children's Emergency Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Abstract

Background

Obstetrical interventions during labour and birth are essential for perinatal care as part of any contemporary obstetric practice. Various underlying biological mechanisms have been proposed in linking obstetrical interventions during labour and birth with breastfeeding, infant's health and children's neurodevelopmental outcomes at later life. These mechanisms include changes in the gut microbiota composition, exposure to different levels of physical stress and stress hormone surges during labour and delivery, as well as epigenetic alteration of gene expression. The available evidence regarding the effect of obstetrical interventions during labour and birth on short-and long-term outcomes is limited. For instance, much of the available evidence was generated from high-income countries. Moreover, many of the previous studies were hampered by non-longitudinal study designs, small sample sizes and inconsistent findings, which may be due to suboptimal control of confounders and other biases. This thesis addresses these issues and utilises data from low-, middle- and high-income country settings.

Aims

The overarching aim of this thesis is to examine the effect of obstetrical interventions during labour and birth on breastfeeding indicators (early initiation of breastfeeding, exclusive breastfeeding under 6 months, and children ever breastfed), neonatal mortality and children's educational outcomes at eight years of age.

Specifically, the aims include:

- To estimate the prevalence and examine sociodemographic factors associated with caesarean section in Ethiopia.
- To examine the changing temporal association between caesarean birth and neonatal death in Ethiopia from 2000 to 2016 as well as to provide an interpretation of the associations using the 'Three Delays Model' in the context of Ethiopia.
- To investigate the effect of caesarean section on breastfeeding indicators—early initiation of breastfeeding (within 1 hour), exclusive breastfeeding under 6 months and children ever breastfed (at least once)—in each of the 33 countries in sub-Saharan Africa, as well as to summarise the magnitude of these within-country effects in an overall estimate using random-effects meta-analyses.
- To examine the effect of Apgar scores of 0-5, 6, 7, 8 and 9 (compared with 10) on children's educational outcomes at eight years of age.
- To estimate the effect of elective induction of labour at 39 weeks of gestation as compared with expectant management on children's educational outcomes at eight years of age.

Methods

Data for this thesis were drawn from the Demographic and Health Surveys (DHS) and the South Australian Early Childhood Data Project (SAECDP). The DHS are widely available high-quality data sources from low- and middle-income countries. The SAECDP is an established project that encompasses high-quality whole-of-population linked administrative data from state and federal sources in South Australia. The DHS data from 33 low- and middle-income countries in sub-Saharan Africa were used for the first three studies while the

SAECDP data from South Australia were used for the final two studies in this thesis. The use of these two different data sources allowed this thesis to capture the effects of obstetrical interventions during labour and birth on women's breastfeeding practices, neonatal health and children's educational outcomes across diverse health system resource settings. For each study, the potential confounding was identified based on *a priori* subject matter and expert knowledge as well as through the use of the Directed Acyclic Graphs (DAGs). The analytic approaches to answer the aims of this thesis included the modified Poisson regression (Log-Poisson regression), augmented inverse probability weighed (AIPW) estimator, negative control outcome (a tool for detecting confounding and bias), random-effects meta-analysis as well as an application of the 'Three Delays Model'.

Results

In the first study, the national caesarean section rate increased from 0.7% in 2000 to 1.9% in 2016, with increases across 7 of the 11 administrative regions in Ethiopia. In the adjusted analysis, women who gave birth in a private health facility had a 78.0% higher risk of caesarean section (adjusted prevalence ratio (aPR) (95% CI) 1.78 (1.22 to 2.58) when compared to women who gave birth in public health facility. Having four or more births was associated with a lower risk of caesarean section compared to first births (aPR (95% CI) 0.36 (0.16 to 0.79)).

In the second study, in Ethiopia, the adjusted prevalence ratios (aPR) for neonatal death among neonates born via caesarean section versus vaginal birth increased over time, from 0.95 (95% CI, 0.29 to 3.19) in 2000 to 2.81 (95% CI, 1.11 to 7.13) in 2016. The association between caesarean birth and neonatal death was stronger among rural women (aPR (95% CI)

3.43 (1.22 to 9.67)) and among women from the lowest quintile of household wealth (aPR (95% CI) 7.01 (0.92 to 53.36)) in 2016. On the other hand, the aggregate-level analysis revealed that increased caesarean section rates were correlated with a decreased proportion of neonatal deaths.

In the third study, the within-country analyses in sub-Saharan Africa showed, compared with vaginal birth, caesarean section was associated with aPR for early initiation of breastfeeding that ranged from 0.24 (95% CI, 0.17 to 0.33) in Tanzania to 0.89 (95% CI, 0.78 to 1.00) in South Africa. The aPR for exclusive breastfeeding under 6 months ranged from 0.58 (95% CI; 0.34 to 0.98) in Angola to 1.93 (95% CI; 0.46 to 8.10) in Cote d'Ivoire, while the aPR for children ever breastfed ranged from 0.91 (95% CI, 0.82 to 1.02) in Gabon to 1.02 (95% CI, 0.99 to 1.04) in Gambia. The meta-analysis combining effect estimates from 33 countries in sub-Saharan Africa showed caesarean section was associated with a 46% lower prevalence of early initiation of breastfeeding (pooled aPR, 0.54 (95% CI, 0.48 to 0.60)). However, the pooled effects indicated there was little association with exclusive breastfeeding under 6 months (pooled aPR, 0.94 (95% CI; 0.88 to 1.01) and children ever breastfed (pooled aPR, 0.98 (95% CI; 0.98 to 0.99) among caesarean versus vaginally born children.

In the fourth study, after adjusting for confounding, the risk differences comparing five-minute Apgar scores of 0-5 with Apgar score of 10 for children scoring at/below the national minimum standard (NMS) on the National Assessment Program—Literacy and Numeracy (NAPLAN) tests for each domain were: reading (0.07 (95% CI -0.16 to 0.29)), writing (0.27 (95% CI -0.14 to 0.68)), spelling (0.15 (95% CI -0.10 to 0.40)), grammar (0.04 (95% CI -0.21 to 0.29)) and numeracy (0.21 (95% CI -0.04 to 0.45)). Risk differences for children performing at/below the NMS were also evident when Apgar score of 6 were compared with Apgar score of 10.

In the fifth (last) study, after adjusting for confounding, the average treatment effects (ATEs) comparing elective induction of labour at 39 weeks of gestation with expectant management for children scoring at/below the NMS on each domain were: reading (0.01 (95% CI -0.02 to 0.03)), writing (0.02 (95% CI -0.00 to 0.04)), spelling (0.01 (95% CI -0.01 to 0.04)), grammar (0.02 (95% CI -0.01 to 0.04)) and numeracy (0.03 (95% CI 0.00 to 0.05)).

Conclusions

The findings from this thesis present a comprehensive analyses of the effect of obstetrical interventions during labour and birth on breastfeeding, neonatal mortality and children's educational outcomes at eight years of age by utilising data from low-, middle-, and high-income countries. The findings of Study 1 highlighted that there were large disparities in caesarean section use in Ethiopia, demonstrating unequal access. The results from Studies 2, 3 and 4 suggest that obstetrical interventions during labour and birth (caesarean section and Apgar score) have an influence on neonatal mortality, breastfeeding and children's educational outcomes at later age. However, the findings of Study 5 suggest that elective induction of labour at 39 weeks of gestation as compared with expectant management did not affect children's educational outcomes at eight years of age.

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Dedication

To my parents

Publications contributing to this thesis

1. Yisma E, Smithers LG, Lynch JW, Mol BW. Cesarean section in Ethiopia: prevalence and sociodemographic characteristics. *J Matern Fetal Neonatal Med* 2019; **32**(7): 1130-5. https://doi.org/10.1080/14767058.2017.1401606

2. Yisma E, Mol BW, Lynch JW, Smithers LG. The changing temporal association between caesarean birth and neonatal death in Ethiopia: secondary analysis of nationally representative surveys. *BMJ Open* 2019; **9**(10):e027235. http://dx.doi.org/10.1136/bmjopen-2018-027235

3. Yisma E, Mol BW, Lynch JW, Smithers LG. Impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa. *BMJ Open* 2019; **9**(9): e027497. http://dx.doi.org/10.1136/bmjopen-2018-027497

4. Yisma E, Mol BW, Lynch JW, Murthy NM, Smithers LG. Associations between Apgar scores and children's educational outcomes at eight years of age. *Aust N Z J Obstet Gynaecol* 2020; 1–7. https://doi.org/10.1111/ajo.13220

5. Yisma E, Mol BW, Lynch JW, Murthy NM, Smithers LG. Elective labour induction vs expectant management in women and children's educational outcomes at 8 years of age. *Ultrasound Obstet Gynecol* 2020. https://doi.org/10.1002/uog.23141

Presentations arising out of this thesis

1. Yisma E, Mol BW, Lynch JW, Smithers LG. The temporal association between caesarean birth and neonatal death in Ethiopia over time. *Australian Public Health Conference,* Adelaide, Australia, September 2019.

2. Yisma E, Mol BW, Lynch JW, Smithers LG. The impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa. *13th Annual Florey Postgraduate Research Conference*, Adelaide, Australia, September 2019.

3. Yisma E, Mol BW, Lynch JW, Smithers LG. The changing temporal association between caesarean birth and neonatal death in Ethiopia. *Australasian Epidemiological Association 2019 Annual Scientific Meeting*, Brisbane, Australia, October 2019.

4. Yisma E, Mol BW, Lynch JW, Smithers LG. The impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa. *Australasian Epidemiological Association 2019 Annual Scientific Meeting*, Brisbane, Australia, October 2019.

5. Yisma E, Mol BW, Lynch JW, Smithers LG. The impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa. The American Public Health Association, Annual Meeting and Expo, Philadelphia, Pennsylvania, USA, November 2019.

Media coverage of findings arising from this thesis

1. ‘World-first research links newborn test with NAPLAN score’, *The Australian,* Sydney, 24 August 2020.

2. ‘Low newborn health score linked to poor year 3 NAPLAN results’, *Scimex (the Science Media Exchange)*, 24 August 2020.

Chapter 1: Introduction

1.1 Background

Obstetrical interventions during labour and delivery are essential for perinatal care as part of any contemporary obstetric practice. Even though the majority of women give birth following spontaneous labour and vaginal delivery, labour induction and caesarean section are the most frequently applied obstetrical interventions during labour and delivery. The rates of obstetrical interventions during labour and birth continue to rise worldwide.[1-4] About 1 in 4 pregnant women had their labour induced in high-income countries while the rate is generally lower in low-and middle-income countries.[1] On the other hand, births that occurred by caesarean section increased from 12.1% in 2000 to 21.1% in 2015 globally.[5] There are also substantial global and regional disparities in the use of obstetric interventions during labour and birth.[5-7] For instance, in low-and middle-income countries,[8,9] labour induction and caesarean section are generally less common due to lack of access and unequal access. However, in high income countries such interventions could be overused without medical indications.[5,10] Although it is essential to increase the obstetric interventions such as caesarean section where access is limited, there is no clear evidence regarding the benefits of caesarean section for women and babies who are not medically eligible for the procedures.

When medically indicated, it is clear that obstetrical interventions during labour and childbirth are effective in preventing adverse outcomes. For instance, while labour induction and caesarean section are effective in improving perinatal outcomes by avoiding obstetric complications, caesarean section alone was associated with reduced risk of urogenital prolapse and urinary incontinence for mothers.[11,12] Moreover, obstetrical interventions during labour and birth reduce maternal and neonatal mortality due to specific conditions (indications). For instance, both induction of labour and caesarean section reduce maternal morbidity and mortality for women suffering from hypertensive disorders of pregnancy after 34 weeks of gestation.[13] Conversely, both labour induction and caesarean section have risks exceeding the risks of spontaneous labour and spontaneous vaginal delivery outcomes, respectively. Induction of labour may cause uterine hyperstimulation and this may increase the risk of uterine rupture.[14] Labour induction could also affect women's overall experience of childbirth because some methods of labour induction have side-effects and/or are painful or unpleasant.[15] Likewise, caesarean birth may have numerous adverse health consequences such as increased risk of asthma, allergies, type 1 diabetes for the child and increased risk of cardiac arrest, hysterectomy and puerperal infection for mothers when compared to vaginal birth.[16-18]

Evidence from recent systematic reviews and meta-analyses, randomised control trials and observational studies of labour induction at or beyond term as compared with expectant management suggest that induction of labour was associated with decreased risk of caesarean deliveries, perinatal deaths and meconium-stained amniotic fluid.[19-25] Nevertheless, older observational studies[26-31] that compared women who were induced with women who gave birth following spontaneous onset of labour at the same gestational age demonstrated that labour induction increases caesarean section rates and adverse perinatal outcomes. However, it has been noted that the comparison of induction of labour and spontaneous labour at same gestational age is incorrect.[32] This is because spontaneous labour is not a definite alternative to induction of labour. In clinical practice, women and obstetric care providers choose either induction of labour or expectant management, but not spontaneous labour or induction of labour at the same gestational age. Although there is a lot of evidence regarding the beneficial short-term perinatal outcomes of induction of labour at or beyond term, there is little evidence of the effect of induction of labour versus expectant management on longer-term neurodevelopmental outcomes in children.

Similarly, evidence shows that caesarean section is linked with a number of short-term and long-term health consequences. The adverse health consequences of caesarean section are likely to be driven by the underlying comorbid conditions for which the procedure is warranted. Sandall and colleagues[12] in their 2018 review of studies that evaluated the short-term and long-term effects of caesarean section revealed that, compared with vaginal birth, caesarean section was associated with increased risks of severe acute maternal morbidity, maternal mortality and adverse outcomes in subsequent pregnancies. In another 2018 systematic review and meta-analysis on long-term benefits and risks of caesarean birth, it was found that caesarean section was associated with increased odds of asthma, future subfertility and a number of subsequent pregnancy risks such as placenta previa, uterine rupture and stillbirth, when compared to vaginal birth.[11] Furthermore, in a 2012 systematic review and meta-analysis involving 53 studies from 33 low-, middle- and high-income countries (with no data from African countries),[33] it was found that early breastfeeding (that is, any initiation or breastfeeding at hospital discharge) was lower among infants delivered by caesarean section (OR, 0.57; 95% CI, 0.50 to 0.64) when compared to infants born vaginally. Longer periods taken to initiate breastfeeding are associated with greater difficulty in establishing breastfeeding and increases in neonatal mortality.[34] The effect of caesarean section on breastfeeding indicators from the perspective of low-and middle-income countries, particularly in sub-Saharan Africa, remains to be elucidated.

There are a number of studies[35-51] that have been conducted to examine the relationship between caesarean section and neonatal mortality, but the results are inconsistent. The majority of the previous studies are at the aggregate-level so that they are comparing changes acting on the population as a whole (i.e., a change in caesarean section rates and neonatal mortality among geographic areas).[35,36,44-51] Studies based on individual-level data[38-41] are more likely to report a considerably increased risk of neonatal mortality associated with caesarean versus vaginally born infants without providing an interpretation of the associations accounting for contextual factors. There seems to be no exploration of why the risk of neonatal mortality following caesarean delivery was increased in studies using individual-level data. Moreover, the previous studies are limited by either inconsistent results or failure to account for contextual factors such as unequal access, infrastructural, structural and health workforce constraints that could play a role in the association between caesarean section and neonatal mortality.

There are three underlying biological mechanisms that provide a possible explanation for how obstetrical interventions during labour and birth (more specifically mode of delivery) could affect children's health and development. The first proposed mechanism is altered bacterial (microbial) colonisation of the infant gut.[52] The microbial colonisation of the infant gut starts during the intrauterine period when the foetus is exposed to maternal microbiota from the maternal gut and/or blood stream that enter the amniotic fluid crossing the placenta.[53] Exposure to the gut colonising bacteria continues at birth as the foetus passes through the birth canal and during the first year of life when the newborn is introduced to oral liquid and solid foods.[53] It has been demonstrated that the colonising microbiota are critical for normal development of host defence and are associated with a lifelong health effects in children, including brain development.[53,54] However, evidence shows that interventions during labour and birth such as caesarean section result in altered gut microbiota patterns, leading to increased susceptibility to disease in children's later life.[52,53] Moreover, it has also been revealed that obstetric interventions such as caesarean section can affect the onset of lactation (i.e., lactogenesis), which results in physiological delay in milk secretion and shortening the duration of breastfeeding.[52] This, in turn, has direct influence on microbiota development because human milk oligosaccharides are thought to shape the diversification of the infant intestinal microbiota (i.e., bifidobacteria colonisation).[55]

The second hypothesis is "exposure to different levels of physical stress and stress hormone surges during delivery."[52] During spontaneous vaginal delivery, the foetus is exposed to maternal stress hormones and physical forces of labour (uterine contraction), as well as a hypoxic journey through the birth canal. Uterine contraction together with the 'hypoxic journey through the birth canal' (that is, the stress of being born) triggers the release of catecholamine and this was found to be important for successful physiological foetal-to-neonatal transition and survival.[56] Moreover, it has been suggested that increased concentrations of stress hormones are important "signals in the infants for development of the hypothalamic–pituitary–adrenal axis, maturation of the immune system, lung and organ maturation, and neurogenesis."[12] However, the timing and degree of the stress are altered when the infant is born following obstetric interventions because there is too little stress in pre-labour caesarean section or too much stress in case of labour induction/augmentation.[57] These conditions are contrary to the normal physiology of parturition. Unnecessary obstetrical interventions during labour and birth, which is often compounded by 'early term' delivery (e.g., planned caesarean section is usually performed from 37-39 weeks while elective induction of labour is offered at 39 weeks of gestation), may influence infants' health and neurodevelopment.

The final hypothesis is epigenetic alteration of gene expression.[52] It has been suggested that adverse prenatal and perinatal stress (i.e., too high and too low stress) may permanently alter neuroendocrine and behavioural responses in later life.[58] Epigenetic alterations, which is alterations that induce heritable changes in gene expression without changes in DNA sequence, was proposed as the possible mechanism for such adaptive responses.[59] The most studied epigenetic control mechanism is DNA-methylation and it was shown that hypermethylation is generally associated with gene silencing while hypomethylation make genes remain switched on.[52] Using umbilical cord blood sample from infants delivered by pre-labour caesarean section and vaginal births to analyse DNA-methylation, Schlinzig and colleagues found that infants delivered by prelabour caesarean section had higher global DNA-methylation in white blood cells than infants born vaginally.[60]

Moreover, in one study that analysed the global DNA-methylation of the hematopoietic stem cell (CD34+) using cord blood from Swedish women, it was found that there were differences in the epigenetic mark-up between caesarean and vaginal birth groups in 343 DNA regions.[61] Furthermore, in addition to caesarean section, EPIgenetic Impact of Childbirth (EPIIC) hypothesis suggested that use of synthetic oxytocin and antibiotics during intrapartum period have effects on neonatal epigenome remodelling processes.[57] According to the EPIIC hypothesis, foetal epigenomic remodelling anomalies, which have an influence on abnormal gene expression, may result from the reduced or elevated levels of adrenalin, oxytocin and cortisol produced during labour.[57] It was thought that this reprogramming could manifest in biobehavioral problems and diseases in infants and in children’s later life, which is also accompanied by environmental exposures that may alter DNA-methylation.[57,62] The pictorial presentation of the three underlying biological mechanisms that provide a possible explanation for how obstetrical interventions during labour and birth could affect children's health and development is provided in **Figure 1.1**.

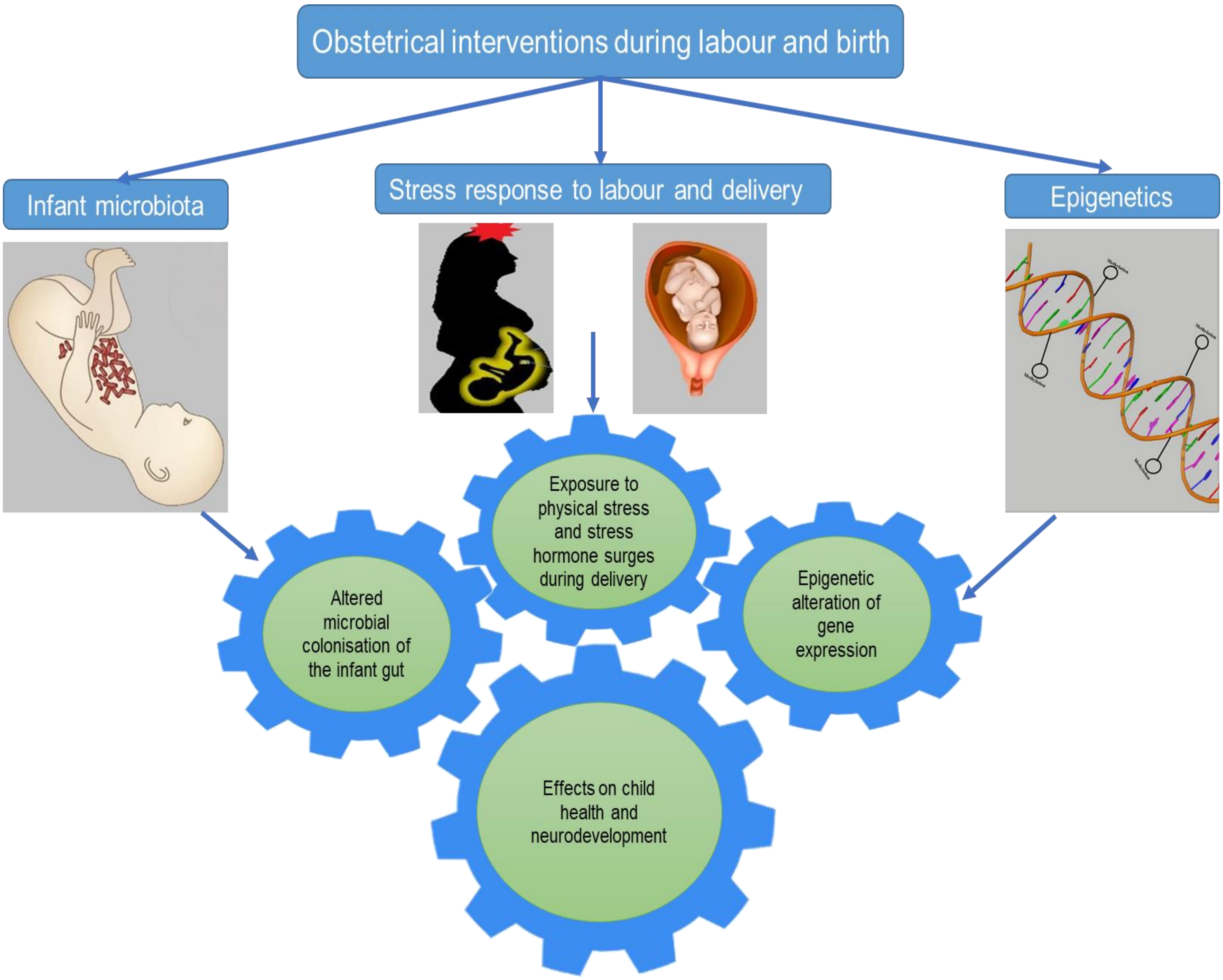

Figure 1.1 Mechanisms by which obstetrical interventions during labour and birth may affect children's health and neurodevelopment.

On the other hand, because of obstetrical interventions during labour and childbirth such as caesarean section and use of anaesthetics and analgesics, there are increased difficulties in successful foetal-to-neonatal transition.[63] For example, it was shown that pre-labour caesarean section reduces the postnatal rise in cortisol, which is a hormone that prepares the foetus for birth and supports the multi-organ extra-uterine transition.[63]

1.2 Thesis aim and research questions

The overall aim of this thesis is to examine the effect of obstetrical interventions during labour and birth on breastfeeding, neonatal mortality and children's educational outcomes. The specific research questions to be addressed in this thesis are as follows.

1. What is the prevalence of caesarean section in Ethiopia and how are sociodemographic characteristics and caesarean section associated in Ethiopia?
2. How is caesarean delivery and neonatal death associated in Ethiopia from 2000 to 2016 and does the application of the 'Three Delays Model' facilitate the interpretation of the association between caesarean birth and neonatal death in Ethiopia?
3. What impact could caesarean section have on breastfeeding indicators—early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed—in each 33 country in sub-Saharan Africa and how big would this effect be when the available evidence (estimate) from each of the 33 countries is summarised in random-effects meta-analysis?
4. Do Apgar scores of 0-5, 6, 7, 8 and 9 (compared with 10) associated with children's educational outcomes at eight years of age?
5. Does elective induction of labour at 39 weeks of gestation as compared with expectant management affect children's educational outcomes at eight years of age?

1.3 Thesis outline

This thesis—which is presented as a 'thesis by publication'—is organised into nine chapters. Chapter 1, this chapter, presents the introduction, including the description of background, the problem being addressed, the overall aim of the thesis, and the five research questions examined.

Chapter 2 provides a comprehensive literature review of studies related to obstetrical interventions during labour and birth such as induction of labour and caesarean section, and their short- and long-term outcomes. This chapter delivers the foundation of knowledge regarding the effect of obstetrical interventions during labour and birth on maternal and child outcomes, including breastfeeding, maternal and neonatal mortality and children's educational outcomes from the existing literature. Chapter 2 also reviews the gaps in the research literature that motivated the five research questions examined in this thesis.

Chapter 3 describes the various research methods that are used by studies in the thesis. This chapter begins with the descriptions of the two data sources—the Demographic and Health Surveys (DHS) and the South Australian Early Childhood Data Project (SAECDP). Then, the chapter describes how the exposures (measures of obstetrical interventions during labour and birth), the outcomes (measures of breastfeeding indicators, neonatal mortality and children's educational outcomes), and the potential confounders were formulated for each study. Finally, Chapter 3 discusses the statistical analysis approaches used to answer the five research questions.

Chapters 4-8 deliver the five studies arising from this thesis. All of these studies are already published in esteemed peer-reviewed journals. Chapter 4 presents the result of the comprehensive analysis concerning the prevalence and sociodemographic characteristics associated with caesarean section in Ethiopia from 2000 to 2016 (Study 1). Chapter 5 examines the temporal association between caesarean birth and neonatal death in Ethiopia from 2000 to 2016, as well as it applies the 'Three Delays Model' to facilitate the interpretation of the association between caesarean birth and neonatal mortality in view of contextual factors in Ethiopia (Study 2). Chapter 6 presents the results of novel analysis examining the impact of caesarean section on breastfeeding indicators in 33 countries in sub-Saharan Africa, as well as it summarises the evidence (estimate) from each of the 33 countries in sub-Saharan Africa regarding the association between caesarean section and breastfeeding indicators using random-effects meta-analysis (Study 3). Chapter 7 presents the results of novel analysis examining the associations between both one- and five-minute Apgar scores of 0-5, 6, 7, 8 and 9 (compared with 10) and children's educational outcomes at eight years of age in South Australia (Study 4). Chapter 8 presents the design and results of the final research article in this thesis (Study 5), which investigates the effect of elective induction of labour at 39 weeks of gestation as compared with expectant management on children's educational outcomes at eight years of age.

Chapter 9, last chapter, summarises the overall research by presenting the key findings and contributions of each study, the strengths and limitations, as well as implications and conclusions.

Chapter 2: Literature review

The purpose of this literature review is to provide a general overview of obstetrical interventions during labour and birth such as induction of labour and caesarean section. Recently, obstetrical interventions during labour and birth have become a growing subject area of research interest. This is largely because the rates of obstetrical interventions during labour and birth have been substantially increasing globally. The first part of this chapter gives a brief description about induction of labour and its effects on perinatal outcomes, including caesarean delivery. Next, this chapter reviews evidence for caesarean section and its effects on maternal and child outcomes, including maternal and neonatal morbidity and mortality, breastfeeding, and children's educational outcomes. Finally, a brief overview of the Apgar scores and its effects on short-term perinatal outcomes, as well as its effects on longer-term neurodevelopmental outcomes in children's later life is given. The research justification for the studies examined in this thesis is also provided at the end of this chapter.

2.1 Induction of labour

Induction of labour is the most frequently applied obstetric intervention to artificially stimulate the start of labour. It is thought that when medically indicated, induction of labour is effective to improve perinatal outcomes by avoiding the effects of prolonged pregnancy. When labour induction is performed without any maternal or foetal indication, including for matters of convenience or preference, it is termed as non-medically indicated induction of labour (also known as elective induction of labour).

Evidence shows that the rate of induction of labour is generally high (more than 1 in 4) in high-income countries.[14] Data from government reports indicate a proportion of induction of labour up to 43.1% (for selected women giving birth for the first time) in Australia in 2017,[64] 27.1% in the United States in 2018,[65] and from 6.8% to 33% in European countries in 2010.[66] In low-and middle-income countries, the rates of labour induction are generally low when compared to the rates in high-income countries. However, high rates have been reported in countries such as Sri Lanka (35.5%)[8] and Cuba (20.1%),[67] where rates of induction of labour are similar to the rates in high-income countries. In African countries, the average rate of induction of labour was 4.4%, ranging from 1.4% in Niger to 6.8% in Algeria.[8]

It is clear that induction of labour is recommended when maternal and neonatal risks are believed to be lower with induction of labour rather than with expectant management. Expectant management is waiting for onset of spontaneous labour or waiting until the occurrence of a medical condition that indicate induction or caesarean delivery. Furthermore, the procedure of labour induction should only be conducted when the vaginal birth is considered to be the most definite method of delivery and/or there is no contraindication to vaginal delivery (e.g., foetus in transverse lie). It also recommended that induction of labour should be undertaken after informed consent.[68] The consent should be accompanied by explanations regarding the medical indications for induction of labour and the benefits, risks and the choice of methods to be used.

2.1.1 Indications for induction of labour and reasons for elective labour induction

Indications for induction of labour vary according to the different guidelines available. There are five widely known guidelines regarding induction of labour. These include the World Health Organization (WHO) recommendations for induction of labour;[14] the Queensland Clinical Guideline;[69] the Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guideline;[68] the American College of Obstetricians and Gynaecologists (ACOG) clinical management guidelines for obstetrician–gynaecologists;[70] and the National Institute for Health and Clinical Excellence (NICE) clinical guidelines.[71] Unlike the other guidelines, the ACOG clinical management guideline provide specific clinical situations (indications) in a series of publications.[72-74]

There is a general agreement among these guidelines in recommending induction of labour for some indications. For instance, for near or beyond term pregnancy, all of the guidelines recommend induction of labour when gestation is between 41 and 42 weeks. Likewise, all guidelines agree that induction of labour should be offered to women with pre-labour rupture of membranes (PROM). Conversely, for suspected foetal macrosomia alone, all guidelines suggest that induction of labour at term is not recommended. Some other most common indications for induction of labour recommended by at least one guideline include abruptio placentae, chorioamnionitis, pregnancy hypertension (pre-eclampsia/eclampsia), preterm pre-labour rupture of membranes (pPROM), intrauterine foetal growth restriction (IUGR) and oligohydramnios.

In addition to the medical reasons (indications) for labour induction, there are others non-medical reasons why women and obstetric care providers choose induction of labour. For instance, because of physical discomfort, scheduling issues, or concerns for maternal, foetal or neonatal complications as the pregnancy continues, women may request induction of labour. Similarly, due to the concern that the quickly progressing labour would prevent timely access to hospital or receiving interventions (such as pain relief), women may want to end their pregnancy.[75] Obstetric care providers may also suggest labour induction not only due to concern about complications that may arise as the pregnancy continues, they may also want to manage women's pregnancy-related discomfort.[75] Some obstetric providers may recommend labour induction because they may be incentivised financially or via their own scheduling preferences.[3,75]

2.1.2 Methods of induction of labour

A variety of methods for induction of labour are discussed in the existing literature.[76-80] These include pharmacological, mechanical, and complementary and alternative methods. Oxytocin and prostaglandins (i.e., prostaglandin E1 (PGE1)—misoprostol and PGE2—dinoprostone) are the pharmacological methods. While oxytocin is available in tablet, gel or insert forms, misoprostol is administered via different routes (oral, oral titrated solution, buccal/sublingual or vaginal).[80,81] It has been demonstrated that PGEs are mainly used when the cervix is unfavorable while oxytocin is often administered when the cervix is favourable.[81]

Some of the mechanical methods of labour induction include Foley catheter and membrane sweeping. Foley catheter is the most common mechanical method of labour induction. The Foley catheter alone[82] or in combination with oxytocin[83-85] and misoprostol[86,87] could be used for pre-induction cervical ripening or labour induction. Evidence shows that when Foley catheter is used together with oxytocin, it increases the rate of delivery within 24 hours in nulliparas.[85] Furthermore, when Foley catheter is used with misoprostol, it reduces the intervention-to-delivery time interval.[88] In a 2020 Cochrane systematic review of 44 randomised studies[89] conducted in high-, middle- and low-income countries, it was suggested that membrane sweeping as a method of labour induction at or above 36 weeks of gestation was probably effective in increasing the chance of achieving spontaneous onset of labour. However, this evidence was of low certainty.

The complementary and alternative methods of labour induction include acupuncture or acupressure,[90] castor oil,[91] breast/nipple stimulation,[92] homeopathy,[93] hypnosis[94] and sexual intercourse.[95] Because of limited evidence available regarding all these complementary and alternative methods, their role for labour induction is less clear.

2.1.3 Induction of labour and caesarean section

Historically, it has been considered that elective induction of labour was unsafe because it increases the risk of caesarean delivery and is associated with poorer perinatal outcomes when compared to spontaneous labour. For example, in their cohort study on 14,409 women between 36 and 42 weeks of gestation attending two large hospitals in Boston, USA from 1998-1999, Heffner and colleagues[96] found that, compared with spontaneous onset of labour, induction of labour was associated with a 70% increase in risk of caesarean delivery in nulliparous (aOR, 1.70; 95% CI, 1.48 to 1.95) and a 49% increase in risk of caesarean delivery in multiparous (aOR, 1.49; 95% CI, 1.10 to 2.00). Moreover, several other studies[26,29,97-100] have demonstrated similar increased risk of caesarean delivery following induction of labour compared with spontaneous onset of labour.

The results of several previous studies, which compared women who were induced (either electively or medically) and women who gave birth following spontaneous onset of labour, have provided a consistent story that induction of labour was associated with increased risk of caesarean delivery. However, over time, it was noted that using spontaneous labour as a control group was inappropriate as a counterfactual for induced labour. In clinical practice, women and obstetric care providers choose either induction of labour or expectant management, but not spontaneous labour or induction of labour at the same gestational age. The more accurate comparison group is expectant management. Women carry inherent risks of developing obstetric complications when they are expectantly managed. As the pregnancy continues, spontaneous labour onset may occur or women may develop complications (such as post-term pregnancy, oligohydramnios or foetal death), or require emergency interventions (i.e., medically-indicated induction or caesarean section).[101] Therefore, it is most plausible to compare the risks of induction of labour with the risks of continuing the pregnancy (expectant management).

Several recent systematic reviews and meta-analyses, randomised control trials and observational studies that evaluated labour induction at or beyond term, compared with expectant management, have been conducted. These studies have found that induction of labour at or beyond term reduces the rate of caesarean delivery. For instance, in 2019, Grobman and colleagues conducted a systematic review and meta-analysis of 6 cohort studies involving 66,019 women who were electively induced at 39 weeks and 584,390 women who were expectantly managed.[20] They found that elective induction of labour at 39 weeks was associated with a 17% decrease in the rate of caesarean delivery compared with expectant management (RR, 0.83; 95% CI, 0.74 to 0.93). Furthermore, a 2014 systematic and meta-analysis by Mishanina *et al*.[102] found, compared with expectant management, lower risk of caesarean delivery among women who were induced even when subgroup analysis by method of induction (e.g., prostaglandin E2, misoprostol, alternative method and mixed method) was performed. Lower rates of caesarean delivery among women who gave birth following labour induction compared with expectant management were also demonstrated by another three systematic reviews and meta-analyses.[19,101,103]

In a 2018 large multicenter randomised control trial involving 6,106 low-risk nulliparous women randomised to elective labour induction at 39 weeks of gestation (n=3,062) or expectant management (n=3,044) groups found that the rates of caesarean delivery were lower among the elective labour induction group (RR, 0.84; 95% CI, 0.76 to 0.93).[21] Evidence from several recent observational studies[22-25] also showed that labour induction at 39 weeks resulted in lower rates of caesarean delivery when women who were induced were compared with women who were expectantly managed. Therefore, it has become clearer that when a more appropriate comparison group (i.e., expectant management) was used, induction of labour was associated with lower rates of caesarean delivery.

2.1.4 Induction of labour and maternal and newborn outcomes

There is evidence regarding whether the policy of induction of labour in women at or beyond term as compared with expectant management has effects on maternal and perinatal health outcomes. For example, in 2018, Middleton and colleagues[104] included 30 randomised control trials from 14 countries in their Cochrane systematic review to evaluate the effect of labour induction at or beyond term compared with expectant management on pregnancy outcomes for the infant and mother. They found that, compared with expectant management, induction of labour was associated with lower perinatal deaths (RR, 0.33; 95% CI, 0.14 to 0.78), fewer stillbirths (RR, 0.33; 95% CI, 0.11 to 0.96), lower rates of neonatal intensive care unit (NICU) admission (RR, 0.88; 95% CI, 0.77 to 1.01) and fewer newborns had five-minute Apgar scores <7 (RR, 0.70; 95% CI, 0.50 to 0.98). For the mother, this review also found that induction of labour was associated with lower rates of caesarean birth (RR, 0.92; 95% CI, 0.85 to 0.99), but an increase in operative vaginal delivery (RR, 1.07; 95% CI, 0.99 to 1.16) when compared with expectant management.

Saccone *et al.* [105] in their 2019 systematic review and meta-analysis involving 7 randomised clinical trials (n= 7,598) demonstrated that induction of labour at full-term, compared with expectant management, was associated with a 68% decrease in the risk of meconium-stained amniotic fluid (RR, 0.32; 95% CI, 0.18 to 0.57) and a 98.96 g lower mean birthweight (mean difference -98.96 g; 95% CI, -126.29 to -71.63). These findings may mean that labour induction at full-term was associated with better meconium outcomes, but lower birth weight. However, Saccone *et al.* suggested that, at full term, a mean difference of about 100 g may not be significant clinically.[105]

Moreover, in other systematic reviews and meta-analyses, randomised control trials and observational studies, induction of labour at or beyond term was associated with reduced risk of perinatal mortality,[21,106] lower rates of maternal and neonatal morbidity,[22,24] reduced risk of hypertensive disease of pregnancy (i.e., hypertension that would manifest later),[19,21,25] reduced risk of meconium aspiration syndrome,[22,107] lower rates of admission to NICU unit,[22,107] and reduced need for neonatal respiratory support[19,23] compared with expectant management.

These previous studies focused on the effect of labour induction from 39-41 weeks of gestation versus expectant management on short-term maternal and perinatal outcomes, including caesarean delivery. The previous studies have demonstrated that labour induction at or beyond term, compared with expectant management, had lower rates of maternal and neonatal morbidity, lower rates of caesarean section, and fewer stillbirths. These findings would appear to be intuitive, given the fact that with advancing gestational age, the rate of stillbirth and neonatal morbidity also increases.[108] This is because as gestational age increases, the placenta may not provide adequate supply of nutrition to the foetus, resulting in placental insufficiency. Moreover, foetal weight also increases as the gestational age increases and may results in foetal macrosomia (i.e., birth weight ≥4500 g).

2.1.5 Elective induction of labour and long-term neurodevelopmental outcomes

Because of the risk of adverse short- and long-term outcomes associated with non-medically indicated deliveries, it has been recommended that deliveries following elective induction of labour for women who are below 39 weeks of gestation should be avoided.[109] However, due to the increased risk of perinatal morbidity and mortality associated with late-term and post-term pregnancies, deliveries following induction of labour should be considered when the gestation is at/above 41 weeks.[14,72] Therefore, the appropriate time when elective induction of labour should be offered to women should be at 39 or 40 weeks of gestation.

Several studies[19-25] have reported the beneficial effects of elective labour induction at 39 weeks on short-term perinatal outcomes, including reduction in caesarean delivery rates. However, there has been limited research reported on the link between labour induction at 39 weeks of gestation and children's longer-term neurodevelopmental outcomes at later life.[110] It would be important to investigate the effect of elective labour induction at 39 weeks of gestation versus expectant management on children's cognitive outcomes because a 2010 study by MacKay and colleagues[111] found that the risk of special educational need increased among children born from 37–39 weeks gestation when compared to children born at 40 weeks. Moreover, it is thought that labour induction increases stress and the presence of adverse prenatal and perinatal stress may result in epigenetic alteration of gene expression, which may permanently change neuroendocrine and behavioural responses in children's later life.[52] However, this mechanism remains to be fully investigated.

2.2 Caesarean section

It is known that obstetric complications such as antepartum haemorrhage, foetal distress, abnormal foetal presentation and hypertensive disease of pregnancy could be life-threatening for mothers and newborns. When such complications occur, caesarean section is the most common obstetric intervention to save the life of mothers and infants, and should be accessible universally.

2.2.1 Caesarean section rates and disparities in caesarean section uses

For the last three decades, the frequency of caesarean section has increased beyond the proportion that was considered to be optimal (10–15% of births) by agencies such as the WHO.[46,112-114] For example, in their 2018 study on the use of and disparities in caesarean sections, Boerma *et al*.[5] estimated that, globally, the total number of births that occurred following caesarean section increased from about 16.0 million (12.1%) in 2000 to about 29.7 million (21.1%) in 2015. Non-medically indicated reasons have been thought to be responsible for this increase in use of caesarean section in many middle- and high-income countries.[44,46,112] In 2015, the WHO released a declaration on caesarean section stating that rates exceeding 10% were not associated with reductions in maternal and neonatal mortality.[113] Molina *et al.* (2015) in their ecological study, however, estimated that the national caesarean section rates up to 19% were associated with lower maternal and neonatal mortality.[35]

Even though there are modest increase in caesarean section use in several low- and middle-income countries (LMICs) such as in sub-Saharan African countries, the national rate of caesarean birth is still less than 10%.[5] This may suggest inadequate access to emergency caesarean section. In sub-Saharan Africa, one of the reasons for the modest increase in the caesarean section rate was an increase in the proportion of deliveries occurring within health facilities. This is because caesarean sections are only performed in health facilities. **Figure 2.1** shows, at a global regional level (using the UNICEF region 2 classification scheme), that caesarean section rates varied from 4.1% in West and Central Africa to 44.3% in Latin America and Caribbean region in 2015.[5]

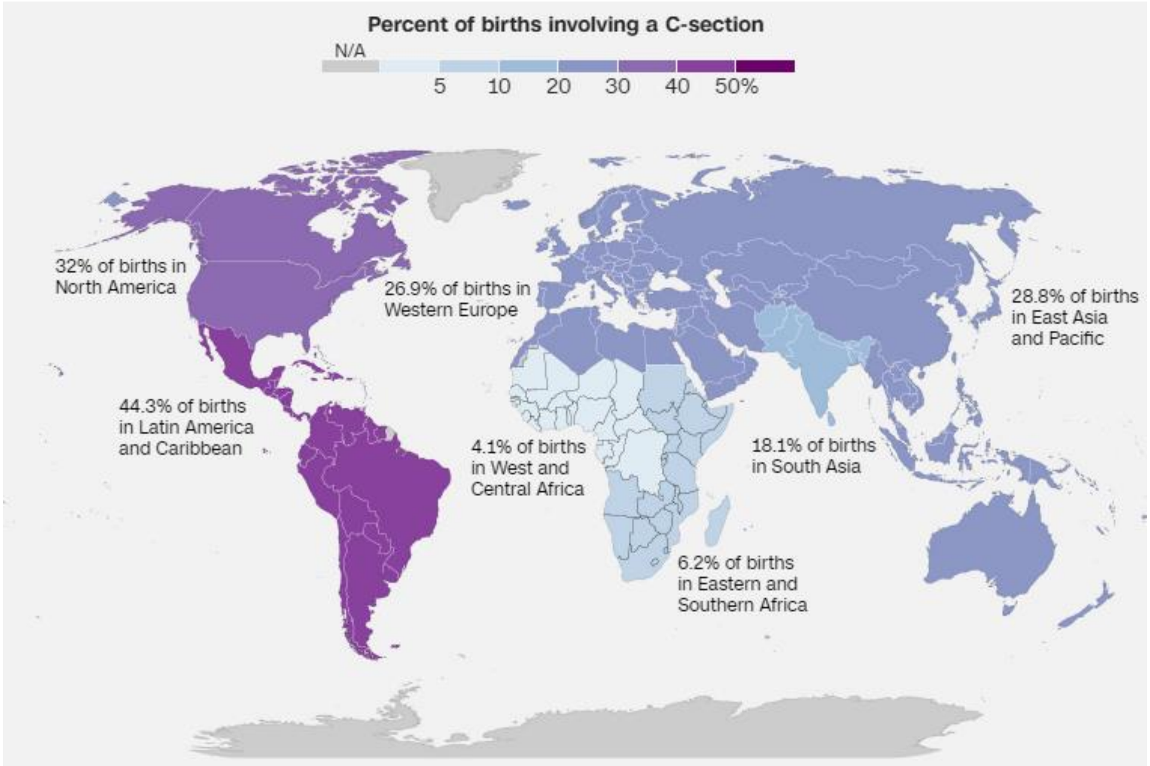

Figure 2.1 Caesarean section rates by regions according to UNICEF region 2 classification scheme.

Source: *Adapted from* CNN. https://edition.cnn.com/2018/10/11/health/c-section-rates-study-parenting-without-borders-intl/index.html.

As shown in **Figure 2.2**, at the country level, caesarean section rates varied widely. For example, the national rate of caesarean section was lowest in South Sudan (0.6%) and highest in Dominican Republic (58.1%) in 2015.[5]

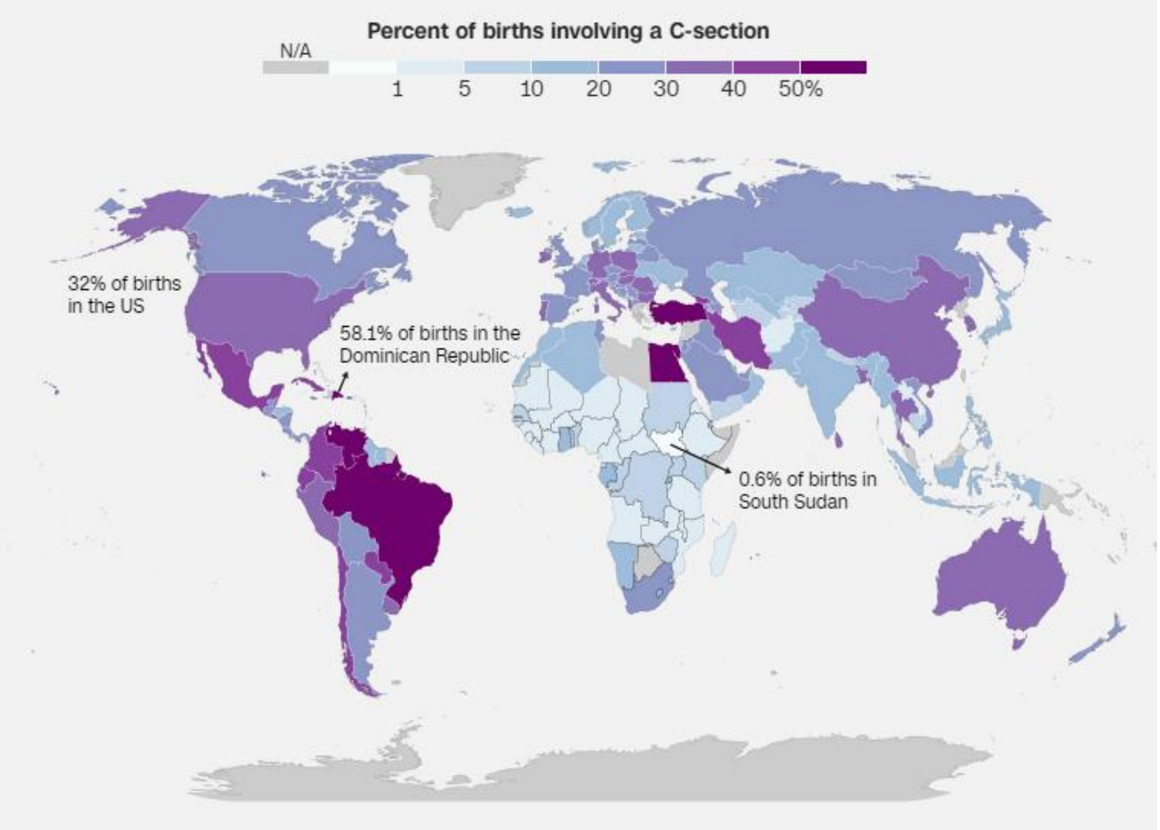

Figure 2.2 Caesarean section rates based on most recently available data across 164 countries.

Source: *Adapted from* CNN. https://edition.cnn.com/2018/10/11/health/c-section-rates-study-parenting-without-borders-intl/index.html.

Moreover, there are a substantial within-country socioeconomic and geographic disparities in caesarean section rates. In LMICs, the rate of caesarean section among births in the richest quintiles of household wealth was about five times more than births from women in the poorest household quintiles.[5] These substantial economic inequalities in caesarean section may suggest inadequate access to emergency caesarean section among the poorest subgroups and increased use without medical indication in the richest subgroups, especially in middle-income countries.[115]

The rates of caesarean section according to within-country geographic differences were also found to be large. For instance, while the national caesarean section rate in Ethiopia is about 2% in 2016, the reported rate for Addis Ababa—capital city of Ethiopia—was 21.4%.[116] Although the national caesarean section rates were 18.5% and 32.7% in China and India, respectively, the inter-state rate varied from 7% to 49% in India and the provincial rate ranged from 4% to 62% in China.[5]

Hoxha and colleagues[117] in their 2017 systematic review and meta-analysis of 11 studies conducted in upper middle income and high income countries, found that the odds of caesarean delivery was about 41% higher for women who gave birth in private (for-profit) hospitals (OR, 1.41; 95% CI, 1.24 to 1.60) than non-profit hospitals. This may suggest that the increase in caesarean section use might be related to an increase in privatisation of obstetric care services.

2.2.2 Indications and drivers of overuse of caesarean section

In clinical practice, the decision to perform caesarean section is based on the presence of life-threatening causes (indications) for the mothers and newborns. **Table 2.1** shows the indications (medical causes) leading to caesarean delivery.

Table 2.1 Indications to perform caesarean section.

Indication*	Description
Cephalo-pelvic disproportion	Small maternal pelvis, making vaginal birth impossible
Chorioamnionitis (amniotic infection syndrome)	Infection of the placenta, necessitating urgent delivery
Maternal pelvic deformity	Anatomical deformity, making vaginal birth complicated/impossible
Eclampsia and HELLP syndrome	Life-threatening problems of pregnancy
Foetal asphyxia or foetal acidosis	Life-threatening circumstances for the foetus, leading to foetal hypoxia
Umbilical cord prolapse	Prolapse of the umbilical cord, resulting in foetal asphyxia
Placenta previa	Abnormal placental position, hindering vaginal delivery
Abnormal lie and presentation	Abnormality of foetal position, making vaginal delivery very difficult/impossible
Uterine rupture	Acute condition threatening the life of both mother and foetus
Failure to progress in labour (prolonged labour, secondary arrest)	Delayed delivery or cessation of labour, resulting in bad outcome for the foetus or newborn
Previous caesarean section	It is generally anticipated that having had one caesarean section makes it difficult to have a vaginal delivery in succeeding pregnancies.

*Source: Mylonas and Friese, 2015.[118]

When caesarean section is performed without any medical indications, it is termed as caesarean delivery on maternal request. And, this may lead to overuse (excess use) and increasing use of caesarean section.[118] Although, it is difficult to determine the optimal caesarean section rate, a 2018 paper in the *Lancet Series*[5] on optimising the use of caesarean section defined population level caesarean section use thresholds of 15% as an indicator of overuse and 10% as an indicator of poor access (underuse).

It has been illustrated that, when the rate of caesarean section is higher than what is needed (≥15%), the drivers of excess use and increasing use of caesarean section could be described in three broader 'categories of reasons.'[119] The first category of reasons is related to the different factors linked to childbearing women, families, communities and the broader society.[119] Women may request caesarean birth due to fears related to labour pain, pelvic floor damage, urinary incontinence and fear of negative effects on their sexuality or sexual relationships.[52,118,119] Other reasons could include perceived belief that caesarean section is safe for the newborn and mother as well as some women also consider caesarean birth as a convenient method of delivery (e.g., along with caesarean section, some women also undergo tubal ligation).[119,120] Moreover, spouses' preference and influence related to convenience, previous negative experience of a partner's labour or birth and a range of other social and cultural pressures are also some of the reasons for increased request for caesarean section.[52,119]

The second category is regarding factors related to health professionals.[119] In most countries, obstetric care provides play a role in the choice of mode of delivery. In addition to women's requests, health-care providers are more likely to make decisions to use caesarean section for financial incentives, convenience and fear of litigation.[119,121] For example, it is believed that caesarean section is a protective procedure, although can be contrary to the scientific evidence.[122] As a consequence of this, obstetric care providers could be less likely to be litigated for performing unnecessary caesarean section rather than for complications that occur during spontaneous vaginal delivery.[122]

The final category of reasons regarding excess and increasing use of caesarean section is related to factors associated with health-care systems, financial reimbursements, and organisational design and cultures.[119] In most settings, caesarean delivery rates are higher in private sectors than in the public health facilities. For instance, the caesarean section rates in private sector in Brazil is about 80–90% while it is about 35–45% in public sector.[123] Such large differences may suggest that there are financial incentives to convince women that caesarean section is the best method of childbirth in private practice. In addition to the hospital infrastructure in the private sector, which may favour caesarean delivery (e.g., due to inadequate delivery rooms or birth centres), it has been suggest that the financial reimbursement offered by private health insurance for vaginal delivery is also low.[123]

Furthermore, inadequate skill or inexperience to perform assisted vaginal delivery (e.g., forceps) may also increase the use of caesarean section.[119,124] Women's mistrust in the health system and its staff because of their experiences of poor-quality antenatal care, equipment and interactions with obstetric care providers make women opt to have caesarean section.[125] This, in turn, results in increased use of caesarean section. In resource-constrained settings, the use of caesarean section has been increasing in referral (tertiary) hospitals. This increased use is partly attributable to unnecessary delays in referring women in labour by unskilled obstetric caregivers in primary health facilities.[124] It is clear that the obstetric complications encountered by mothers in primary health facilities will be compounded by delays when they are referred. The referred women are more likely to arrive late at the tertiary hospital in critical condition and they often undergo emergency caesarean section as it is the only available option.

2.2.3 Caesarean section and maternal morbidity and mortality

Timely caesarean intervention can successfully decrease maternal and perinatal morbidity as well as mortality when the mothers and/or foetus encounter obstetric complications. However, it was demonstrated that the proportion of maternal morbidity and mortality was higher following caesarean than spontaneous vaginal delivery.[12] For example, a 2018 study on short-term and long-term effects of caesarean section found that, compared with vaginal birth, caesarean section is associated with increased risk of maternal severe acute morbidity and mortality, including an increased risk of adverse outcomes in subsequent pregnancy.[12] Furthermore, a large study conducted by Villar *et al.*[38] in 410 health facilities in 24 areas in eight randomly selected Latin American countries found that, compared with vaginal delivery, both intrapartum and elective caesarean section were associated with 2.0 (95% CI, 1.6 to 2.5) and 2.3 (95% CI, 1.7 to 3.1) times higher odds of severe maternal morbidity, respectively.

As maternal mortality rate is higher in low- and middle-income countries when compared to high income countries, it was also found that the maternal mortality rate following caesarean birth is higher in low-resource settings than in high-resource settings. For instance, a 2019 systematic review and meta-analysis by Sobhy *et al*.[126] which included 196 studies, covering 12 million pregnancies in 67 LMICs, found that the risk of maternal death following caesarean section was 7.6 per 1000 procedures (95% CI, 6.6 to 8.6). This figure is about 100 times higher than the risk in high-income countries (e.g., the risk in UK is eight deaths per 100,000 caesarean sections).[126,127] They also found that a quarter of all maternal deaths in

LMICs were related to caesarean section (23.8%; 95% CI, 21.0 to 26.7), and women who underwent emergency caesarean section were twofold more likely to die than women who underwent elective caesarean section.[126]

Bishop *et al.*[128] in their 2019 African Surgical Outcomes Study followed more than 3,500 women having caesarean section in 183 hospitals across 22 countries in Africa. They found that in-hospital maternal mortality rate following caesarean delivery was 5.43 per 1000 operations (95% CI, 3.1 to 7.8). This figure shows that African women are may be 50 times more likely to die following caesarean delivery when compared to maternal mortality rates in high-income countries.[129,130] Moreover, about 1 in 6 women developed complications after caesarean delivery in Africa, which is approximately about three times the rate in the USA (a high income country).[130]

In high income countries, it is more likely that caesarean section is undertaken for reasons other than medical indications but it leads to lower risks of mortality and morbidity. However, the increased risks of maternal morbidity and mortality following caesarean delivery in LMICs when compared with high-income countries is probably due to the limited access to comprehensive obstetric care in LMICs.[37,38,131] For example, in Africa, the caesarean section rate is low and this may mean that several women who would benefit from caesarean section do not access the procedure. This situation is often accompanied by lack of skilled birth attendants and poor health infrastructure (e.g., shortage of medical care institutions, deficiencies in surgical facilities, surgical and anaesthesia personnel and equipment, and blood transfusion capacity). Further study is needed to inform the public health policy regarding the benefit of increasing timely access to caesarean section and timely decision for caesarean delivery in LMICs. This may help decrease maternal morbidity and mortality rates in LMICs.

2.2.4 Caesarean section and neonatal mortality

As any surgical procedure, caesarean section has risks of complications. However, it may be overused for non-medical reasons in high-resource settings. Caesarean section is also underused in resource constrained settings due to low rates of facility births, lack of health infrastructure and shortage of skilled birth attendants.[132] Both low and high rates of caesarean section have been associated with increased risks of maternal and newborn adverse health outcomes.[132]

Given this concern, several studies[35-51] have been conducted to examine the relationship between caesarean section rates and neonatal mortality. However, the results of these studies conducted using aggregate- and individual-level data are inconsistent. For example, Molina *et al.*[35] in their ecological study conducted using worldwide country-level data found that caesarean section was associated with lower neonatal mortality. However, in another ecological study using data from 159 countries, it was shown that there is no association between caesarean section rates and neonatal mortality, where caesarean section rates were higher than 10%.[44] This finding may indicate that the benefit of caesarean delivery to lower maternal and neonatal mortality was confined to those who actually require the procedure medically.

Inconsistent results for the association between caesarean birth and neonatal mortality were also reported by different studies based on individual-level data conducted in Africa, Latin America, Asia and United States of America.[37-42] For instance, Villar *et al*.[38] in their large prospective cohort study based on WHO global survey conducted in 410 health facilities in 24 areas in eight Latin American countries found that, with cephalic presentation, both intrapartum and elective caesarean section were associated with 1.66 (95% CI, 1.26 to 2.20) and 1.99 (95% CI, 1.51 to 2.63) times higher odds of neonatal mortality up to hospital discharge, respectively. Conversely, another study using data from the same WHO global survey completed in nine countries in Asia found that both pre-labour (aOR, 0.2; 95% CI, 0.1 to 0.3) and intrapartum caesarean sections (aOR, 0.3; 95% CI, 0.2 to 0.4) were associated with improved perinatal outcomes following breech presentation.[37] The findings from these two studies may suggest that the relationship between caesarean section and perinatal outcomes is inconsistent due to the possible regional differences.

It is clear from the existing literature that most of the previous studies regarding the association between caesarean section rate and neonatal mortality rate are at the aggregate-level so that they are comparing changes acting on the population as a whole (i.e., a change in caesarean section rates and neonatal mortality among geographic areas).[35,36,44-51] Many of these studies,[45,47-50] however, failed to adjust for socioeconomic position, which can affect the likelihood of having caesarean section and neonatal mortality.

In contrast, studies based on individual-level data are more likely to report a considerably increased risk of neonatal mortality associated with caesarean versus vaginally born infants. There seems to be no study that explored why the risk of neonatal mortality was increased following caesarean delivery using individual-level data. Moreover, the previous studies are limited by either inconsistent results or failure to account for contextual factors such as unequal access, infrastructural, structural and health workforce constraints that could play a role in the association between caesarean section and neonatal mortality, particularly in

LMICs. A further study is needed to understand the association between caesarean section and neonatal mortality by taking into account contextual factors from the perspective of developing country settings to better inform the public health policy for intervention.

2.2.5 Caesarean section and breastfeeding

Given the rising proportions of labour induction and caesarean section, there is a concern that interventions during labour and childbirth may influence breastfeeding. It is well known that the first hours after birth are critical for establishing mother-infant interaction and breastfeeding.[133,134] The timing of the first breastfeeding is also a key determinant for child and maternal health. For example, in a large 2016 study (n= 99,938) using pooled data from three randomised trials conducted in Ghana, India and Tanzania, it was found that initiation of breastfeeding within one hour after birth reduces neonatal and early infant mortality.[135] The study suggested that early initiation of breastfeeding reduces mortality not only through increasing the chance of exclusive breastfeeding, it is but also by additional mechanisms. The additional mechanisms are probably related to some of the biologically plausible explanations such that early initiation of breastfeeding directly reduces the use of prelacteal feeds, guarantees that the newborn receive ‘colostrum’ (the first breastmilk) and promotes intestinal maturation as well as some immunological protection.[136-138]

However, breastfeeding experiences of women who underwent caesarean section can be influenced by several factors, which include timing of initiation of breastfeeding (due to delays in maternal-infant interaction), mothers’ emotional reactions to the surgery as well as infants’ health and behavior. For instance, as the postoperative pain may be severe, particularly in the first 24 hours, it may restrict maternal mobility and influence breastfeeding.[139,140] Likewise, due to the potential for physical separation of the mother and infant after caesarean delivery, given the higher risk of infant admission to NICU as a consequence of respiratory problems, there might be a lesser likelihood of timely initiation of breastfeeding.[141]

It is hypothesised that the hormonal pathway that stimulates the onset of lactation (lactogenesis) may be disturbed by caesarean section due to maternal stress and/or decreased oxytocin secretion.[142-145] This, in turn, may delay milk production. It has been supposed that maternal stress may interfere with the release of oxytocin, a hormone that results in milk ejection (let-down reflex). Maternal stress may also affect the level of prolactin, a hormone involved in lactation.[145] Similarly, newborns who were exposed to different level of stress due to obstetrical interventions during labour and birth, such as caesarean section may have disorganised sucking skills and low level of alertness, making the newborns unable to attach and suckle effectively at the breast.[145] These conditions impair lactogenesis and may result in physiological delay in milk secretion and shortening the duration of breastfeeding.[52] This, in turn, has direct impact on microbiota development because human milk oligosaccharides are thought to shape the diversification of the infant intestinal microbiota.[55]

There are studies which have been conducted to investigate the relationship between caesarean section and breastfeeding outcomes. However, because of inconsistent findings, small sample sizes, use of effect estimates from unadjusted analysis and lack of clarity on how breastfeeding outcomes were measured (or not using standard definition of breastfeeding outcomes), the results of these previous studies are less clear. For instance, Prior *et al*.[33] in their 2012 systematic review and meta-analysis involving 53 studies from 33 low-, middle-, and high-income countries (with no data from African countries) found that early breastfeeding (i.e., any initiation or breastfeeding at hospital discharge) was lower among infants delivered by caesarean section (OR, 0.57; 95% CI, 0.50 to 0.64) when compared to infants born vaginally. Nevertheless, according to Prior *et al*., breastfeeding as an outcome of interest by mode of delivery was not reported as a primary outcome in 74% (39 of 53 studies) of the studies included in their systematic review and meta-analysis. Their meta-analysis also showed a high level of heterogeneity between studies, but they have attempted to investigate the sources of heterogeneity by doing meta-regression and subgroup analysis. Moreover, the majority of the studies included in their meta-analysis did not collect data on potential confounders and reported unadjusted estimates. Under these circumstances, the association between caesarean section and early initiation of breastfeeding is unclear.

Liston and colleagues,[146] in their a 15-year cohort study that examined the impact of caesarean section on neonatal outcomes in Nova Scotia, found that compared with spontaneous vaginal delivery, breastfeeding at hospital discharge was lower in both caesarean section without labour (aOR, 0.64; 95% CI, 0.60 to 0.67) and caesarean section in labour (aOR, 0.79; 95% CI, 0.77 to 0.83). This finding suggests that the negative association between caesarean section and breastfeeding at discharge appears to be stronger in pre-labour caesarean section than caesarean section in labour (emergency). As planned caesarean births (pre-labour caesarean) are usually performed prior to the onset of labour, there is a possibility that decreased early initiation of breastfeeding may be attributed to physiological reasons. In a study conducted in Canada, it was found, compared to women who gave birth vaginally, that women who gave birth following planned caesarean section have a 61% higher odds of early cessation of breastfeeding (i.e., having breastfed for 12 weeks or less) (OR, 1.61; 95 % CI, 1.14 to 2.26).[147] Moreover, several other studies that compared the effect of caesarean section (either emergency or planned) versus vaginal delivery have also found that caesarean section influences breastfeeding outcomes.[148-151] However, the results of some studies comparing the effect of caesarean section on breastfeeding outcomes are inconsistent (i.e., some studies reported no association while the other reported negative associations between caesarean section and breastfeeding outcomes). The inconsistent findings from the previous studies are may be due to suboptimal control of confounders and other biases. Further research, particularly using rigorous study design and standard breastfeeding outcome definitions, is needed to understand the impact of caesarean section on breastfeeding outcomes.

2.2.6 Caesarean section and school outcomes

By linking the routine perinatal data with children's school achievement data, MacKay *et al*. conducted a study in 2010 aimed at examining the need for special education across the full range of gestation.[111] They noted that risk for special education need decreased as gestational age is increased. For instance, the odds ratio for special education need at 37-39 weeks was 1.16 (95% CI, 1.12 to 1.20) while the odds ratios at 33–36, 28–32 and 24–27 weeks were 1.53 (95% CI, 1.43 to 1.63), 2.66 (95% CI, 2.38 to 2.97), and 6.92 (95% CI, 5.58 to 8.58), respectively.[111] The need for special education is defined as a learning difficulty that necessitates educational support for children born, specifically, at 37-39 weeks of gestation. As planned caesarean section are usually performed from 37-39 weeks of gestation,[152] it would be important to investigate the impact of caesarean section on children's educational outcomes. Moreover, as the intrauterine brain maturation continues until the end of gestation, elective caesarean section may interrupt this process and this may has adverse effects on neurodevelopment in children's later life.[152]

It has also been supposed that gestational age contributes to the microbial composition of the infant's gut. For instance, by using 16S rRNA amplicon pyrosequencing technology, Barret *et al*. (2013) [153] found that the microbiota of preterm infants lack two of the main bacterial genera (i.e., *Bifidobacterium* and *Lactobacillus*) usually present in full-term infants. Thus, gestational age seems to be relevant because it may influence the neurodevelopment of infants through alteration in the composition of microbiota.

Curran *et al*. in their large 2017 study (n = 1,489,925) using data from Swedish medical birth register and national school register revealed that elective caesarean section (aOR, 1.06; 95% CI, 1.03 to 1.09) and emergency caesarean section (aOR, 1.12; 95% CI, 1.09 to 1.15) were associated with children's poor school achievement.[154] However, by considering the complex nature of the relationship between caesarean section and cognitive outcome, they stated that their findings should be interpreted carefully. Moreover, in a 2016 study involving 153,730 infants born at ≥32 weeks of gestation in New South Wales, Australia, it was found that children born following caesarean section had a 14% higher risk of being classified as developmentally vulnerable at school entry when compared to children born by spontaneous vaginal delivery (aRR, 1.14; 95% CI, 1.06 to 1.22).[155]

Using data from the Longitudinal Study of Australian children (n = 3,666), Polidano *et al*.[156] in their 2017 study examined the differences in child cognitive performance among caesarean versus vaginally born children. They found that children born following caesarean section performed lower by up to 1/10 of a standard deviation in numeracy test scores at age 8–9 compared with vaginally born children. However, another 2016 study (n= 3,609) using whole-of-population administrative data from South Australia by Smithers *et al*.[157] found no association between elective caesarean birth and children's poor school performance as measured by Australian National Assessment Program—Literacy and Numeracy (NAPLAN) tests at age eight.

In summary, the effect estimates of the studies that examined the association between caesarean section (compared with vaginal birth) and children's educational or cognitive performance range from no association to little association (i.e., a <15% increased risk of poor school performance). The different results reported by these studies may be due to suboptimal control of confounders and the little effects observed may be explained away by residual confounding.

2.3 Apgar scores

The Apgar score was devised and introduced in early 1950s by Dr Virginia Apgar as an overall measure of a baby's vitality at one minute after birth.[158] A five-minute Apgar score was introduced later as it had been shown to be a better predictor of neonatal survival rather than one-minute Apgar score.[159] For decades, the Apgar score has been routinely reported at one and/or five minutes for all newborns in almost every country in the world. The Apgar score is also reported every five minutes up to 20 minutes if the five-minute Apgar score is less than 7.[160] The Apgar score comprises five physiological signs, including heart rate, respiratory effort, reflex irritability, muscle tone and skin colour. A rating of 0, 1 or 2 is given for each sign, reflecting whether it was absent, present but not adequate, or normal.[160,161] These result in a total score that ranges from 0 to 10.

Apgar scores can also be used as a physiological indicator of how well a newborn is making the transition from *in-utero* to the *ex-utero* environment, where the oxygen concentration is about 21%.[162] For example, the skin color is evaluated to determine the perfusion of the skin with oxygenated blood; heart rate reflects the success in the delivery of oxygen to organs; reflex irritability can be used as a marker for nervous system integration; muscle tone (activity) represents the locomotor capacity of the newborn and respiratory rate represents pulmonary function, which facilitate the neuro-feedback-mediated effort to breathe.[162] **Figure 2.3** shows where Apgar score falls in the course of birth-related events.

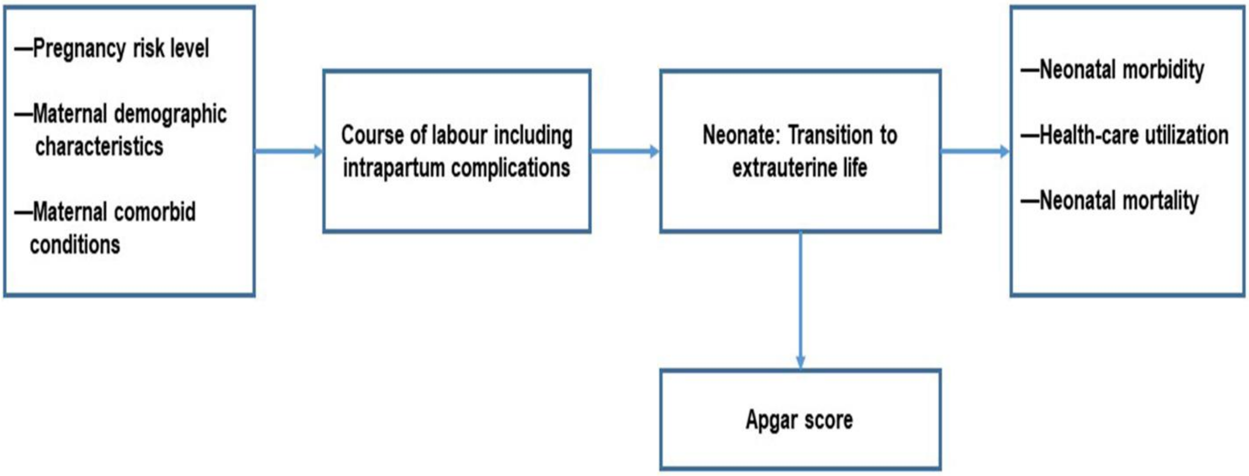

Figure 2.3 A conceptual model that demonstrate where Apgar score falls in series of pregnancy and perinatal events.

Source: Adapted and redrawn from Bovbjerg *et al* (2019).[163]

2.3.1 Apgar scores and short-term perinatal outcomes

There are several previous studies that investigated the association between Apgar scores and short-term perinatal outcomes. For example, Razaz and colleagues[164] in their 2019 study included 1,551,436 singleton infants, with Apgar score of ≥ 7 at 1, 5 and 10 minutes in Sweden to examine the association between Apgar scores and neonatal morbidity and mortality. They found that, compared with infants with Apgar score of 10, the risks of neonatal morbidity and mortality among infants with low Apgar score values within the normal range (7-10) is high, particularly at 5 and 10 minutes.

By linking routine discharge and mortality data for all births in Scotland, UK between 1992 and 2010, Iliodromiti *et al*.[165] analysed data on 1,029,207 live singleton births between 22 and 44 weeks of gestation to examine the strength of the association between five-minute Apgar score and the risk of neonatal and infant mortality. They found that low five-minute

Apgar score (0-3) was linked with increased risk of neonatal and infant death across all gestational age. For instance, compared with normal Apgar score (7-10), a low Apgar score (0–3) was associated with aRR of 359.4 (95% CI, 277.3 to 465.9) for early neonatal death whereas it was 30.5 (95% CI, 18.0 to 51.6) and 50.2 (42.8 to 59.0) for late neonatal death and infant death, respectively. For intermediate Apgar score (4-6), Iliodromiti *et al*. also noted similar associations, but with lower magnitude.[165]

Furthermore, several other previous studies[166-169] have shown that Apgar scores of <7 were related to morbidity, including neonatal respiratory distress, meconium aspiration, hypoxic-ischaemic encephalopathy and infant mortality. It has been suggested that the association between Apgar score of <7 and neonatal and infant mortality is mostly attributed to infections or anoxia.[165] It is clear from the existing literature that low Apgar score can predict neonatal morbidity and mortality. This may have important implications for obstetric practice and research.

2.3.2 Apgar scores and children's educational outcomes

Two large studies published in 2008 and 2011 involving 176,524 and 19,559 children in Sweden [170,171] have demonstrated that low Apgar score (i.e. <7) is associated with poorer cognition or school achievement. For example, compared with infants with Apgar scores ≥7 at 0-5 minutes, infants with low Apgar score (<7) had 1.14 times higher odds of low intelligence quotient (IQ) (OR, 1.14; 95% CI, 1.03 to 1.27).[170]

After a study of literature regarding the association between the value and duration of Apgar score and death or neurologic disability across 17 studies, Ehrenstein (2009)[172] observed dose dependant patterns between the value and duration of low Apgar score and neurologic disability and death among infants. Nonetheless, less than 5% risk for neurologic disability was observed.[172] In another 2009 study in Sweden, compared with infants with Apgar scores of $\geq$7 at five-minutes, infants with low Apgar score had a four-fold higher risk of neurologic disability (PR, 4.0; 95% CI, 2.2 to 7.2).[173]

The majority of the available evidence regarding the association between Apgar scores and IQ comes from studies conducted by linking birth data with routine IQ test results at conscription around age 18.[170,173,174] Moreover, almost all of the previous studies compared Apgar scores dichotomised at the familiar cut-points (i.e., <7 or <4). There seems no study that investigated whether Apgar score when left as a quasi-continuous measure (i.e., each of the Apgar score values (compared with 10)) is associated with children's educational outcomes. As each total value of the Apgar score may indicate different physiological conditions, it would be important to examine the associations between Apgar scores when left as quasi-continuous measure and children's later neurodevelopmental outcomes.

2.4 Research justification

Given the concern that the rates of obstetrical interventions during labour and birth such as induction of labour and caesarean section have been substantially increasing globally, there is growing interest in research examining the short-and longer-term effects of obstetrical interventions during labour and birth. This literature review has identified several studies regarding the effect of obstetrical interventions on short-and longer-term outcomes.

However, the studies reviewed in this chapter have highlighted a number of gaps. First, much of the available evidence regarding the impact of obstetrical interventions during labour and birth on short-and long-term outcomes were generated from high-income countries. Second, although the short-term effect of obstetrical interventions (more specifically induction of labour) are well described in the literature, studies investigating longer-term effects of elective labour induction at 39 weeks versus expectant management on children's educational outcomes have not been available.

Third, despite reporting on the associations between caesarean section and maternal and neonatal mortality, previous studies are limited in providing interpretations of what the findings mean using contextual models (i.e., by considering contextual factors such as unequal access, infrastructural, structural and health workforce constraints that could play a role in the association between caesarean section and neonatal mortality), particularly in LMICs, where there is less evidence. Finally, inferences from several previous studies appear to be limited methodologically. For instance, many of the previous studies are hampered by non-longitudinal study design, small sample sizes and inconsistent findings, which may be due to suboptimal control of confounders and other biases.

This thesis helps fill these research gaps and uses data from low-, middle- and high-income countries. The thesis reports the design and results of five studies using data from 33 sub-Saharan African countries (LMICs) and Australia (a high income country). The first two studies present results of the analyses concerning caesarean section in Ethiopia. The next study presents novel analyses examining caesarean section and breastfeeding in sub-Saharan Africa. The final two studies add to knowledge about Apgar scores and children's educational outcomes, and labour induction and children's education outcomes using high-quality whole-of-population linked administrative data from South Australia.

Specifically, the studies investigated:

1. The prevalence and sociodemographic characteristics of caesarean section in Ethiopia;
2. The temporal association between caesarean birth and neonatal death within the context of Ethiopia from 2000 to 2016 and the interpretation of the association using the 'Three Delays Model';
3. The impact of caesarean section on breastfeeding indicators—early initiation of breastfeeding (within 1 hour), exclusive breastfeeding under 6 months and children ever breastfed (at least once)—in 33 sub-Saharan African countries;
4. The associations between Apgar scores and children's educational outcomes at eight years of age in South Australia
5. The effect of elective labour induction at 39 weeks versus expectant management on children's educational outcomes at eight years of age.

Chapter 3: Methodology

The five research questions of this thesis, a review of the literature, and research justification were presented in Chapters 1 and 2. This chapter describes: (1) the two data sources used in this thesis, (2) the organisation of information on the exposure (measures of obstetrical interventions during labour and birth), the outcome and the confounders from the two data sources, and (3) the statistical analytic approaches used to answer the five research questions.

3.1 Data sources

Data for this thesis were drawn from the Demographic and Health Surveys (DHS) and the South Australian Early Childhood Data Project (SAECDP). The DHS are widely available high-quality nationally-representative household surveys in more than 90 low- and middle-income countries (LMICs). The SAECDP is an established project that encompasses high-quality whole-of-population linked administrative data from state and federal sources in South Australia. In this thesis, the DHS data of 33 LMICs in sub-Saharan Africa and the SAECDP data from Australia (high-income country) were utilised to answer the five research questions related to how obstetrical interventions during labour and birth affect breastfeeding, neonatal health and children's educational outcomes. The two data sources encompass datasets that span low-, middle-, and high-income country contexts. **Figure 3.1** shows countries (highlighted in blue) where the data from the two data sources were drawn for this thesis.

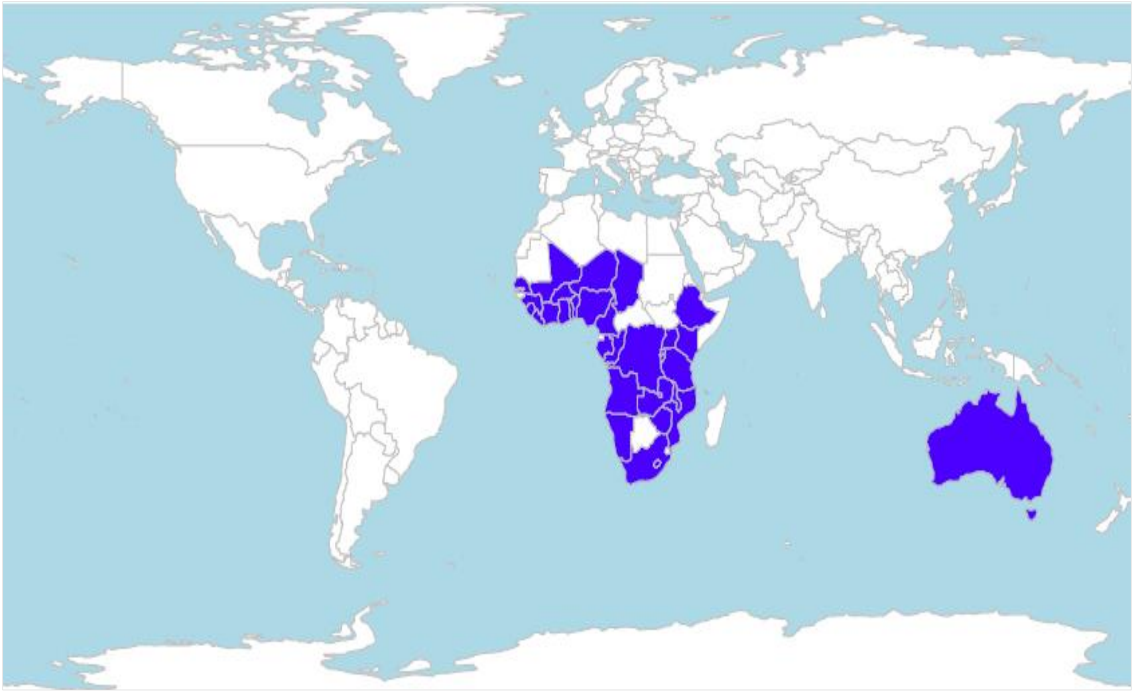

Figure 3.1 Countries (highlighted in blue) where the data for studies included in the thesis were drawn.

Table 3.1 summarises the research questions addressed in the thesis and the data sources used to answer each research question. The use of two different data sources (i.e., DHS and SAECDP) allowed this thesis to capture the effects of obstetrical interventions during labour and birth on breastfeeding, neonatal mortality and children's educational outcomes across diverse health system resource settings. Both DHS and SAECDP contain rich information on a range of maternal, perinatal and sociodemographic characteristics as well as information on a range of maternal and child health outcomes. Moreover, the SAECDP contains rich information on children's longer-term neurodevelopmental outcomes (e.g., ~8-year-old children's school assessments). The detailed descriptions regarding the design, sampling and methodology of each data source are provided below.

Table 3.1 Data sources used to examine each research aim.

Research aim	Data source
1. To estimate the prevalence and examine sociodemographic factors associated with caesarean section in Ethiopia.	DHS
2. To examine the changing temporal association between caesarean birth and neonatal death in Ethiopia from 2000 to 2016 as well as to provide an interpretation of the associations using the 'Three Delays Model' in the context of Ethiopia.	DHS
3. To investigate the effect of caesarean section on breastfeeding indicators in each of the 33 countries in sub-Saharan Africa, as well as to summarise the magnitude of these within-country effects in an overall estimate using random-effects meta-analyses.	DHS
4. To examine the effect of Apgar scores of 0-5, 6, 7, 8 and 9 (compared with 10) on children's educational outcomes at eight years of age.	SAECDP
5. To estimate the effect of elective induction of labour at 39 weeks of gestation as compared with expectant management on children's educational outcomes at eight years of age.	SAECDP

3.1.1 The Demographic and Health Surveys (DHS)

The DHS are nationally-representative surveys that are conducted at household level to collect data on health topics, including maternal and child health, nutrition, environmental health, malaria, HIV/AIDS and reproductive health in over 90 LMICs. The DHS began in 1984 funded by USAID (U.S. Agency for International Development).[175] In order to allow comparison over time, the DHS surveys are usually conducted approximately every five years. The DHS are implemented by a single national implementing agency such as a National Statistical Office, a Ministry of Health or a university in LMICs. For instance, in Ethiopia, the DHS was implemented by the Central Statistical Agency of Ethiopia.

The DHS study design, sampling and methodology were standardised and replicable with quality assurance measures. For instance, each of the DHS surveys involved two-stage, stratified clustered probability sampling design.[175] The samples were drawn from an existing sampling frame (commonly the latest national census). The DHS uses stratification to minimise sampling errors and samples are stratified by geographic region and by urban/rural areas within each region. The samples are designed and selected independently within each stratum. In the first stage of selection, the primary sampling units (PSUs)—usually the national census enumeration areas—are selected with probability proportional to size within each stratum. The PSU makes up the survey cluster. In the second stage, a complete list of households was conducted for each cluster. Subsequently, a fixed number of households—about 25-30 households per cluster—were selected by equal probability systematic sampling in the selected cluster. The total number of households (sample size) included in each round of DHS in LMICs were generally between 5,000 and 30,000 households.

All women aged 15-49 years old and all men aged 15-54(59) years old who were either permanent residents of the selected households or visitors who stayed in the household the night before the survey were eligible for face-to-face interviews. The DHS use a ‘standard model questionnaires’ to collect data that are comparable across countries. Moreover, the DHS also have optional ‘questionnaire modules’ for special information on topics that are not contained in the model questionnaires. Each country adopts and applies the model questionnaires although they can also add some questions of their particular interest to model questionnaires. In many surveys, a household, women’s, and men’s questionnaires were completed. Data on children aged 0-59 months in each household were also collected. Some DHS standard surveys also collected additional data including biomarkers (e.g., anthropometry, anaemia testing, and HIV testing) and geographic information (e.g., GPS data). Data were collected by local field teams, electronically entered, manually and automatically cleaned, and made publicly available by 'The DHS Program' (https://dhsprogram.com/Data/).

Each of the DHS surveys protocols were approved by Institutional Review Board (IRB) of each country as well as by the ICF IRB. The DHS Program required an application to obtain permission to use the DHS data for research purposes. Data approval was sought and granted for use of the data from sub-Saharan African countries by DHS administrators for this thesis. The detailed information regarding the methodology and standards for protecting the privacy of study participants in all DHS can be accessed from The DHS Program online (https://dhsprogram.com/What-We-Do/methodology.cfm).

3.1.2 The South Australian Early Childhood Data Project (SAECDP)

The SAECDP is an innovative population-based linked administrative research database in South Australia. The project encompasses more than 30 different government administrative datasets from state and federal sources, and include all children in South Australia who were born from 1999 to 2013.[176] The advantage of the SAECDP is that it has rich information on child health and development from the perinatal period into adolescence, which is important to investigate the short- and long-term outcomes in children. The datasets held by the SAECDP are diverse and includes[176] multiple datasets from the Births and Deaths Registry, Perinatal Statistics, the Birth Defects Registry, Public Hospital Inpatient and Emergency Presentation data, Congenital Abnormality data, Child Health Records, Family Home Visiting Program, the Edinburgh Postnatal Depression Scale, Postnatal Risk Questionnaire, Childhood Immunisations, Neonatal Hearing, Public School Enrolment Census, Reading achievement levels, English as an Additional Language/Dialect, the National Assessment

Program—Literacy and Numeracy (NAPLAN), the Australian Early Development Census, Child Protection, Youth Justice and Public Housing.

De-identified linkage keys were generated by an independent data linkage agency (SA-NT DataLink) using basic personal identifiers such as name, address, date of birth and sex. All the SAECDP datasets are supplied in de-identified form. In this thesis, the Perinatal database and NAPLAN datasets were used and the de-identified linkage keys were used to merge these datasets.

Ethical approval for the SAECDP project was already obtained from South Australian Department for Health and Ageing Human Research Ethics Committee and the use of data from the SAECDP for this thesis was approved by the South Australian Department for Health and Ageing (HREC/13/SAH/106/AM08).

3.2 Exposures: - measures of obstetrical interventions during labour and birth

Consistent with epidemiologic literature, statistical analyses in this thesis were organised in three different sets of variables—the exposure (treatment), the outcome and the confounders. The exposures and outcomes were determined by the five research questions related to how obstetrical interventions during labour and birth affect breastfeeding, neonatal mortality and children's educational outcomes. The exposures examined in this thesis included—caesarean section (Studies 2 and 3), Apgar scores (Study 4) and elective induction of labour at 39 weeks of gestation (Study 5).

3.2.1 Caesarean section

The data on caesarean section was captured in DHS based on mother's self-report. For example, the self-reported data on caesarean section were collected by asking mothers a question that reads, 'Was (NAME) delivered by caesarean section, that is, did they cut your belly open to take the baby out?' in the 2016 Ethiopian DHS.[116] A reliability study conducted by Stanton *et al*.,[177] demonstrated that the recall of caesarean section in DHS was good in developing countries. Singleton last born infants delivered by caesarean section versus infants born vaginally were used as exposure in research questions 2 and 3 (Chapters 5 and 6).

3.2.2 Apgar scores

In the perinatal database held by the SAECDP, both 1 and 5 minute total Apgar scores were captured. Scores on each of the five Apgar score components—heart rate, respiratory effort, reflex irritability, muscle tone and skin colour—were not collected. Infants with a range of both 1 and 5 minutes Apgar scores (i.e., 0-5, 6, 7, 8 and 9 (compared with 10)) were served as the exposure of interest in research question 4 (more details in Chapter 7). The grouping of Apgar scores 0-5 was done because the sample size for each Apgar score within this group (0-5) was very small.

3.2.3 Elective induction of labour at 39 weeks of gestation

In South Australia, the perinatal database included information about onset of labour, reason for induction of labour and gestational age at birth. Gestational age (at birth) dating was determined predominately based on early dating ultrasound. However, in the small number of women when dating ultrasound was not available, gestational age was determined from the first day of the last menstrual period and estimates at birth. Based on these three variables—onset of labour, reason for induction of labour and gestational age—'elective induction of labour at 39 weeks of gestation' variable was computed and used as the exposure of interest in research question 5 (Chapter 8). The comparison (unexposed) group for elective induction of labour at 39 weeks of gestation was 'expectant management', which was defined as deliveries following spontaneous labour and elective induction of labour or medically-indicated induction or caesarean from 40-42 weeks of gestation.

3.3 Outcomes

The outcome variables examined in this thesis included caesarean section (Study 1), neonatal death (Study 2), breastfeeding indicators—early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed—(Study 3), and children's educational outcomes (Studies 4 and 5).

3.3.1 Neonatal death

Neonatal death was defined as infants who were born alive, regardless of gestational age at birth, but died within the first 28 days of life. The DHS collected information from mothers whether their all biological children were alive or dead at the time of interview. Mothers reported the age of all children alive and age at death for deceased children. Thus, neonatal death, as a binary outcome variable, was measured from two variables (whether the child is alive and age at death (in days)). Neonatal death was used as an outcome of interest in research question 2 (Chapter 5).

3.3.2 Breastfeeding indicators

In each DHS, respondents were asked a number of questions regarding breastfeeding practices, the length of breastfeeding, about children's consumption of liquids and solid food and micronutrient supplementation. Breastfeeding questions captured in DHS included whether the child was ever breastfed; how long after birth before the newborn was put to the breast; whether the baby was given anything to drink or eat other than breast milk; the type of drink given to the child and whether the child was still breastfeeding. Based on this information, a standard set of indicators for assessing breastfeeding practice, which are consistent with the WHO and partners definitions,[178] were defined. These included 'early initiation of breastfeeding', 'exclusive breastfeeding under 6 months' and 'children ever breastfed'.

According to the WHO and partners definitions of indicators for assessing infant and young child feeding practices,[178] 'early initiation of breastfeeding' is defined as being put to the breast within one hour of birth (i.e., the proportion of children born in the last 24 months who were put to the breast within an hour of birth). 'Exclusive breastfeeding under 6 months' was defined as the percentage of infants aged 0-5 months who were consumed only breast milk (no other liquids or foods). 'Children ever breastfed' is the proportion of children born in the last 24 months who were ever breastfed. These three breastfeeding indicator variables were used as outcome of interest in research question 3 (Chapter 6).

3.3.3 Children's educational outcomes

In Australia, children's educational outcomes are assessed by the National Assessment Program—Literacy and Numeracy (NAPLAN) tests at year (grade) 3, 5, 7 and 9 annually. The NAPLAN gives an opportunity to assess how children are making progress against the national standards in literacy and numeracy in all year levels (i.e., from year 3 to year 9). NAPLAN has five test domains including reading, writing, spelling, grammar and numeracy. For each domain, NAPLAN results are reported as both direct scores (range from 0 to 1000) and grouped into proficiency bands (range from 1 to 10). For each year level, the reported proficiency bands are different. For instance, for year 3, the reported proficiency bands range from 1–6 while for year 5, 7 and 9, the reported proficiency bands range from 3-8, 4-9 and 5-10, respectively. The proficiency bands are used to identify children's educational outcomes relative to the National Minimum Standard (NMS), which is also dissimilar for each year level. For year 3, band 2 is the NMS, whereas bands 4, 5 and 6 are the NMS for year 5, 7 and 9, respectively.

The NAPLAN test data at year 3 (~8 years of age), which is administered by South Australian Department for Education were used as children's educational outcomes measures in research questions 4 and 5 (more details in Chapters 8 and 9). The NAPLAN test scores at year 3 (~8 years of age) were used in this thesis to maximize the eligible study population in South Australia. Consistent with national reporting of NAPLAN scores, this thesis reports results where NAPLAN was categorised into children performing at/below the NMS (≤ band 2) and above NMS (bands 3–6). However, the SAECDP did not include NAPLAN scores from students attending private schools as these have not been made available for linkage. Private school attendance accounted for about 34% of the population of year 3 students in South Australia from 2008 to 2015.[179]

3.4 Confounding

Confounder selection in this thesis was based on the modern epidemiological definition, which is a common causes of the exposure and the outcome. The confounders were identified based on *a priori* subject-matter and expert knowledge, as well as through the use of Directed Acyclic Graphs (DAGs). It has been emphasised by a number of authors that confounder identification should be based on *a priori* subject-matter or expert knowledge (i.e., based on the understanding of the causal network linking the variables under study).[180-183]

DAGs are causal diagrams that visually encode assumptions about causal links among exposure, outcome and confounders (covariates).[184] DAGs have arrows that function unidirectionally to infer causality. **Figure 3.2** shows an example of a DAG representing Study 3 in this thesis. The use of DAGs help identify variables that can be used to block all backdoor paths between exposure and outcome. The variables identified and adjusted for in statistical analyses in each study to eliminate confounding were described in detail in Chapters 5-8.

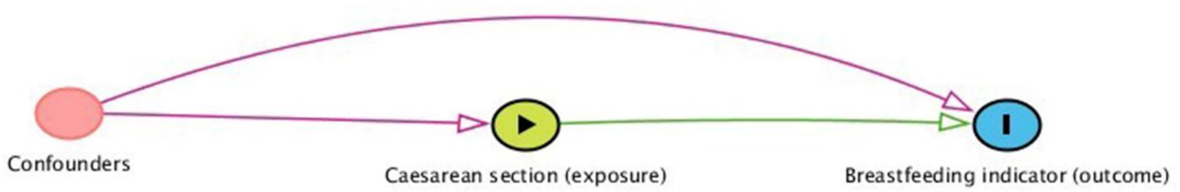

Figure 3.2 DAG for the association between caesarean section and breastfeeding indicators.

3.5 Statistical Analysis

Table 3.2 shows the different statistical analysis approaches used in each study in this thesis. All statistical analyses were conducted using STATA/SE V.15.1 (StataCorp, College Station, TX, USA).

Table 3.2 Studies in the thesis and their statistical analysis approaches.

Study	Analytic approaches
1. Caesarean section in Ethiopia: prevalence and sociodemographic characteristics	• Log-Poisson regression
2. The changing temporal association between caesarean birth and neonatal death in Ethiopia: secondary analysis of nationally representative surveys	• Log-Poisson regression • Linear regression • Application of the 'Three Delays Model'
3. Impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa	• Modified Poisson regression • Random-effects meta-analysis
4. Associations between Apgar scores and children's educational outcomes at eight years of age	• Augmented Inverse Probability Weighted (AIPW) estimator • Negative control outcome
5. Elective labour induction versus expectant management in women and children's educational outcomes at eight years of age	• AIPW estimator

3.5.1 Log-Poisson regression/modified Poisson regression

Log-Poisson regression (i.e., using a generalised linear model with a log link function and a Poisson distribution for response)[185] was used to calculate prevalence ratios (PR) in Studies 1 and 2. Log-Poisson regression is an alternative to logistic regression, which directly yields an estimated incidence rate ratio (IRR) rather than odds ratio (OR). However, as the mathematical computations for IRR is identical to the PR or relative risk (RR), the effect estimate from log-Poisson regression (i.e., IRR) was interpreted in terms of PR. It has been widely discussed in literature and was concluded that the RR (PR) is a preferred effect estimate over the OR.[186-188] This is because the OR was found to overestimate the strength of associations (i.e., odds ratios overestimate relative risks when the outcome is common).[189] The other reason is when estimating OR, changing the reference category of a binary variable will produce 'reciprocal' estimates while that is not the case when estimating PR.[189] Nevertheless, when the outcome is rare (i.e., <10%), OR can be used because it is reasonably a good estimate of RR.

Moreover, it was demonstrated by Zou[190] that the RR (PR) can be estimated directly using a modified Poisson regression (i.e., Poisson regression with a robust error variance). This approach, which allows the RR to be estimated directly, was termed as the modified Poisson Regression by Zou. In Study 3, the modified Poisson regression models was used to calculate unadjusted and adjusted PR and their 95% CIs for each breastfeeding indicator—early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed—associated with caesarean section versus vaginal birth in each 33 country in sub-Saharan Africa. The formula for the modified Poisson regression is given as follows: [190]

$$\log[\pi(x_i)] = \alpha + \beta x_i$$

$$l(\alpha, \beta) = C. \sum_{i=1}^{n} [y_i(\alpha + \beta x_i) - \exp(\alpha + \beta x_i)]$$

3.5.2 Random-effects meta-analysis

In Study 3, random-effects meta-analyses were also conducted to summarise the evidence (estimate) from each of the 33 countries in sub-Saharan Africa regarding the association between caesarean section and breastfeeding indicators. Random-effects meta-analysis using inverse variance weighting was selected to account for between-country variation in effect estimates. Statistical heterogeneity was measured using I^2 and the possible sources of heterogeneity were also explored using *a post hoc* subgroup analyses (more details in Study 3).

3.5.3 Augmented Inverse Probability Weighted (AIPW) estimator

In Studies 4 and 5, the average treatment effects (ATEs) or risk differences were calculated using AIPW estimator.[191] The AIPW estimator is also called a doubly-robust estimator.[192,193] The AIPW estimator was chosen over traditional regression because it delivers a marginal rather than a conditional estimate, and it fits regression models for both the exposure and outcome providing a doubly-robust property if either the regression model for the outcome or the exposure is correctly specified.[192]

In this thesis, the AIPW estimator fit logistic regression models for the exposures conditional on each confounder listed in Studies 4 and 5 to estimate propensity scores for each individual. The propensity scores were used to weight the observed data. The AIPW also fit logistic regression models for the outcomes conditional on all confounders for each category of the exposures to obtain predicted outcomes for each individual in Studies 4 and 5. After estimating the propensity scores and predicted outcomes, the AIPW estimator combines the estimated values along with observed values to calculate the doubly robust estimates of outcomes for each level of exposure for each individual.

Finally, the mean of the estimates of outcome under exposed (e.g., elective induction of labour (Study 5)) and unexposed (expectant management) was calculated. These estimated means were used to calculate ATE, which is a mean difference in outcome among exposed and unexposed groups.

3.5.4 Negative control outcome

Sensitivity analysis via 'negative control outcome'[194]—a tool for detecting confounding and other bias—was used to examine the potential for residual confounding in Study 4. The negative control outcome is a means of ruling out the possible non-causal interpretations of results in epidemiologic studies. In the negative control outcome analysis, the estimate of the associations between the exposure (e.g., Apgar score, in Study 4) and the outcome (e.g., children's school performance), as well as the estimate of the associations between the exposure and the negative control outcome (e.g., family possession of school card, in Study 4) were compared. If the associations are of similar magnitude, this suggests that the association between the exposure and the outcome could be due to residual confounding.

3.5.5 Application of the 'Three Delays Model'

The 'Three Delays Model' is a conceptual framework developed by Thaddeus and Maine to examine factors contributing to maternal mortality with a specific focus on those that affect the 'interval between the onset of obstetric complication and its outcome'.[195] The 'Three Delays Model' summarises the various factors that affect this interval in three phases of delay—delay in deciding to seek care (phase I delay); delay in identifying and reaching medical facility (phase II delay); and delay in receiving adequate and appropriate treatment (phase III delay). Some of the key factors that shape the model include the status of women; distance from health facility; availability and cost of transportation; condition of roads; distribution of health facilities; shortage of supplies, equipment and skilled birth attendants and adequacy of referral system.[195] **Figure 3.3** shows the pictorial presentation of the 'Three Delays Model'. Study 2, in this thesis, was guided by the 'Three Delays Model' to facilitate the interpretation of the association between caesarean section and neonatal mortality by considering the contextual factors in Ethiopia.

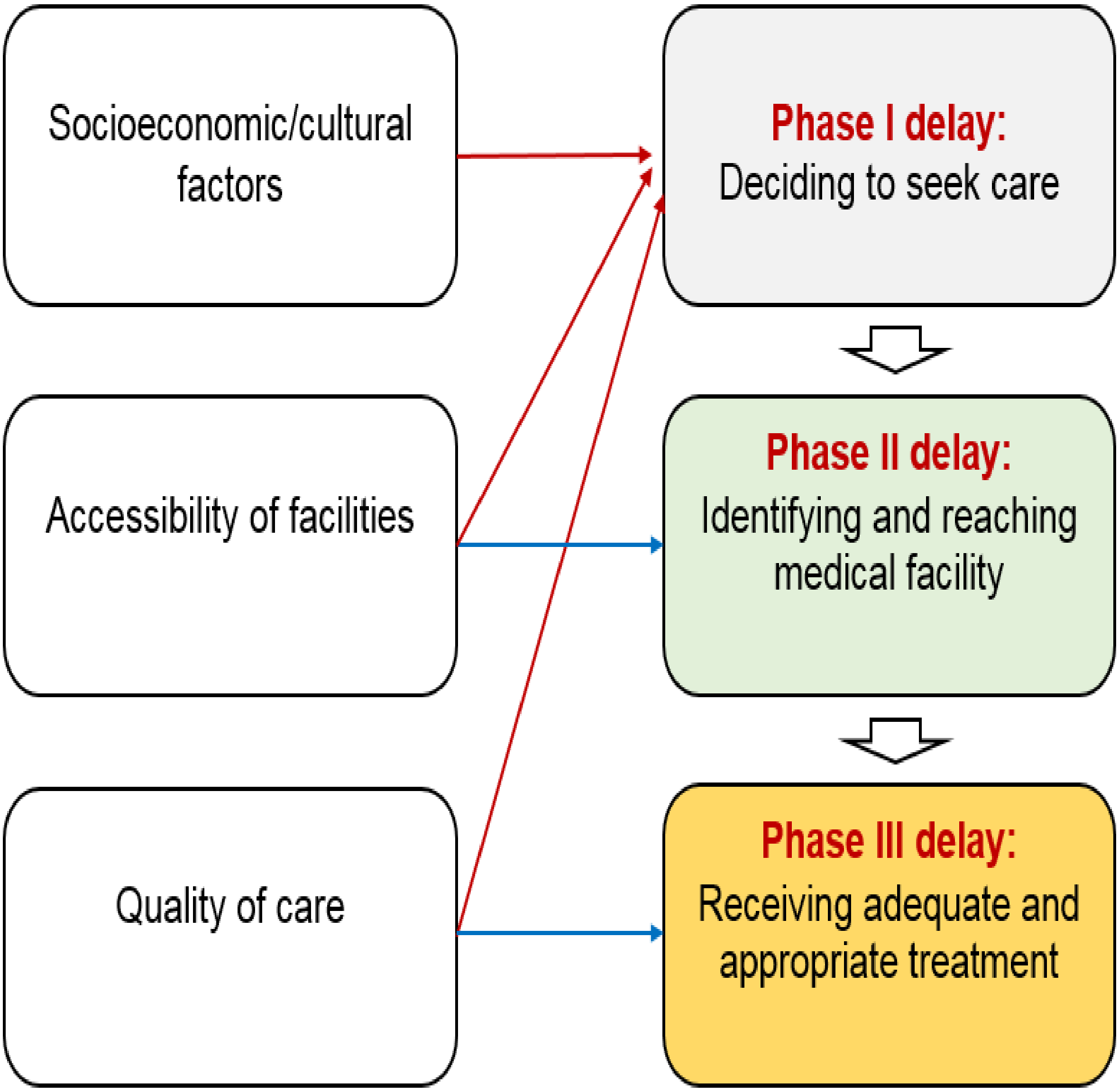

Figure 3.3 The ‘Three Delays Model’.

Source: Adapted and redrawn from *Soc Sci Med*, 1994; **38**(8): 1091-110.[195]

Chapter 4: Caesarean section in Ethiopia: prevalence and sociodemographic characteristics

4.1 Preface

This chapter contains the first of the five studies contributing to this thesis. This study was published in *The Journal of Maternal-Fetal & Neonatal Medicine* in 2017 and examines the prevalence and sociodemographic characteristics of caesarean section in Ethiopia.

This chapter utilised high-quality nationally representative data collected for Ethiopian Demographic and Health Surveys in 2000, 2005, 2011 and 2016 to comprehensively assess the prevalence and sociodemographic characteristics associated with caesarean section in Ethiopia from 2000 to 2016. Although a review of the literature revealed that there have been studies that report on caesarean section in Ethiopia, all previous studies focused on specific geographic area within Ethiopia at a particular point in time. Thus, this study addresses an important research gap and may have important policy and practice implications.

4.2 Publication

Yisma E, Smithers LG, Lynch JW, Mol BW. Cesarean section in Ethiopia: prevalence and sociodemographic characteristics. *J Matern Fetal Neonatal Med 2019*; **32**(7): 1130-1135.

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Contribution to the Paper	Conceived and designed the study, performed the statistical analysis, interpreted the data, and drafted the manuscript.		
Overall percentage (%)	85%		
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	5-Aug-2020

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	Lisa G Smithers
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Chapter 5: The changing temporal association between caesarean birth and neonatal death in Ethiopia: secondary analysis of nationally representative surveys

5.1 Preface

This chapter contains the second of the five studies contributing to this thesis. The study was published in *BMJ Open* in 2019 and examines the association between caesarean birth and neonatal mortality in the context of Ethiopia over time.

In this chapter, both individual- and aggregate-level data analyses were first performed to examine the association between caesarean section and neonatal death using DHS data collected over a period in which the availability of caesareans increased in Ethiopia. The chapter then applied the ‘Three Delays Model’ to facilitate the interpretation of the association between caesarean section and neonatal mortality both empirically and theoretically. The different analyses conducted helped to explain pathways and differentials in caesarean section use and its association to neonatal mortality in Ethiopia by considering contextual factors such as unequal access, infrastructural, structural and health workforce constraints that could play a role in the association between caesarean section and neonatal mortality. This investigation is important to inform policy and practice because policy makers and program planners may consider context-specific health interventions to decrease maternal and neonatal mortality.

5.2 Publication

Yisma E, Mol BW, Lynch JW, Smithers LG. The changing temporal association between caesarean birth and neonatal death in Ethiopia: secondary analysis of nationally representative surveys. *BMJ Open* 2019; 9(10):e027235. http://dx.doi.org/10.1136/bmjopen-2018-027235.

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Name of Principal Author (Candidate)	Engida Yisma		
Contribution to the Paper	Conceived and designed the study, performed the statistical analysis, interpreted the data, and drafted the manuscript.		
Overall percentage (%)	85%		
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	5-Aug-2020

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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
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BMJ Open

The changing temporal association between caesarean birth and neonatal death in Ethiopia: secondary analysis of nationally representative surveys

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ABSTRACT

Objective To examine the changing temporal association between caesarean birth and neonatal death within the context of Ethiopia from 2000 to 2016.

Design Secondary analysis of Ethiopian Demographic and Health Surveys.

Setting All administrative regions of Ethiopia with surveys conducted in 2000, 2005, 2011 and 2016.

Participants Women aged 15–49 years with a live birth during the 5 years preceding the survey.

Main outcome measures We analysed the association between caesarean birth and neonatal death using log-Poisson regression models for each survey adjusted for potential confounders. We then applied the 'Three Delays Model' to 2016 survey to provide an interpretation of the association between caesarean birth and neonatal death in Ethiopia.

Results The adjusted prevalence ratios (aPR) for neonatal death among neonates born via caesarean section versus vaginal birth increased over time, from 0.95 (95% CI: 0.29 to 3.19) in 2000 to 2.81 (95% CI: 1.11 to 7.13) in 2016. The association between caesarean birth and neonatal death was stronger among rural women (aPR (95% CI) 3.43 (1.22 to 9.67)) and among women from the lowest quintile of household wealth (aPR (95% CI) 7.01 (0.92 to 53.36)) in 2016. Aggregate-level analysis revealed that an increased caesarean section rates were correlated with a decreased proportion of neonatal deaths.

Conclusions A naïve interpretation of the changing temporal association between caesarean birth and neonatal death from 2000 to 2016 is that caesarean section is increasingly associated with neonatal death. However, the changing temporal association reflects improvements in health service coverage and secular shifts in the characteristics of Ethiopian women undergoing caesarean section after complicated labour or severe foetal compromise.

Strengths and limitations of this study

- This was the first study to examine the temporal association between caesarean birth and neonatal death within the context of Ethiopia from 2000 to 2016.
- A number of analyses conducted after adjustment for potential confounders helped develop the possible scenarios to better understand the interpretation of the changing associations.
- We have used additional supporting evidence from the 2016 Ethiopian Demographic and Health Survey data which allowed us interpret the association between caesarean birth and neonatal death in view of contextual factors in Ethiopia using the 'Three Delays Model'.
- Given the very low base rates of caesarean delivery in Ethiopia, the interpretation of our findings may not reflect the context of other low-income and middle-income countries.

INTRODUCTION

Globally, 2.6 million neonatal deaths occurred within the first 28 days after birth, which accounted for 46% of all under-five deaths in 2016.[1] The majority of these deaths were from low-income and middle-income countries. According to the United Nations Interagency Group for Child Mortality Estimation, Southern Asia (39%) and sub-Saharan Africa (38%) comprised the top two regions with the highest proportion of newborn deaths, while five countries (India, Pakistan, Nigeria, the Democratic Republic of the Congo and Ethiopia) accounted for 50% of all newborn deaths.[1] Evidence shows that, compared with mortality among children aged 1–59 months, neonatal mortality is decreasing more slowly.[1] If the current trend continues, more low-income and middle-income countries will fail to achieve the Sustainable Development Goal target for neonatal mortality at least as low as 12 deaths per 1 000 live births.[1 2]

In contemporary obstetric practice, caesarean section remains an important intervention in preventing neonatal mortality and other adverse birth outcomes.[3] However, caesarean section may be prone to misuse because of unequal access, social and cultural factors.[4–6] In developing country settings, due to limited medical provisions and/or lack of skilled birth attendants, some women may not benefit from caesarean birth though they are medically eligible, while ineligible women may sometimes have increased access. In the last decades, caesarean section rates have been increasing in low-income, middle-income and high-income countries.[7–9] The World Health Organization (WHO) suggests that 'every effort should be made to provide caesarean sections to women in need, rather than striving to achieve a specific rate'.[10]

Previous studies conducted using aggregate-level and individual-level data have yielded inconsistent results about the association between caesarean birth and neonatal mortality. For instance, two ecological studies[11 12] conducted using worldwide country-level data have found that caesarean birth was associated with lower neonatal mortality, while another two ecological studies[13 14] showed no association between caesarean birth and neonatal mortality, where caesarean section rates were higher than 10%. Inconsistent results for the association between caesarean birth and neonatal mortality were also reported by different studies based on individual-level data conducted in Africa, Latin America, Asia and USA.[15–20] For example, a large study conducted by Villar *et al* in 410 health facilities in 24 areas in eight Latin American countries found that, with cephalic presentation, both intrapartum and elective caesarean were associated with 1.66 (95% CI: 1.26 to 2.20) and 1.99 (95% CI: 1.51 to 2.63) times higher odds of neonatal mortality up to hospital discharge, respectively.[16] However, another study based on WHO global survey completed in nine countries in Asia found that both prelabour (adjusted odds ratio (aOR) 0.2 (95% CI: 0.1 to 0.3)) and intrapartum caesarean sections (aOR 0.3, 95% CI: 0.2 to 0.4) were associated with improved perinatal outcomes following breech presentation.[15]

On the other hand, using both country-level and individual-level data collected for nationally representative Demographic and Health Surveys (DHS), Kyu *et al* found an increased risk for neonatal death associated with caesarean versus vaginal births in countries with low (<5%) and medium (5%–15%) caesarean section rates.[21] However, factors associated with caesarean section that increase risk for neonatal death in countries with low and moderate caesarean section rates remain ill-defined. Previous studies are limited by either inconsistent results or lack the interpretation of findings by considering the contextual factors.[11–21] In addition to the underlying indications for caesarean interventions like 'fetal distress', 'cord prolapse', 'prolonged and obstructed labour', 'fetal mal-presentation', 'major antepartum haemorrhage' and 'placenta praevia',[22 23] several contextual factors such as unequal access, infrastructural and health workforce constraints could play a role in the association between caesarean section and neonatal death.

In low-income and middle-income countries, the DHS are the most representative and widely available high-quality data sources for studies related to maternal and child health. We use Ethiopian DHS data from 2000, 2005, 2011 and 2016 to examine the changing temporal association between caesarean birth and neonatal death. We then apply the 'Three Delays Model' developed by Thaddeus and Maine[24] to facilitate the interpretation of the association between caesarean birth and neonatal death in Ethiopia using the 2016 data.

METHODS

Study design and data samples

We used data from the Ethiopian DHS completed in 2000, 2005, 2011 and 2016. The Ethiopian DHS are nationally representative cross-sectional surveys conducted in nine regional states (Tigray, Affar, Amhara, Oromia, Somali, Benishangul-Gumuz, SNNPR, Gambela and Harari) and two city administrations (Addis Ababa and Dire Dawa). Each of the surveys involved a two-stage, stratified, clustered sampling design. The survey datasets are deidentified and made freely available online. Permission to use these data was granted by the DHS Program. The details about the methodology and standards for protecting the privacy of study participants in all DHS can be accessed online (http://www.dhsprogram.com/What-We-Do/methodology.cfm).

Exposure

The DHS questionnaire asks women about pregnancy, antenatal and delivery care for live births they have reported in the past 5 years. The data on caesarean section and other variables in the DHS were collected based on mothers' self-report. For example, the self-reported data on caesarean section were collected by asking mothers a question that reads, 'Was (NAME) delivered by caesarean section, that is, did they cut your belly open to take the baby out?' in the 2016 survey. Stanton and colleagues[25] in their study demonstrated that the DHS caesarean section rates, compared with facility-based records of caesarean section rates, are reliable for national and global monitoring in developing countries. For this study, the exposure group were infants delivered by caesarean section and unexposed group comprised infants born vaginally.

Outcome

Neonatal death includes infants who were born alive in the 5 years before each survey, but died within the first 28 days of life. The outcome variable, neonatal death, was measured from two variables (whether the child is alive and age at death (in days)).

Confounding

The following potential confounders were identified based on a priori subject-matter and expert knowledge. They included place of delivery (public, private, non-governmental organisation and home), type of residence (urban/rural), sex of child (male/female), size of baby at birth (very large, larger than average, average, smaller than average, very small and do not know), mother's age at birth (in years), mother's education (no education, primary, secondary and higher), birth order (1, 2–3 and

4+) and household wealth quintile (poorest, poorer, middle, richer and richest). The size of baby at birth was assessed based on mother's perception (estimate) of baby size at birth. It has previously been shown that, in the absence of complete enumeration of birth weight, mother's perception of baby size at birth can be used as a proxy to birth weight in nationally representative surveys.[26] Mother's age at birth was calculated as a difference (in years) between infant's date of birth and mother's date of birth. The DHS computes the wealth index for each survey based on household assets using principal components analyses[27] and categorises households into wealth quintiles. These asset-based measures represent the wealth distribution relative to other households within the country. They are widely used and are consistent with comparisons to household expenditures and the measurement of inequalities in child mortality, education and healthcare use in low-income and middle-income countries.[28]

Statistical analysis

Missing information is uncommon in DHS because the data are collected by a trained interviewers at a face-to-face interview. All analyses (ie, Ethiopian DHS 2000, 2005, 2011 and 2016) were weighted to be nationally representative. As women may have had more than one births within the 5-year survey periods, we also accounted for both clustering of caesarean deliveries within women as well as the complex survey design during the data analyses using the unit of analysis (ie, children) study number and sample weights. We then conducted both individual-level and aggregate-level analyses. Our 2016 data analysis was also supplemented by an application of the 'Three Delays Model' to interpret the association between caesarean birth and neonatal death both empirically and theoretically. All analyses were conducted using STATA/SE V.15.1 (Stata Corporation).

Individual-level analysis

Associations between caesarean birth and neonatal death at individual-level were analysed using log-Poisson regression models using data from Ethiopian DHS conducted in 2000, 2005, 2011 and 2016. We calculated unadjusted and adjusted prevalence ratios (aPR) and their 95% CIs for each survey. We have then compared the strength of association between caesarean birth and neonatal death across all surveys analysed.

After noting the increasing association between caesarean birth and neonatal death over time, we conducted a series of analyses to explore what was during the change. We used the 2016 data because the association was more pronounced. We first restricted the analysis to participants living in regions with the highest caesarean section rates to examine whether the increased access to caesarean section affected the proportion of neonatal deaths. We then estimated the effect of caesarean birth on neonatal death in regions with low caesarean section rate (ranged: 0.4%–5.3%) or where access to caesarean section is limited, by excluding births in relatively high caesarean section rate regions—Addis Ababa (21.4%) and Harari (9.0%).[29] Both low-level and high-level of caesarean use has risks exceeding the risks of spontaneous vaginal deliveries.[15 30] It was demonstrated that low levels of caesarean are related to lack of access and can contribute to maternal and newborn deaths.[21 31]

Given the very large rural–urban differences in caesarean section rates in Ethiopia,[29 32] we also conducted similar analyses separately for rural women. In addition, we evaluated the association by restricting the analyses to births from the lowest quintile of household wealth, births from the highest quintile of household wealth, and births in public health facilities separately. These alternative analyses were exploratory in nature and helped us understand contextual factors leading to inequalities in caesarean use that may occur not only due to inadequate access among the poorest women, but also due to overuse among the richest population subgroups.[33 34] The subgroup analyses allowed us to explain how contextual factors such as unequal access, infrastructural and workforce constraints could play role in the association between caesarean section and neonatal death because these factors will result in delay in accessing emergency caesarean section, which is usually accessible at specialised health facilities.

The 2016 DHS included an additional question regarding 'timing of decision to conduct caesarean section (ie, whether it was before or after the onset of labour pains)'. We used this variable as a proxy to the types of caesarean birth (indicative of intrapartum or prelabour caesarean section) and conducted analysis to examine the association between types of caesarean section and neonatal death. As this was confined only to 2016 data, we have provided the results in online supplementary table A1.

Aggregate-level analysis

Data on the caesarean section rates and proportion of neonatal deaths were disaggregated by urban–rural areas for each of the nine regional states and two city administrations in Ethiopia for each of the surveys completed in 2000, 2005, 2011 and 2016. However, the urban–rural stratification for Addis Ababa is only available for the 2005 survey. These results in a total of 85 data points (observations). In order to assess the correlation between caesarean section and neonatal death at the aggregate level, we conducted simple linear regression for overall surveys together and for individual surveys separately.

Application of the 'Three Delays Model'

The 'Three Delays Model' is a conceptual framework developed by Thaddeus and Maine to examine factors contributing to maternal mortality with specific focus on those that affect the 'interval between the onset of obstetric complication and its outcome'.[24] The 'Three Delays Model' summarises the various factors that affect *this interval* into three phases of delay—delay in deciding to seek care (*phase I delay*); delay in identifying and reaching medical facility (*phase II delay*); and delay in receiving adequate and appropriate treatment (*phase III delay*). Some of the key factors that shape the model include status of women; distance from health facility; availability and cost of transportation; condition of roads; distribution of health facilities; shortage of supplies, equipment and skilled birth attendants and adequacy of referral system.[24] The pictorial presentation of the 'Three Delays Model' is provided in online supplementary figures A1–A4.

As maternal and neonatal mortality share many risk factors, we adopted the 'Three Delays Model' as a framework to help interpret the association between caesarean birth and neonatal mortality within the context of Ethiopia using the 2016 survey because factors contributing to the 'three delays' aggravate the underlying medical indications for caesarean intervention that make neonatal death difficult to prevent. The 2016 survey was selected for interpretation of the association between caesarean birth and neonatal death using the 'Three Delays Model' because the association was more pronounced in the 2016 data. Previous studies conducted in India,[35] Tanzania[36] and Uganda[37] have applied the 'Three Delays Model' to their analyses of perinatal deaths.

We have identified some contributing factors underlying the 'Three Delays Model' from the 2016 survey. For example, information regarding problems faced by women of reproductive age (15–49 years) in accessing healthcare to obtain medical advice or treatment for themselves when they are sick were gathered. It consisted of four questions: distance to health facility (big problem/not big problem); getting money for treatment (big problem/not big problem); getting permission to go for treatment (big problem/not big problem) and not wanting to go alone (big problem/not big problem). Furthermore, data on skilled assistance during delivery, and women's socioeconomic and demographic status are also available in the DHS. This information can particularly be important to understand and address the barriers that women face in seeking care during pregnancy and delivery.[32] We have, therefore, analysed the 2016 data to describe these factors empirically in the context of Ethiopia.

Patient and public involvement

This research was done without patient involvement in setting the research question or the outcome measures, and in the design and implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of this research to study participants or the relevant patient community.

RESULTS

Table 1 shows the characteristics of mothers and children according to mode of delivery for each of the surveys conducted in 2000, 2005, 2011 and 2016. Across the four DHS waves, women who underwent caesarean delivery were more likely to live in urban areas, had a higher level of education and were from the richest quintile of household wealth. They were also more likely to have male children. Caesarean deliveries were more frequent in women in the age category of 20–29 years, and among infants who had either very large or larger than average size of baby at birth. Figure 1 shows that the proportion of institutional deliveries increased from 5.0% in 2000 to 26.3% in 2016, whereas the national caesarean section rate increased from 0.7% in 2000 to 1.9% in 2016. However, the rate of caesarean delivery in Ethiopia varied widely across administrative regions (figure 2). For instance, Addis Ababa had the highest (21.4%) rate, while Somali had the lowest (0.4%) in 2016. The national proportion of neonatal deaths decreased from 4.8% in 2000 to 2.9% in 2016 (figure 1), but the proportion varies among administrative regions of Ethiopia (online supplementary table A2).

Table 2 shows that the aPR for neonatal death associated with caesarean versus vaginal births in 2000 survey was 0.95 (95% CI: 0.29 to 3.19) while in 2005, it was 1.53 (95% CI: 0.52 to 4.50). In 2011, the aPR for neonatal death associated with caesarean versus vaginal births was 1.15 (95% CI: 0.45 to 2.93), while it was 2.81-fold higher risk of neonatal death (aPR, 2.81; 95% CI: 1.11 to 7.13) in 2016.

Table 3 summarises the findings of the subgroup analyses based on the 2016 data. When women living in urban settings—Addis Ababa (caesarean section rate (21.4%)) and Harari (9.0%)—were excluded from the analyses, the corresponding aPR for neonatal death was increased to 3.55 (95% CI: 1.31 to 8.56). Similarly, when we restricted the analyses to include only rural women, the prevalence ratio for neonatal death associated with caesarean versus vaginal births was found to be 3.43 (95% CI: 1.22 to 9.67). The respective risk of neonatal death increased to 7.01 (95% CI: 0.92 to 53.36) when the analysis was limited to women from the lowest quintile of household wealth.

When we restricted the analyses to Addis Ababa, the capital of Ethiopia, the relative risk for neonatal death associated with caesarean versus vaginal births was 1.07 (95% CI: 0.20 to 5.73). Moreover, when the analysis was confined to women from the highest quintile of the household wealth, the risk of neonatal death was 2.72 (95% CI: 0.55 to 13.38).

Finally, figure 3 shows that an increase in caesarean section rate is weakly correlated with a decrease in the proportion of neonatal deaths (correlation coefficient (r)=–0.1839) when aggregate-level data for all surveys together were analysed. However, the relationship between caesarean birth and neonatal death is variable when the analysis is restricted to each survey year separately (figure 4).

Interpretation

The primary individual-level analyses showed that the aPR for neonatal death associated with caesarean versus

Table 1 Characteristics of the study participants according to the mode of delivery, Ethiopia DHS 2000, 2005, 2011 and 2016

	Mode of delivery							
	DHS 2000		DHS 2005		DHS 2011		DHS 2016	
	Caesarean (n=86) %	Vaginal (n=12 174) %	Caesarean (n=111) %	Vaginal (n=11 052) %	Caesarean (n=175) %	Vaginal (n=11 697) %	Caesarean (n=213) %	Vaginal (n=10 810) %
Neonatal death								
Yes	4.5	4.8	6.7	3.9	5.5	3.7	8.3	2.7
No	95.5	95.2	93.3	96.1	94.5	96.3	91.7	97.3
Types of residence								
Urban	76.2	9.9	68.8	6.7	70.9	12.0	60.4	10.1
Rural	23.8	90.1	31.2	93.3	29.1	88.0	39.6	89.9
Region								
Tigray	4.0	6.4	5.4	6.3	12.5	6.2	6.8	6.5
Affar	2.5	1.0	0.6	1.0	1.4	1.0	0.4	1.0
Amhara	3.7	26.3	15.2	23.6	19.4	22.4	22.1	18.7
Oromia	46.3	40.7	28.5	39.6	14.6	42.6	21.2	44.5
Somali	2.3	1.2	4.2	4.3	1.4	3.1	1.0	4.7
Benishangul-Gumuz	3.1	1.0	0.1	0.9	1.0	1.2	0.6	1.1
SNNPR	18.5	21.2	21.6	22.4	17.4	21.1	21.0	20.8
Gambela	0.6	0.2	0.5	0.3	2.0	0.3	0.2	0.2
Harari	0.9	0.2	0.7	0.2	1.2	0.2	1.1	0.2
Addis Ababa	16.9	1.4	22.1	1.2	27.6	1.5	24.5	1.8
Dire Dawa	1.1	0.3	1.2	0.3	1.4	0.3	1.2	0.4
Mother's age at birth								
<20	19.4	12.0	13.3	13.4	10.5	10.9	6.4	10.0
20–29	70.8	51.3	59.8	51.2	62.8	55.7	58.4	54.6
30–39	9.8	30.0	24.1	29.3	23.7	28.7	31.7	30.9
40–49	0.0	6.7	2.9	6.2	3.3	4.7	3.4	4.5
Mother's education								
No education	15.7	82.5	30.1	79.7	19.9	70.0	22.8	66.9
Primary	21.8	13.0	14.5	16.6	44.7	26.8	35.1	26.6
Secondary	56.4	4.3	46.5	3.4	22.2	1.9	15.3	4.5
Higher	6.2	0.2	8.9	0.3	13.2	1.2	26.8	2.0
Place of delivery*								
Public	96.3	4.0	90.2	3.9	83.5	7.6	84.0	23.6

Continued

Table 1 Continued

	Mode of delivery							
	DHS 2000		DHS 2005		DHS 2011		DHS 2016	
	Caesarean (n=86) %	Vaginal (n=12 174) %	Caesarean (n=111) %	Vaginal (n=11 052) %	Caesarean (n=175) %	Vaginal (n=11 697) %	Caesarean (n=213) %	Vaginal (n=10 810) %
Private	1.3	0.1	5.9	0.3	13.6	0.8	13.7	0.9
NGO	2.4	0.2	3.8	0.1	3.0	0.2	2.4	0.2
Home	0.0	95.6	0.0	95.7	0.0	91.4	0.0	75.2
Birth order								
1	75.5	18.6	53.2	17.0	53.5	18.5	41.4	18.2
2	17.5	16.5	26.0	15.5	17.0	17.0	25.6	16.0
3	2.2	13.7	5.7	14.5	10.3	14.2	18.2	14.2
4	1.0	11.3	1.5	12.9	6.0	12.6	3.3	12.5
5	0.6	10.4	2.2	10.8	8.4	10.5	5.3	11.4
6+	3.2	29.5	11.4	29.4	4.7	27.2	6.3	27.6
Sex of child								
Male	61.8	51.2	51.3	51.3	57.2	51.9	54.0	51.9
Female	38.2	48.8	48.7	48.7	42.8	48.1	46.0	48.1
Size of baby at birth†								
Very large	9.8	5.3	30.7	22.3	25.8	19.2	26.5	17.6
Larger than average	32.0	25.4	11.4	9.5	11.7	12.7	16.0	13.8
Average	34.6	35.7	37.4	40.0	42.3	38.2	36.1	41.7
Smaller than average	19.7	27.5	9.4	7.3	4.9	8.7	7.0	10.1
Very small	3.7	5.9	9.5	20.6	14.8	20.6	12.7	16.0
Do not know	0.2	0.2	1.1	0.4	0.6	0.4	1.7	0.8
Wealth quantile								
Poorest	1.9	21.1	0.6	22.1	2.0	23.1	7.2	24.2
Poorer	4.9	21.0	5.9	21.3	8.4	22.6	12.2	23.1
Middle	4.1	22.0	3.9	22.5	9.0	20.7	10.8	20.9
Richer	6.1	20.5	9.7	20.0	6.5	19.3	9.3	18.3
Richest	83.0	15.5	79.9	14.2	74.1	14.2	60.4	13.5

n=weighted.
*Missing for 2000 (n=9).
†Mother's estimate of baby's size at birth.
DHS, Demographic and Health Survey; NGO, Non-governmental Organisation.

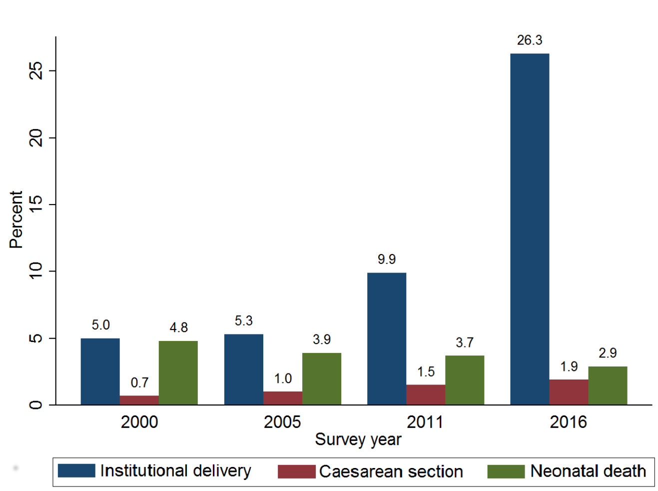

Figure 1 Trends in proportion of institutional deliveries, caesarean section and neonatal death in the 5 years before each of the surveys, Ethiopia DHS 2000, 2005, 2011 and 2016.

vaginal births increased from 0.95 (95% CI: 0.29 to 3.19) in 2000 to 2.81 (95% CI: 1.11 to 7.13) in 2016. These findings suggest that the circumstances for foetuses born in 2000 survey were different from the foetuses in 2016. Our subgroup analyses using 2016 data suggest that the association between caesarean birth and neonatal death was stronger among rural women (aPR (95% CI) 3.43 (1.22 to 9.67)) and among women from the lowest quintile of household wealth (aPR (95% CI) 7.01 (0.92 to 53.36)), but not for births in areas with wider availability of caesarean such as Addis Ababa (aPR (95% CI) 1.07 (0.20 to 5.73)). The changing association between caesarean birth and neonatal death over time, and the stronger association observed among different subgroup analyses may be attributable to changes in the pattern of confounding by indication due to contextual factors such as unequal access, structural health-system deficiencies (insufficient equipment, supplies and drugs), infrastructural and health workforce constraints.

The national caesarean section and institutional delivery rates in Ethiopia are still low though increases in the past decade are notable. There is also substantial disparity in caesarean section rates, with very low rates in rural areas and among the poorest women,[29] suggesting unequal access which may be as a consequence of a range of geographic, social and economic barriers. The low caesarean rates may also be due to lack of skilled birth attendants, and poor health infrastructure (eg, shortage of medical care institutions, deficiencies in surgical facilities, surgical and anaesthesia personnel and equipment, and blood transfusion capacity).[38–40] For instance, in Ethiopia, there are only 820 obstetricians, 10 846 general practitioners, 996 emergency obstetric surgeons, 6 345 health officers, 41 009 nurses, 8 635 midwives, 233 anaesthesiologists and 33 320 health extension workers for the population of over 90 million in 2015.[41] Similarly, there are only 3 547 functional health centres, 16 447 functional health posts and 189 functional hospitals in 2015.[42]

We know from previous research that inadequate access to timely caesarean section may result in perinatal asphyxia, uterine rupture, obstructed labour, and these can contribute to maternal and newborn deaths.[43] Conversely, it was demonstrated that maternal and neonatal mortality due to obstetric complications can be prevented with

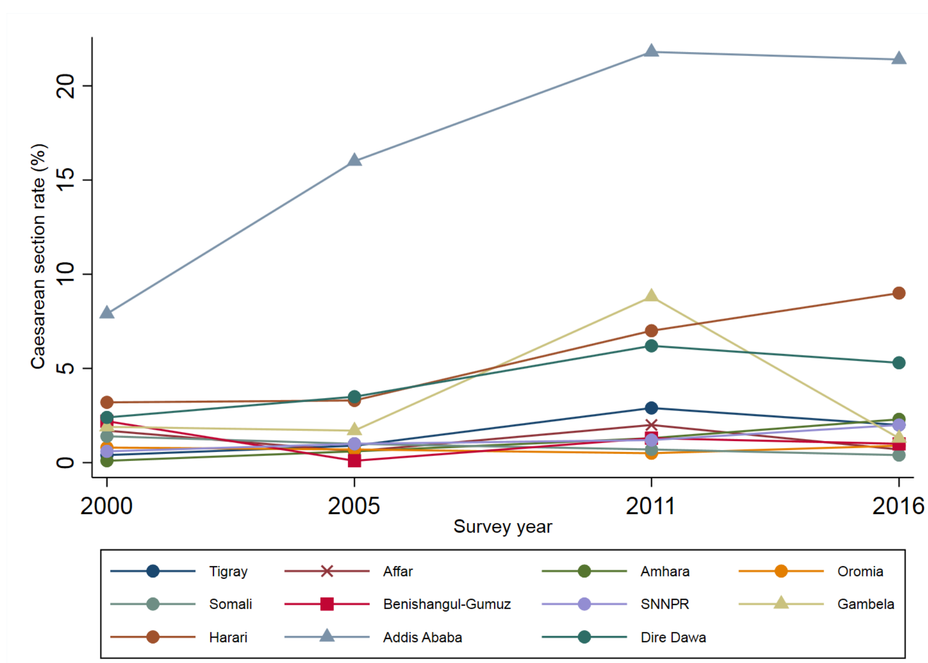

Figure 2 Trends in caesarean section rates in the 5 years before each of the surveys according to the nine regional states and two city administrations, Ethiopia DHS 2000, 2005, 2011 and 2016.

Table 2 Crude and multivariable-adjusted prevalence ratios for neonatal death associated with caesarean versus vaginal delivery, Ethiopia DHS 2000, 2005, 2011 and 2016

	Prevalence ratio (95% CI) for neonatal death
Ethiopia DHS 2000	
Vaginal delivery	1 (*Ref.*)
Caesarean delivery, crude (n=10 873)	0.93 (0.38 to 2.30)
Caesarean delivery, model 1* (n=10 853)	0.95 (0.29 to 3.19)
Ethiopia DHS 2005	
Vaginal delivery	1 (*Ref.*)
Caesarean delivery, crude (n=9 861)	1.74 (0.67 to 4.51)
Caesarean delivery, model 1* (n=9 861)	1.53 (0.52 to 4.50)
Ethiopia DHS 2011	
Vaginal delivery	1 (*Ref.*)
Caesarean delivery, crude (n=11 654)	1.49 (0.62 to 3.61)
Caesarean delivery, model 1* (n=11 654)	1.15 (0.45 to 2.93)
Ethiopia DHS 2016	
Vaginal delivery	1 (*Ref.*)
Caesarean delivery, crude (n=10 641)	3.02 (1.37 to 6.66)
Caesarean delivery, model 1* (n=10 641)	2.81 (1.11 to 7.13)

*Adjusted for place of delivery, type of residence (urban/rural), sex of child, size of baby at birth, mother's age at birth, mother's education, birth order and household wealth.
DHS, Demographic and Health Surveys.

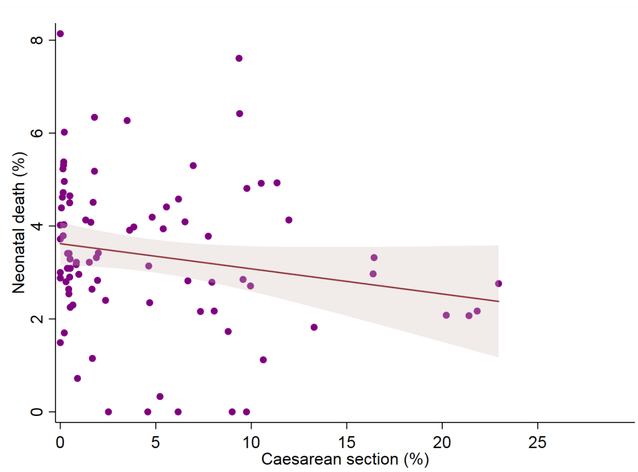

Figure 3 The relationship between caesarean section rate and neonatal death in Ethiopia (2000 to 2016).

Table 3 Crude and multivariable-adjusted prevalence ratios for neonatal death associated with caesarean versus vaginal delivery, Ethiopia DHS 2016

	Prevalence ratio (95% CI) for neonatal death
Main analysis	
Vaginal delivery	1 (*Ref.*)
Caesarean delivery, crude (n=10 641)	3.02 (1.37 to 6.66)
Caesarean delivery, model 1* (n=10 641)	2.81 (1.11 to 7.13)
Subgroup analyses	
Restricted to Addis Ababa† (n=461)	1.07 (0.20 to 5.73)
Excluded Addis Ababa and Harari* (n=9 575)	3.35 (1.31 to 8.56)
Restricted to births in public facility* (n=3 023)	2.78 (1.16 to 6.63)
Restricted to rural mothers† (n=8 636)	3.43 (1.22 to 9.67)
Restricted to women from lowest quintile of household wealth‡ (n=3 958)	7.01 (0.92 to 53.36)
Restricted to women from highest quintile of household wealth‡ (n=2 092)	2.72 (0.55 to 13.38)

*Adjusted for place of delivery, type of residence (urban/rural), sex of child, size of baby at birth, mother's age at birth, mother's education, birth order and household wealth.
†Adjusted for place of delivery, sex of child, size of baby at birth, mother's age at birth, mother's education, birth order and household wealth.
‡Adjusted for place of delivery, sex of child, size of baby at birth, mother's age at birth, mother's education and birth order.

timely access to caesarean section.[43 44] Delay, therefore, emerges as relevant factor in worsening the underlying obstetric indications for caesarean intervention thereby contributing to neonatal death. Context-specific factors that delay access to caesarean section may have the capacity to make women with labour problems undergo caesarean section after severe complication of labour or severe foetal compromise. Therefore, our interpretation is that caesarean section conducted after severe foetal compromise may not prevent neonatal deaths because they have already experienced such severity of complications that although live born, neonatal death is difficult to prevent.

There are two possible scenarios leading to caesarean section in Ethiopia. First, when women who have previously had a caesarean section, with breech presentation, or other risk factors such as eclampsia attend specialised health facilities, they are usually allowed to undergo caesarean section. Their caesarean section is commonly classified as 'elective or scheduled caesarean section'. Second, when caesarean section is performed for 'emergency reasons'. Full-term mothers with or without signs of labour will be admitted to health facilities where their progress is monitored and labour-augmenting or inducing medications may be administered. Decisions to perform caesarean section in these facilities or decision to refer

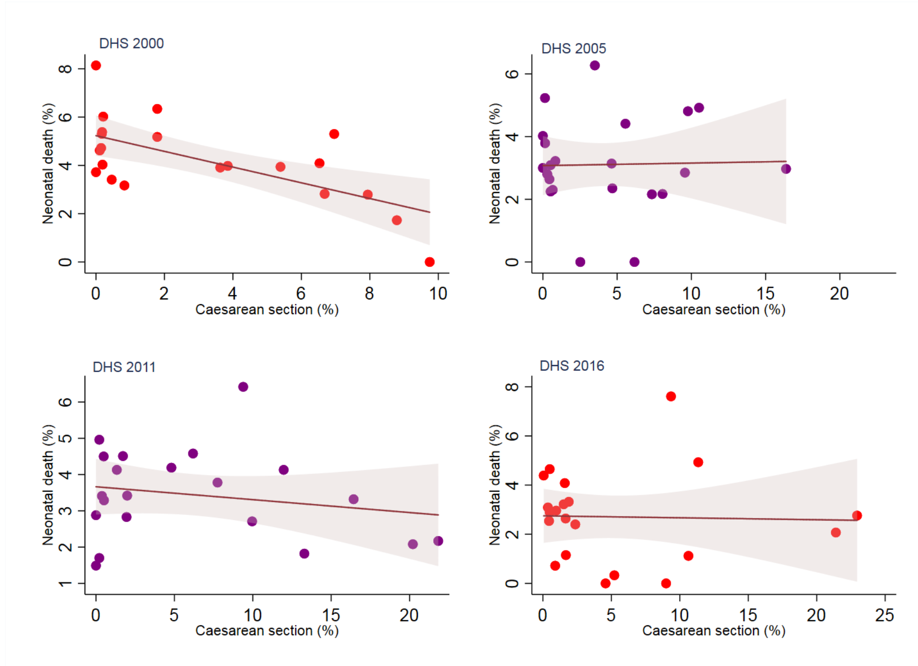

Figure 4 The relationship between caesarean section rate and neonatal death by survey years.

the mother to nearby hospitals for caesarean delivery or other action depends on the condition of the mother and fetus during the progress of labour. In primary health facilities (ie, health posts and health centres), obstetric care providers usually use a 'Partograph',[45 46] a routine labour monitoring instrument (chart) which helps the healthcare providers to identify slow progress in labour and take appropriate action. In hospitals, the decision to perform a caesarean section is reached when the labour is prolonged and/or the second stage of labour is complicated risking the life of mother and fetus.

Given these pathways to caesarean delivery in mind, our interpretation of the association between caesarean birth and neonatal death in Ethiopia using the 2016 survey may be shaped by examining factors contributing to delays in the 'Three Delays Model'. This is because delays to caesarean section aggravate the underlying medical indications for caesarean intervention. Table 4 shows factors affecting the length of delays in the 'Three Delays Model' according to sociodemographic characteristics in the 2016 survey.

Phase I delay: deciding to seek care

In Ethiopia, poorer and less-educated women are more likely to select a nearby health facility, especially in rural areas, where there is limited access to caesarean section and the possibility of benefiting from caesarean section is mainly through referral to higher levels of care. Women are more likely to undergo a caesarean section if they present to specialised health facilities. However, the outcome of delivery depends on how quick/competent the healthcare provider is in referring the mother or on intervening, and the severity of the underlying obstetric complications for caesarean intervention which may be affected by the delay in women's or family's decision to seek care. Poor health decision-making depends on numerous factors such as educational status, distance to health facility, economic status, sociocultural factors (eg, unsupportive spouse and lack of autonomy) and quality of care.[24 47 48]

Table 4 shows that 'distance to health facility' was a big problem in accessing healthcare for about 60% of rural and 17% of urban women in Ethiopia. Similarly, 'getting money for treatment' is a big problem to access healthcare and was reported by 61% of rural and 35% of urban women in 2016. On the other hand, the status of women in a given society affects the decision to seek care. For instance, efforts to seek timely care are influenced by women's limited mobility because they need permission to travel from spouse and/or mother-in-law.[24] In Ethiopia, about 37% of rural and 15% of urban women reported 'getting permission to go for treatment' was a big problem to access healthcare.

Phase II delay: identifying and reaching a medical facility

Delay in reaching healthcare may occur when women who encounter obstetric complication live farther from health facilities, where the availability and cost of transportation is problematic. In one study conducted in rural India, Kumar *et al*[47] found that health facility births occur less likely among women living farther away from the health facilities, suggesting distance as an important barrier to in-facility births for rural women. In addition to the travel distance, the scarcity of transportation which may be accompanied by poor roads is also another obstacle for women with labour complications to timely reach even the closest health facility. As a result of this, women who arrive at the nearby facility

Table 4 Factors contributing to the 'Three Delays Model', according to sociodemographic characteristics, Ethiopia DHS 2016

	Delivery by skilled provider*	Number of births	Problems in accessing healthcare by women aged 15–49 years†					
			Distance to health facility	Getting money for treatment	Getting permission to go for treatment	Not wanting to go alone	At least one problem accessing healthcare	Number of women
Types of residence								
Urban	80.1	1 216	17.0	34.7	15.1	21.4	45.6	3 476
Rural	21.2	9 807	59.8	60.5	37.0	47.9	76.9	12 207
Region								
Tigray	59.3	716	37.4	46.1	15.3	24.6	60.7	1 129
Affar	16.4	114	54.3	51.7	28.2	41.8	66.6	128
Amhara	27.7	2 072	33.7	35.3	15.4	34.6	55.7	3 714
Oromia	19.7	4 851	68.9	70.1	58.3	57.0	82.9	5 701
Somali	20.0	508	47.3	63.0	25.7	32.2	72.6	459
Benishangul-Gumuz	28.6	122	57.4	62.4	36.5	43.8	76.8	160
SNNPR	28.6	2 296	52.7	59.1	18.4	39.5	75.4	3 288
Gambela	46.9	27	41.0	44.3	24.3	33.7	61.2	44
Harari	51.2	26	18.1	28.2	16.3	13.8	30.8	38
Addis Ababa	96.8	244	10.8	29.2	8.7	14.5	40.0	930
Dire Dawa	56.7	47	57.4	64.5	58.7	55.2	71.4	90
Mother's education								
No education	17.2	7 284	59.2	62.9	37.6	47.1	78.0	7 498
Primary	38.6	2 951	50.3	55.7	31.9	43.2	71.1	5 490
Secondary	78.4	514	27.8	33.2	18.2	27.8	48.1	1 817
More than secondary	93.2	274	20.6	23.8	15.9	20.4	39.8	877
Wealth quintile								
Poorest	11.0	2 636	67.7	70.9	40.0	54.5	85.3	2 633
Poorer	20.8	2 520	66.8	67.0	42.1	52.7	82.9	2 809
Middle	24.2	2 280	59.4	61.0	35.2	47.6	77.3	2 978
Richer	28.5	1 999	49.8	50.2	33.8	41.2	68.2	3 100
Richest	70.3	1 588	22.1	35.2	17.0	23.4	47.7	4 163
Total	27.7	11 023	50.3	54.8	32.1	42.0	70.0	15 683

*Percentage delivered by a skilled provider (ie, doctor, nurse, midwife, health officer and health extension worker).
†Percentage of women aged 15–49 who reported that they have serious problems in accessing healthcare for themselves when they are sick, by type of problem, according to sociodemographic characteristics, Ethiopia DHS 2016.

following obstetric complications probably will travel further to specialised hospital due to emergency referral. It is clear that the obstetric complications encountered by mothers reaching nearby primary health facilities will be compounded by additional delays when they are referred for caesarean section. These scenarios highlight the likelihood of adverse delivery outcome followed by aggravated obstetric complications due to delays in reaching medical facility as high.

In Ethiopia, about 50% of women of reproductive age (15–49 years) reported 'distance to health facility' as a big problem to access healthcare (table 4). Moreover, access to caesarean situation in Ethiopia is worse than in most other settings.

Phase III delay: receiving adequate and appropriate treatment

Phase III delays occur within any health facilities and are indicators of inadequate care due to lack of facilities; inadequately trained obstetric care givers (skilled birth attendants) and deficiencies in surgical facilities, surgical and anaesthesia personnel and equipment, and blood transfusion as well as inadequate and inappropriate referral systems. These deficiencies will limit women's access to lifesaving procedures such as caesarean section. In Ethiopia, only 28.0% of all births were delivered by 'skilled providers' (ie, doctor, nurse, midwife, health officer and health extension worker) in the 2016 survey. Table 4 also shows that there are disparities in the proportion of births attended by skilled birth attendants by urban–rural place of residence, region, level of mother's education and household wealth. It is quite clear that insufficient number of skilled birth attendants at any health facility will lead to delay in receiving appropriate treatment among women with obstetric complications. Although health posts and health centres (primary healthcare unit) are the most accessible to the general population in Ethiopia, they are not fully equipped to deal with obstetric complications.[41 42] As a result of this, women with obstetrics complications will have to travel on to better equipped institutions (secondary and tertiary levels of healthcare) with caesarean section capacity (eg, general hospitals and specialised hospitals) through referral. By the time women reach these well-equipped health facilities, the delays will have further aggravated the obstetric complications on the way. A schematic representation of the Ethiopian health system structure is provided in online supplementary figure A5.

On the other hand, delay in caesarean intervention may even happen if mothers with less severe obstetric complications were referred and presented to specialised health facilities in a timely manner. This is because a trial of labour is usually attempted before a decision to have caesarean section. For instance, some women who are referred from primary health facilities undergo induction and augmentation of labour because these interventions are only provided in health facilities with the capacity to provide caesarean section in Ethiopia. These practices, in turn, will result in delay in receiving caesarean section leading to worsening of the already existing obstetric complications. Thus, any delays to caesarean intervention have a higher chance of aggravating the already existing complications and increase the risk of neonatal death.

DISCUSSION

Our study examined the changing temporal association between caesarean birth and neonatal death within the context of Ethiopia from 2000 to 2016. The association between caesarean section and neonatal death increased over time and was variable among population subgroups. These changes over time, and variation across population subgroups may be attributable to changes in the pattern of confounding by indication due to contextual factors such as improvement in health service coverage, unequal access (eg, due to a range of geographic, social and economic barriers) and structural and health workforce constraints.

In Ethiopia, the proportion of women aged 15–49 years who received any antenatal care from a skilled provider has increased from 27% in 2000 to 62% in 2016.[32] Health facility-based deliveries have increased from 5% in 2000 to 26% in 2016 (increased from 2% in 2000 to 20% in 2016 for rural women, and increased from 32% in 2000 to 79% in 2016 for urban women).[32] The proportion of births in health facilities assisted by skilled birth attendants increased from 6% in 2000 to 28% in 2016.[32] These figures reflect improvement in health service coverage in Ethiopia.

Moreover, since 2003, with the implementation of the Health Extension Program—a community-based primary healthcare program—the Ethiopian government has increased the number of health posts from 4 211 in 2005 to 16 447 in 2015.[42 49] Likewise, the number of health centres was increased from 600 in 2005 to 3 586 in 2015.[42 49] However, due to limitations in proper monitoring of labour for making timely decisions, especially on whether or not to initiate a referral from primary health facilities to higher level facilities, and due to poor transport and road networks which are still the common problems in low-income countries,[50] the underlying medical indications for caesarean intervention will be worsened by factors contributing to 'delays'. Delay in receiving adequate and appropriate care is still a common problem in low-income countries due to deficiencies in surgical facilities, surgical and anaesthesia personnel and equipment, blood transfusion capacity and shortage of skilled birth attendants.[51–53] There is also an inequitable distribution of the health workforce across urban and rural areas. For example, the majority of specialist doctors in Ethiopia serve in urban areas, where the total population distribution is only 19.4%.[41 42] These situations often result in poor quality care to rural women, and the caesarean section conducted after a complicated labour may be associated with increased neonatal mortality due to confounding by indication.

Unlike previous studies, the present study takes into account the interpretation of the association between caesarean birth and neonatal death within the context of Ethiopia using DHS data. The change in the strength of effect estimates across DHS waves, and the different subgroup analyses suggest that neonatal mortality can be reduced by increasing timely access to caesarean section and timely decision for caesarean delivery via increasing health service coverage, improving infrastructure (eg, increasing number of health facilities), increasing the number of skilled birth attendants, improving quality of care and increasing awareness about antenatal care and health facility delivery among women. Moreover, provision of training to skilled birth attendants on close monitoring of labour and early detection of complications, equipping the primary health facilities (eg, health centres) to the level of caesarean capacity, and continuous financial investment in primary health facilities will be an important strategy to reduce neonatal mortality.

It appears that previous studies which used individual-level data are more likely to report an increased risk of neonatal death among infants born by caesarean section than the ecological studies. This may be due to the indications for the caesarean delivery (eg, the severity of the underlying causes) was involved in causing both caesarean delivery and neonatal death in studies which used individual-level data, suggesting the role of confounding by indication in the association between caesarean birth and neonatal death because an intended effect of caesarean birth is prevention of neonatal death. Therefore, the increased risk for neonatal death associated with caesarean birth, compared with vaginal birth, would appear to be intuitive given the fact that neonatal death rates after emergency caesarean section is strongly dependent on the underlying medical indication (eg, antenatally diagnosed foetal malformation or foetal growth restriction) for caesarean intervention.

In Ethiopia, the national rate of caesarean section increased from 0.7% in 2000 to 1.9% in 2016. On the other hand, neonatal mortality rate declined from 49 deaths per 1 000 live births in 2000 to 29 deaths per 1 000 births in 2016.[32] Similarly, the pregnancy-related mortality ratio decreased from 871 pregnancy-related deaths per 100 000 live births in 2000 to 412 pregnancy-related deaths per 100 000 live births in 2016.[32] Our analyses based on aggregate-level data from Ethiopian DHS showed that an increase in caesarean section rate is correlated with a decrease in the proportion of neonatal deaths. Even though similar context-specific interpretation is applicable to ecological studies, additional explanation may also be necessary to interpret the association. For example, a change in neonatal mortality rate may be attributable to changes acting on the population as a whole—that is, changes in health coverage indicators, such as an increase in births attended by skilled birth attendants (increased from 6% in 2000 to 28% in 2016)[32] and immunisation coverage (was 86.4% in 2015).[42]

We acknowledge the following limitations of this study. First, as both the proportion of institutional deliveries and caesarean section rate is low in Ethiopia, especially in rural areas, the number of neonatal deaths following caesarean section may be low. However, since our analyses are weighted, we believe that the weight improves the representativeness of the data in terms of size, distribution and characteristics of the Ethiopian population. The weight may also ensure that our estimates are unbiased though the CI for some subgroup analyses are somewhat wide. Second, the interpretation of our study is specific to the context of Ethiopia and may not be generalisable to other developing countries in Africa or elsewhere. Another limitation is the mother's recall of the child's size at birth was used as a substitute for the child's birth weight in this study because the data for birth weight were not collected for more than 50% of the neonates in DHS.

CONCLUSIONS

A naïve interpretation of the changing temporal association between caesarean birth and neonatal death from 2000 to 2016 is that caesarean section is increasingly associated with neonatal death. However, the changing temporal association likely reflects improvements in health service coverage and secular shifts in the characteristics of Ethiopian women undergoing caesarean section after complicated labour or severe foetal compromise.

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Chapter 6: Impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa

6.1 Preface

This chapter contains the third of the five studies contributing to this thesis. The study was published in *BMJ Open* in 2019.

The previous chapter, Chapters 5, of this thesis examined the association between caesarean birth and neonatal mortality from the perspective of one country's context and suggests that timely access and timely caesarean intervention is important to reduce neonatal mortality in Ethiopia. Chapter 6 expands on caesarean section, as one of the most common obstetrical interventions during childbirth, and examined the consequences of caesarean section on three different breastfeeding outcomes—early initiation of breastfeeding within one hour, exclusive breastfeeding under 6 months and children ever breastfed (at least once)—in 33 countries in sub-Saharan Africa. This chapter presents the results of novel analysis on the effect caesarean section on breastfeeding outcomes (indicators), which were analysed in two phases. In the first phase, to understand how the estimates of caesarean section on breastfeeding differ across countries, analyses were conducted for each of the 33 countries in sub-Saharan Africa. As there were three breastfeeding outcomes, three different outcome regression analysis were performed for each country. In the second phase, the evidence (estimates) from each of the 33 countries were summarized in an overall estimate using random-effects meta-analysis for each breastfeeding outcome.

As there is no previous studies that have comprehensively assessed the impact of caesarean section on breastfeeding indicators in sub-Saharan Africa covering a large number of countries, this article (Study 3) addresses an important research gap. Study 3 also provides high-quality public health evidence regarding the link between caesarean section and breastfeeding from the perspective of low-and middle-income countries in sub-Saharan Africa.

6.2 Publication

Yisma E, Mol BW, Lynch JW, Smithers LG. Impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa**.** *BMJ Open* 2019; **9**(9): e027497.

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Name of Principal Author (Candidate)	Engida Yisma		
Contribution to the Paper	Conceived and designed the study, performed the statistical analysis, interpreted the data, and drafted the manuscript.		
Overall percentage (%)	85%		
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	5-Aug-2020

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.

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Impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa

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ABSTRACT

Objective To examine the impact of caesarean section on breastfeeding indicators—early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed (at least once)—in sub-Saharan Africa.

Design Secondary analysis of Demographic and Health Surveys (DHS).

Setting Thirty-three low-income and middle-income countries with a survey conducted between 2010 and 2017/2018.

Participants Women aged 15–49 years with a singleton live last birth during the 2 years preceding the survey.

Main outcome measures We analysed the DHS data to examine the impact of caesarean section on breastfeeding indicators using the modified Poisson regression models for each country adjusted for potential confounders. For each breastfeeding indicator, the within-country adjusted prevalence ratios (aPR) were pooled in random-effects meta-analysis.

Results The within-country analyses showed, compared with vaginal birth, caesarean section was associated with aPR for early initiation of breastfeeding that ranged from 0.24 (95% CI 0.17 to 0.33) in Tanzania to 0.89 (95% CI 0.78 to 1.00) in South Africa. The aPR for exclusive breastfeeding under 6 months ranged from 0.58 (95% CI 0.34 to 0.98) in Angola to 1.93 (95% CI 0.46 to 8.10) in Cote d'Ivoire, while the aPR for children ever breastfed ranged from 0.91 (95% CI 0.82 to 1.02) in Gabon to 1.02 (95% CI 0.99 to 1.04) in Gambia. The meta-analysis showed caesarean section was associated with a 46% lower prevalence of early initiation of breastfeeding (pooled aPR, 0.54 (95% CI 0.48 to 0.60)). However, meta-analysis indicated little association with exclusive breastfeeding under 6 months (pooled aPR, 0.94 (95% CI 0.88 to 1.01)) and children ever breastfed (pooled aPR, 0.98 (95% CI 0.98 to 0.99)) among caesarean versus vaginally born children.

Conclusions Caesarean section had a negative influence on early initiation of breastfeeding but showed little difference in exclusive breastfeeding under 6 months and children ever breastfed in sub-Saharan Africa.

Strengths and limitations of this study

- This study used nationally representative Demographic and Health Surveys (DHS) data on a large number of countries (n=33 countries) over a long time period (2010–2017/2018).
- We performed analyses adjusted for potential confounders for each of the 33 countries in sub-Saharan Africa to examine the impact of caesarean section on breastfeeding indicators, and this helped us understand how the estimates (adjusted prevalence ratios) differ across countries.
- In addition to the within-country adjusted analyses, we conducted random-effects meta-analysis to summarise the available evidence regarding the estimate of the impact of caesarean section on breastfeeding indicators in sub-Saharan Africa.
- DHS data do not distinguish whether the caesarean section was medically indicated or not.

INTRODUCTION

Breastfeeding provides protection against infection, prevents neonatal death and improves childhood nutritional status.[1 2] Moreover, breastfeeding has other numerous benefits for newborns, including reduction in risk of diarrhoea and respiratory tract infections, otitis media, asthma and allergies.[1 3–7] Breastfeeding has also been shown to reduce risks of type 2 diabetes,[1 8] breast and ovarian cancer for mothers.[1 9] The World Health Organization (WHO) recommends mothers initiate breastfeeding within 1 hour of birth and exclusive breastfeeding under 6 months of life, with continued breastfeeding together with complementary feeding for 2 years to enhance growth, development and health of the child.[10 11] However, only 37% of infants younger than 6 months are exclusively breastfed in low-income and middle-income countries,[1] suggesting the need for interventions to increase uptake and duration of breastfeeding.

Obstetrical interventions during labour and childbirth, such as caesarean section, influence women's breastfeeding practices and are among the causes for concern, given the rising caesarean section rates worldwide. The breastfeeding experiences of women who underwent caesarean section can be influenced by several factors, including mothers' health and emotional reactions to the surgery as well as infant health and behaviour. For instance, women's restricted mobility in the early days after caesarean birth may hinder efforts to provide basic infant care, including breastfeeding.[12] As the postoperative pain may be severe, particularly in the first 24 hours, it affects the breastfeeding experience of women.[13 14] Likewise, due to the potential for physical separation of the mother and infant, given the higher risk of infant admission to neonatal intensive care unit as a consequence of respiratory disorders, there might be a lesser likelihood of timely initiation of breastfeeding.[15]

On the other hand, it is hypothesised that the hormonal pathway that stimulates 'lactogenesis' may be disturbed by caesarean section due to maternal stress or decreased oxytocin secretion, and this, in turn, may delay milk production.[16–18] As planned caesarean births are usually performed prior to the onset of labour, there is a possibility that decreased breastfeeding initiation may be attributed to these physiological reasons.

Previous evidence suggested that caesarean birth was associated with lower prevalence of early initiation of breastfeeding among mothers. For instance, in a study conducted in Canada, it was demonstrated that fewer women who had planned caesarean birth reported the practice of early initiation of breastfeeding when compared with women who did not have planned caesarean birth or had vaginal birth.[19] Similarly, in a systematic review and meta-analysis involving 53 studies from 33 low-income, middle-income and high-income countries with no country from Africa, it was found that early initiation of breastfeeding was lower among infants delivered by caesarean section (pooled OR, 0.57; 95% CI 0.50 to 0.64) compared with infants born vaginally.[20]

Currently, much of the available evidence regarding the impact of caesarean section on breastfeeding is generated from high-income countries. In low-income and middle-income countries, even though the caesarean section rate is increasing, there is substantial inequalities which may suggest inadequate access among the poorest women and overuse of caesarean section for non-medical indications among the richest population subgroups.[21] Moreover, unequal access to caesarean section due to deficiencies in transport, surgical facilities and shortage of skilled birth attendants will result in delay in accessing emergency caesarean section, which is usually accessible at specialised health facilities, and this may lead to negative outcomes.[22–24] For example, breastfeeding after emergency caesarean section performed due to complicated labour may be more stressful for both mother and baby. However, there is limited insight regarding the impact of caesarean section on breastfeeding indicators—early initiation of breastfeeding (within the first hour), exclusive breastfeeding under 6 months and children ever breastfed (at least once)—in low-income and middle-income countries in sub-Saharan Africa. The purpose of this study was to examine the impact of caesarean section on breastfeeding indicators in 33 countries in sub-Saharan Africa and to summarise the findings in a random-effects meta-analysis by combining the effect estimates analysed individually to provide a consolidated effect estimate of the impact of caesarean section on breastfeeding indicators in sub-Saharan Africa.

METHODS

Data sources

We obtained data from most recent Demographic and Health Surveys (DHS) conducted in 33 sub-Saharan African countries from 2010 to 2017/2018. These countries were selected based on the availability of the most recent standard DHS data in each nation. We restricted our analysis to sub-Saharan Africa to avoid incomparability issues and the time period (2010-2017/2018) was selected to insure enough coverage of a full range of contemporaneous events in DHS within each country (eg, increase in caesarean section rates and changes in breastfeeding practices).

The DHS are widely available high-quality data source in low-income and middle-income countries and are comparable for studies across nations. DHS uses a standardised methodology and identical core questionnaire to collect nationally representative information about sociodemographic characteristics and health indicators such as maternal and child health, nutrition, HIV/AIDS, malaria and family planning. The details about the methodology and standards for protecting the privacy of study participants in all DHS can be accessed from the DHS Program (https://dhsprogram.com/What-We-Do/methodology.cfm). The DHS Program produces the final edited data files and make freely available to data users worldwide. The DHS Country Report, which includes the comprehensive survey results and country survey specificities (ie, sample design, non-response rate, estimates of sampling errors, data quality tables) for each country can also be accessed online (https://dhsprogram.com/publications/publications-by-type.cfm).

Exposure

The DHS questionnaire asks women about pregnancy, antenatal care and methods of delivery, including caesarean section for the most recent birth in the 2 years before the survey. The self-reported data on caesarean section rates collected for DHS, compared with facility-based records of caesarean sections, are found to be reliable in developing countries.[25] In the current study, the exposure group comprised singleton last born children delivered by caesarean section while the unexposed group comprised children born vaginally in the 2 years before the survey.

Outcome

Respondents were asked a number of questions regarding breastfeeding practices, the length of breastfeeding, about children's consumption of liquids and solid food and micronutrient supplementation. Breastfeeding questions included whether the child was ever breastfed; how long after birth before the newborn was put to the breast; whether the baby was given anything to drink or eat other than breast milk; the type of drink given to the child and whether the child was still breastfeeding. Based on this information, three breastfeeding indicator variables—early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed—were computed and used as an outcome of interest for this study. According to the WHO definitions,[11] 'early initiation of breastfeeding' is defined as being put to the breast within an hour of birth. 'Exclusive breastfeeding under 6 months' is consuming only breastmilk (no other fluids or foods) from 0 to 5 months. 'Children ever breastfed' is the proportion of children born in the last 24 months who were ever breastfed (at least once).

Confounding

The following potential confounders were identified based on a priori subject matter and expert knowledge. They included pregnancy planning, birth weight, region of residence, sex of child, mother's age at birth (in years), mother's education, birth order, number of antenatal visits, maternal tobacco use, place of delivery, household wealth quintile, mother's occupation, distance to health facility and urban/rural residence. Mother's age at birth was calculated as a difference (in years) between infant's date of birth and mother's date of birth. DHS computes the wealth index for each survey based on household assets using principal components analyses[26] and categorises households into wealth quintiles. These asset-based measures represent the wealth distribution relative to other households within each country. They are widely used and are consistent with comparisons to household expenditures and the measurement of inequalities in child mortality, education and healthcare use in low-income and middle-income countries.[27] The detail description of the variables included in this study along with Directed Acyclic Graph (DAG) are presented in online web appendices 1–5.

Statistical analysis

All analyses were weighted to be nationally representative and the analyses involved two phases. First, the modified Poisson regression models (using generalised linear model with a log link and a Poisson distribution in STATA[28]) was used for each country to calculate unadjusted and adjusted prevalence ratios (aPR) and their 95% CIs for each breastfeeding indicator (early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed) associated with individual-level caesarean delivery versus vaginal birth. The formula for the modified Poisson regression is given by Zou[29]:

$$log\left[\pi\left(x_i\right)\right] = \alpha + \beta x_i$$

$$l\left(\alpha,\beta\right) = C.\sum_{i=1}^{n}\left[y_i\left(\alpha+\beta x_i\right) - exp\left(\alpha+\beta x_i\right)\right]$$

Second, meta-analyses were done to obtain pooled aPR of these associations for each breastfeeding indicator. To account for between-country variation in effect estimates, we conducted random-effects meta-analysis using inverse variance weighting using 'metan' command in STATA. All the 33 countries data analysed individually were included in the meta-analyses of the effect of caesarean section on early initiation of breastfeeding and children ever breastfed. However, for exclusive breastfeeding under 6 months, data from Chad were unable to be included because of small sample with almost no exclusive breastfeeding under 6 months and the model could not coverage. We used the I^2 to measure statistical heterogeneity and the possible sources of heterogeneity were explored using a post hoc subgroup analyses based on the following subgroups: (1) categorising the countries by region—East Africa, Southern Africa, West Africa and Central Africa; (2) by rate of caesarean section categories—low (<5%), medium (5%–15%) and high (>15%) and (3) by prevalence of early initiation of breastfeeding categories—≤50% and>50%. The subcategories for geographic regions are according to United Nations geoscheme while the subcategories for caesarean section rates and prevalence of early initiation of breastfeeding were decided based on a previous study[30] and expert opinion, respectively. All analyses in this study were conducted using STATA/SE V.15.1 (Stata Corporation).

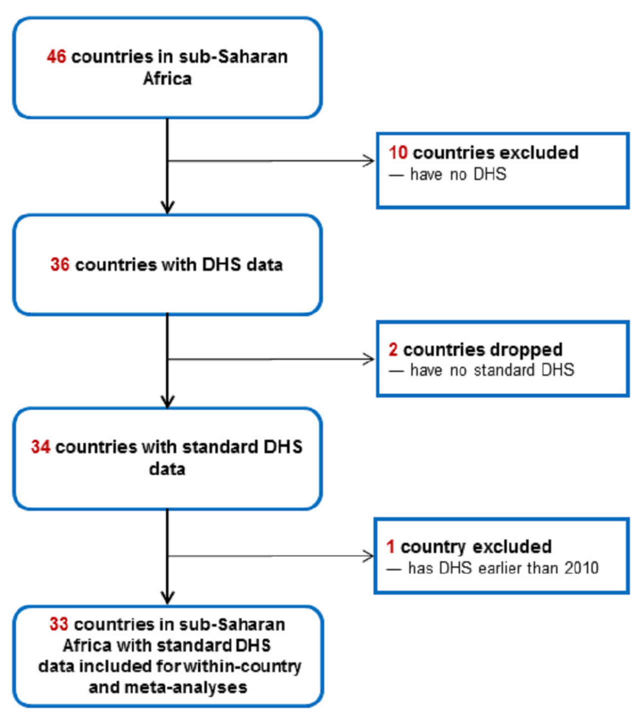

Figure 1 Flow scheme for country selection based on inclusion and exclusion criteria. DHS, Demographic and Health Surveys.

Table 1 Among last-born children who were born in the last 2 years before the survey, percentage of live singleton births delivered by caesarean section, prevalence of early initiation of breastfeeding, prevalence of exclusive breastfeeding under 6 months and prevalence of children ever breastfed, 33 sub-Saharan African countries (2010–2017/2018)

Country	Year of DHS	Caesarean section rate (%)	Prevalence of early initiation of BF (%)	Prevalence of exclusive BF under 6 months (%)	Prevalence of children ever breastfed (%)
Ethiopia	2016	2.6	73.5	57.8	96.9
Namibia	2013	15.6	71.5	48.7	95.8
Burkina Faso	2010	2.0	42.3	24.7	99.2
Burundi	2016–2017	5.3	85.4	83.6	99.0
Togo	2013–2014	7.1	60.8	57.1	98.1
Benin	2017–2018	4.9	54.3	41.5	96.7
Cameroon	2011	4.7	39.8	20.2	97.4
Comoros	2012	11.4	33.8	12.5	93.1
Congo Bra	2011–2012	6.6	23.5	20.6	94.8
Congo DR	2013–2014	5.1	52.2	47.7	98.2
Cote d'Ivoire	2011–2012	2.9	31.0	12.4	96.8
Gabon	2012	10.1	32.6	6.1	89.9
Senegal	2010–2011	4.8	48.3	39.2	97.8
Gambia	2013	1.9	51.7	46.8	98.8
Ghana	2014	12.0	55.6	52.7	98.4
Guinea	2012	3.0	16.4	20.7	98.1
Liberia	2013	4.1	61.6	55.8	98.4
Mali	2012–2013	2.9	57.9	33.8	97.3
Mozambique	2011	3.9	76.8	41.3	97.4
Niger	2012	1.2	53.2	23.3	98.9
Nigeria	2013	2.1	33.3	17.5	97.9
Rwanda	2014–2015	13.0	80.8	88.0	98.8
Sierra Leone	2013	3.8	54.4	32.5	97.2
Zambia	2014–2015	4.5	65.9	73.0	97.8
Chad	2014–2015	1.5	23.0	0.3	98.1
Angola	2015–2016	3.9	48.4	37.5	95.0
Tanzania	2015–2016	6.3	51.5	59.2	98.4
Zimbabwe	2015	5.7	58.0	47.3	98.4
Malawi	2015–2016	6.4	76.7	61.2	97.9
Lesotho	2014	9.9	65.3	66.9	95.4
Kenya	2014	8.0	62.3	61.9	98.8
Uganda	2016	7.2	66.2	65.6	97.6
South Africa	2016	24.3	67.6	32.2	84.4

BF, breastfeeding; Congo Bra, Congo-Brazzaville; Congo DR, Democratic Republic of the Congo; DHS, Demographic and Health Surveys.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures nor were they involved in the design and implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

The preparation of a DAG a priori helped identify the minimum set of variables needed to reduce confounding in the association between the exposure (caesarean section) and the outcomes (breastfeeding indicators). The DAG is shown in online supplementary appendix 1.

Data were eligible for inclusion in this study if they were from a sub-Saharan Africa and involved standardised DHS

Table 2 Crude and multivariable-adjusted prevalence ratios for early initiation of breastfeeding associated with caesarean versus vaginal births

Country	Year of DHS	Sample size	Unadjusted PR (95% CI)	Adjusted PR* (95% CI)
Ethiopia	2016	4021	0.50 (0.35 to 0.71)	0.46 (0.32 to 0.66)
Namibia	2013	2021	0.71 (0.62 to 0.81)	0.71 (0.62 to 0.80)
Burkina Faso	2010	5745	0.90 (0.68 to 1.18)	0.77 (0.60 to 1.00)
Burundi	2016–2017	5182	0.40 (0.34 to 0.48)	0.40 (0.33 to 0.47)
Togo	2013–2014	2707	0.60 (0.48 to 0.75)	0.55 (0.45 to 0.68)
Benin	2017–2018	5337	0.46 (0.37 to 0.58)	0.47 (0.38 to 0.59)
Cameroon	2011	4604	0.86 (0.68 to 1.09)	0.82 (0.65 to 1.04)
Comoros	2012	1228	0.50 (0.31 to 0.81)	0.52 (0.33 to 0.83)
Congo Bra	2011–2012	3754	0.42 (0.22 to 0.82)	0.44 (0.23 to 0.85)
Congo DR	2013–2014	7189	0.47 (0.36 to 0.60)	0.44 (0.34 to 0.57)
Cote d'Ivoire	2011–2012	3037	0.44 (0.24 to 0.81)	0.48 (0.26 to 0.90)
Gabon	2012	2452	0.27 (0.14 to 0.50)	0.29 (0.15 to 0.56)
Senegal	2010–2011	4809	0.59 (0.43 to 0.81)	0.57 (0.42 to 0.78)
Gambia	2013	3429	0.69 (0.43 to 1.11)	0.77 (0.47 to 1.25)
Ghana	2014	2281	0.47 (0.36 to 0.60)	0.46 (0.35 to 0.59)
Guinea	2012	2748	0.49 (0.16 to 1.50)	0.47 (0.15 to 1.46)
Liberia	2013	3001	0.43 (0.28 to 0.65)	0.45 (0.30 to 0.69)
Mali	2012–2013	3884	0.64 (0.50 to 0.82)	0.60 (0.47 to 0.77)
Mozambique	2011	4519	0.80 (0.70 to 0.91)	0.79 (0.70 to 0.90)
Niger	2012	4668	0.75 (0.54 to 1.03)	0.58 (0.42 to 0.81)
Nigeria	2013	12 175	0.62 (0.47 to 0.81)	0.49 (0.38 to 0.64)
Rwanda	2014–2015	3127	0.50 (0.45 to 0.57)	0.50 (0.45 to 0.57)
Sierra Leone	2013	4569	0.70 (0.56 to 0.87)	0.68 (0.56 to 0.84)
Zambia	2014–2015	5013	0.58 (0.48 to 0.71)	0.56 (0.47 to 0.68)
Chad	2014–2015	6493	0.32 (0.13 to 0.75)	0.35 (0.15 to 0.82)
Angola	2015–2016	5738	0.52 (0.36 to 0.74)	0.47 (0.34 to 0.67)
Tanzania	2015–2016	4153	0.29 (0.21 to 0.41)	0.24 (0.17 to 0.33)
Zimbabwe	2015	2330	0.36 (0.26 to 0.51)	0.35 (0.25 to 0.49)
Malawi	2015–2016	6561	0.66 (0.58 to 0.74)	0.67 (0.60 to 0.75)
Lesotho	2014	1368	0.58 (0.45 to 0.75)	0.59 (0.46 to 0.76)
Kenya	2014	3762	0.49 (0.38 to 0.61)	0.49 (0.39 to 0.61)
Uganda	2016	5892	0.54 (0.46 to 0.63)	0.49 (0.42 to 0.57)
South Africa	2016	1358	0.85 (0.75 to 0.96)	0.89 (0.78 to 1.00)

*Adjusted for pregnancy planning, birth weight, region of residence, sex of child, mother's age at birth, mother's education, number of antenatal visits, birth order, maternal tobacco use, place of delivery, types of residence (rural/urban), distance to health facility, mother's occupation and household wealth.
Congo Bra, Congo-Brazzaville; Congo DR, Democratic Republic of the Congo; DHS, Demographic and Health Surveys; PR, prevalence ratio.

survey collection processes that enabled calculation of the breastfeeding indicators. Furthermore, to ensure contemporaneous analyses, only surveys with data collected from 2010 or later were included. The flow scheme for country selection is displayed in figure 1.

A descriptive overview of the data is presented in table 1. The last three columns provide the prevalence of breastfeeding indicators while the third column provides the caesarean section rates among singleton last-born children who were born in the past 2 years before the survey. The proportion of live singleton births delivered by caesarean section ranged from 1.2% in Niger to 24.3% in South Africa. The prevalence of early initiation of breastfeeding was highest in Burundi (85.4%) and lowest in Guinea at 16.4%. The prevalence of exclusive breastfeeding under 6 months varied from 0.3% in Chad

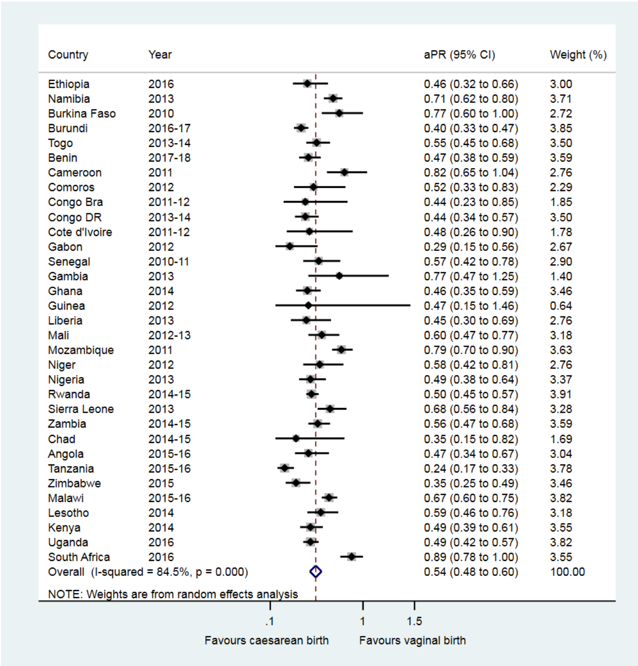

Figure 2 Association between caesarean birth and early initiation of breastfeeding in sub-Saharan Africa. aPR, adjusted prevalence ratio; Congo Bra, Congo-Brazzaville; Congo DR, Democratic Republic of the Congo.

to 88.0% in Rwanda. The prevalence of children ever breastfed is high across sub-Saharan African countries, with 97% of these countries have a prevalence of more than 90%.

Early initiation of breastfeeding

At the individual country level, the fully adjusted analyses in table 2 show that, compared with vaginal birth, caesarean section was associated with aPR for early initiation of breastfeeding that ranged from 0.24 (95% CI 0.17 to 0.33) in Tanzania to 0.89 (95% CI 0.78 to 1.00) in South Africa. Figure 2 shows the random-effects meta-analysis where caesarean birth was associated with a 46.0% lower prevalence of early initiation of breastfeeding (pooled aPR, 0.54 (95% CI 0.48 to 0.60)). However, the heterogeneity associated with pooled estimates for early initiation of breastfeeding was high (χ^2 p value=0.000, I^2=84.5%).

Subgroup analyses

Subgroup analyses were conducted to understand the possible source of heterogeneity associated with pooled estimate of the association between caesarean section and early initiation of breastfeeding based on geographic regions, rate of caesarean section and prevalence of early initiation of breastfeeding. These investigations did not indicate that any of these variables are important sources of heterogeneity (ie, the heterogeneity remains high). The forest plots from these subgroups investigation are presented in online web appendix 6, figures A-C.

Exclusive breastfeeding under 6 months

At the individual country level, the fully adjusted analyses in table 3 show that, compared with vaginal birth, caesarean section was associated with aPR for exclusive breastfeeding under 6 months that ranged from 0.58 (95% CI 0.34 to 0.98) in Angola to a high aPR of 1.93 (95% CI 0.46 to 8.10) in Cote d'Ivoire. Figure 3 shows the random-effects meta-analysis where caesarean birth was associated with a 6.0% lower prevalence of exclusive breastfeeding under 6 months (pooled aPR, 0.94 (95% CI 0.88 to 1.01)).

Children ever breastfed

At the individual country level, the fully adjusted analyses in table 4 show that, compared with vaginal birth, caesarean section was associated with aPR for children ever breastfed that ranged from 0.91 (95% CI 0.82 to 1.02) in Gabon to 1.02 (95% CI 0.98 to 1.06) in Guinea and 1.02 (95% CI 0.99 to 1.04) in Gambia. Figure 4 shows the random-effects meta-analysis which indicated a 2% lower prevalence of children ever breastfed among caesarean versus vaginally born children (pooled aPR, 0.98 (95% CI 0.98 to 0.99)).

DISCUSSION

Main findings

Our study examined the impact of caesarean section on breastfeeding indicators—early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed—in sub-Saharan Africa. The within-country aPR for early initiation of breastfeeding and exclusive breastfeeding under 6 months varies widely across countries but not for children ever breastfed. On the other hand, our finding in meta-analysis, combining the 33 countries data from sub-Saharan Africa shows that caesarean section had a negative influence on early initiation of breastfeeding (a 46% reduction in the prevalence of early initiation of breastfeeding). Our other meta-analyses showed little difference in exclusive breastfeeding under 6 months and children ever breastfed between infants born by caesarean section versus vaginal birth in sub-Saharan Africa.

Interventions such as physical and psychological support for women to initiate and establish successful breastfeeding after caesarean birth may be essential because early initiation of breastfeeding is linked to a greater success in establishing breastfeeding, helps the uterus to return to its normal size quickly, guarantees that the newborn receive 'colostrum' (the first breastmilk), avoids baby needing artificial feeds and reduces neonatal mortality.[31–33]

In this study, the rate of caesarean section in the past 2 years before the surveys ranged from 1.2% in Niger to 24.3% in South Africa. This figure may reveal that caesarean section rate is low among some countries in sub-Saharan Africa which may be due to inadequate access, especially among the poorest women.[34] The prevalence

Table 3 Crude and multivariable-adjusted prevalence ratios for exclusive breastfeeding under 6 months associated with caesarean versus vaginal births

Country	Year of DHS	Sample size	Unadjusted PR (95% CI)	Adjusted PR* (95% CI)
Ethiopia	2016	1081	0.87 (0.55 to 1.37)	0.80 (0.50 to 1.26)
Namibia	2013	517	0.88 (0.66 to 1.19)	0.90 (0.66 to 1.22)
Burkina Faso	2010	1433	1.01 (0.48 to 2.14)	0.95 (0.46 to 1.95)
Burundi	2016–2017	1213	0.95 (0.84 to 1.08)	0.97 (0.86 to 1.09)
Togo	2013–2014	589	1.24 (0.99 to 1.55)	1.10 (0.88 to 1.38)
Benin	2017–2018	1339	0.99 (0.69 to 1.42)	1.01 (0.73 to 1.39)
Cameroon	2011	1094	2.18 (1.37 to 3.47)	1.64 (1.06 to 2.52)
Comoros	2012	318	1.13 (0.40 to 3.19)	1.29 (0.49 to 3.35)
Congo Bra	2011–2012	934	0.78 (0.34 to 1.80)	1.02 (0.38 to 2.78)
Congo DR	2013–2014	1895	0.88 (0.60 to 1.29)	0.75 (0.51 to 1.11)
Cote d'Ivoire	2011–2012	760	2.51 (1.03 to 6.09)	1.93 (0.46 to 8.10)
Gabon	2012	621	1.05 (0.20 to 5.55)	1.10 (0.15 to 8.05)
Senegal	2010–2011	1308	1.18 (0.79 to 1.78)	1.14 (0.75 to 1.71)
Gambia	2013	939	0.80 (0.37 to 1.72)	0.84 (0.39 to 1.79)
Ghana	2014	598	0.98 (0.72 to 1.32)	1.01 (0.74 to 1.37)
Guinea	2012	701	0.98 (0.23 to 4.13)	0.67 (0.19 to 2.45)
Liberia	2013	708	1.36 (1.01 to 1.84)	1.46 (1.09 to 1.97)
Mali	2012–2013	984	1.51 (1.01 to 2.25)	1.53 (1.02 to 2.31)
Mozambique	2011	1025	0.91 (0.57 to 1.45)	0.84 (0.54 to 1.30)
Niger	2012	1281	0.83 (0.30 to 2.24)	0.69 (0.24 to 1.92)
Nigeria	2013	2881	1.69 (1.02 to 2.82)	0.77 (0.48 to 1.26)
Rwanda	2014–2015	690	0.91 (0.81 to 1.01)	0.92 (0.82 to 1.02)
Sierra Leone	2013	1095	1.11 (0.68 to 1.82)	1.30 (0.85 to 1.99)
Zambia	2014–2015	1170	0.84 (0.65 to 1.09)	0.89 (0.68 to 1.17)
Angola	2015–2016	1588	0.65 (0.36 to 1.18)	0.58 (0.34 to 0.98)
Tanzania	2015–2016	997	0.80 (0.58 to 1.09)	0.76 (0.55 to 1.07)
Zimbabwe	2015	590	0.95 (0.61 to 1.47)	1.09 (0.73 to 1.64)
Malawi	2015–2016	1605	1.20 (1.03 to 1.39)	1.16 (0.99 to 1.37)
Lesotho	2014	322	0.96 (0.68 to 1.34)	1.10 (0.85 to 1.44)
Kenya	2014	845	0.79 (0.55 to 1.13)	0.73 (0.53 to 1.00)
Uganda	2016	1459	0.91 (0.75 to 1.10)	0.90 (0.75 to 1.09)
South Africa	2016	339	0.69 (0.42 to 1.13)	0.76 (0.49 to 1.19)

*Adjusted for pregnancy planning, birth weight, region of residence, sex of child, mother's age at birth, mother's education, number of antenatal visits, birth order, maternal tobacco use, place of delivery, types of residence (rural/urban), distance to health facility, mother's occupation and household wealth.
Congo Bra, Congo-Brazzaville; Congo DR, Democratic republic of the Congo; DHS, Demographic and Health Surveys; PR, prevalence ratio.

of early initiation of breastfeeding ranged from 16.4% to 85.4% across the 33 sub-Saharan African countries with one-third of these countries have a prevalence of less than 50%, suggesting a considerable proportion of newborns are not breastfed within 1 hour postbirth. Similarly, there were a substantial disparities in the prevalence of exclusive breastfeeding under 6 months in sub-Saharan Africa (ranged from 0.3% to 88.0%), with a very low prevalence in Chad (0.3%) and Gabon (6.1%). The very low prevalence of exclusive breastfeeding under 6 months in Chad and Gabon may warrant the need for urgent interventions such as improving counselling skills of health workers on exclusive breastfeeding and increasing the family and/or community support for breastfeeding[35] in these countries. However, the prevalence of children ever breastfed is high (90% plus) among the majorities of countries (ie, 32 countries) and ranged from 84.4% in South Africa to 99.2% in Burkina Faso.

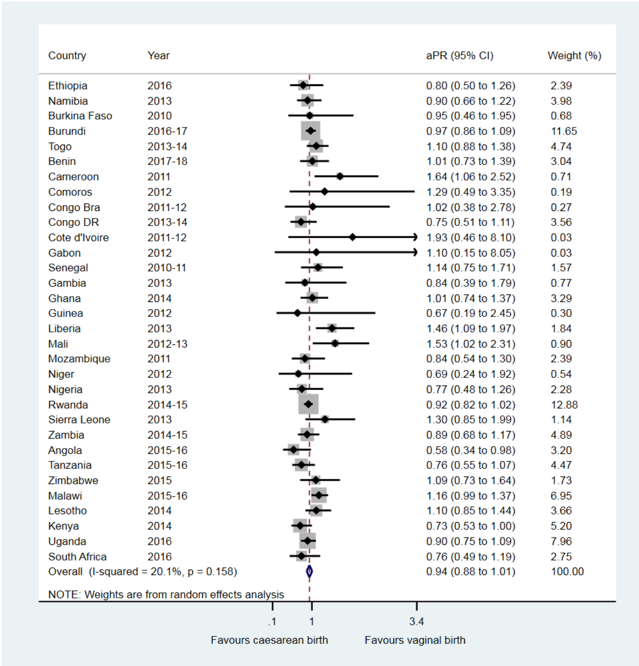

Figure 3 Association between caesarean birth and exclusive breastfeeding under 6 months in sub-Saharan Africa. aPR, adjusted prevalence ratio; Congo Bra, Congo-Brazzaville; Congo DR, Democratic Republic of the Congo.

Early initiation of breastfeeding

Our within-country adjusted analyses and random-effects meta-analysis of 33 countries revealed that the prevalence of early initiation of breastfeeding was lower among infants delivered by caesarean section compared with infants born vaginally. This finding is consistent with a previous study conducted in Canada that reported more women who underwent planned caesarean birth did not initiate breastfeeding.[19] Moreover, Takahashi *et al*[36] in their study conducted based on WHO global surveys completed in 24 countries in Africa, Latin America and Asia found that caesarean delivery was negatively associated with the rate of early initiation of breastfeeding. It has been suggested that early initiation of breastfeeding has numerous benefits for newborns. For example, early initiation of breastfeeding, which can be supported and facilitated by skin-to-skin contact between mother and infant, may promote exclusive breastfeeding under 6 months of life. Findings from our meta-analysis which showed a 46% reduction in the practice of early initiation of breastfeeding among infants born by caesarean versus vaginal births is of public health importance, and health programmes and healthcare providers in low-income and middle-income countries should consider interventions to promote and support early initiation of breastfeeding.

Support to improve early initiation of breastfeeding should be a priority to improve neonatal survival and enhance long-term health of infants. Not initiating breastfeeding within an hour is associated with an increased risks of neonatal mortality and reduced opportunity of benefiting from the immune properties that the 'colostrum' provides to the newborns.[32 33]

An earlier meta-analysis that included studies conducted outside of Africa[20] reported a similar result to ours: the negative effect of caesarean section on early initiation of breastfeeding is more pronounced among children born after caesarean section than after vaginal birth. Interventions such as immediate or early skin-to-skin contact, parent education and use of hand expressed breastmilk (to establish and maintain an adequate milk supply) may help mothers to practice early initiation of breastfeeding following caesarean birth in sub-Saharan Africa.

Exclusive breastfeeding under 6 months and children ever breastfed

The present study showed that the within-country aPR for exclusive breastfeeding under 6 months associated with caesarean versus vaginally born infants varied from a low aPR of 0.58 (95% CI 0.34 to 0.98) in Angola to a high aPR of 1.93 (95% CI 0.46 to 8.10) in Cote d'Ivoire. These findings suggest that caesarean section favours the practice of exclusive breastfeeding under 6 months for some countries, while it has adverse effects for others. These associations would appear to be counter-intuitive, given that caesarean section may be a barrier for exclusive breastfeeding under 6 months, yet given that institutional delivery, where the procedure is performed, caesarean section is among the facilitators of exclusive breastfeeding.[37] In developing countries, most poor women give birth at home assisted by traditional birth attendants. Cultural beliefs and traditional feeding practices may prevent women from initiating breastfeeding immediately postbirth, which, in turn, affects the practice of exclusive breastfeeding under 6 months.[2 38] Therefore, when poor and/or uneducated women undergo caesarean section in developing countries, there is a possibility that women fed their newborn exclusively breast milk because health workers provide immediate breastfeeding support at delivery in health facilities. This was confirmed by a previous study which reported interventions such as individual immediate breastfeeding support at delivery, counselling or group education and lactation management increase exclusive breastfeeding by 49% (95% CI 33 to 68) and any breastfeeding by 66% (95% CI 34 to 107).[39]

On the other hand, the findings of our meta-analysis suggested little influence in exclusive breastfeeding under 6 months (pooled aPR, 0.94 (95% CI 0.88 to 1.01) and children ever breastfed (pooled aPR, 0.98 (95% CI 0.98 to 0.99) among caesarean versus vaginally born infants in sub-Saharan Africa. The current findings are comparable with two previous studies which found that caesarean section has little influence on exclusive breastfeeding (risk ratio, 1.08; 95% CI 0.82 to 1.41)[39] and any breastfeeding practice at 6 months among mothers who initiated breastfeeding (pooled OR, 0.95; 95% CI 0.89 to 1.01).[20]

Table 4 Crude and multivariable-adjusted prevalence ratios for children ever breastfed, associated with caesarean versus vaginal births

Country	Year of DHS	Sample size	Unadjusted PR (95% CI)	Adjusted PR* (95% CI)
Ethiopia	2016	4021	0.93 (0.84 to 1.04)	0.93 (0.84 to 1.04)
Namibia	2013	2021	0.99 (0.96 to 1.03)	1.00 (0.96 to 1.03)
Burkina Faso	2010	5745	0.98 (0.94 to 1.01)	0.98 (0.94 to 1.02)
Burundi	2016–2017	5182	0.98 (0.96 to 1.01)	0.98 (0.96 to 1.01)
Togo	2013–2014	2707	0.97 (0.94 to 1.00)	0.97 (0.94 to 1.01)
Benin	2017–2018	5337	0.99 (0.96 to 1.02)	0.99 (0.97 to 1.02)
Cameroon	2011	4604	0.98 (0.95 to 1.01)	1.00 (0.96 to 1.03)
Comoros	2012	1228	0.97 (0.91 to 1.04)	0.98 (0.92 to 1.04)
Congo Bra	2011–2012	3754	0.93 (0.86 to 1.01)	0.94 (0.87 to 1.02)
Congo DR	2013–2014	7189	0.98 (0.96 to 1.00)	0.98 (0.96 to 1.01)
Cote d'Ivoire	2011–2012	3037	0.97 (0.91 to 1.04)	0.99 (0.93 to 1.06)
Gabon	2012	2452	0.90 (0.80 to 1.02)	0.91 (0.82 to 1.02)
Senegal	2010–2011	4809	0.95 (0.91 to 1.00)	0.95 (0.91 to 1.00)
Gambia	2013	3429	1.00 (0.98 to 1.02)	1.02 (0.99 to 1.04)
Ghana	2014	2281	0.97 (0.94 to 1.00)	0.97 (0.94 to 1.01)
Guinea	2012	2748	1.00 (0.97 to 1.03)	1.02 (0.98 to 1.06)
Liberia	2013	3001	0.95 (0.88 to 1.02)	0.94 (0.88 to 1.01)
Mali	2012–2013	3884	1.00 (0.98 to 1.03)	1.01 (0.98 to 1.03)
Mozambique	2011	4519	1.00 (0.98 to 1.02)	1.01 (0.99 to 1.04)
Niger	2012	4668	0.96 (0.89 to 1.04)	0.97 (0.89 to 1.05)
Nigeria	2013	12 175	0.93 (0.89 to 0.97)	0.93 (0.89 to 0.98)
Rwanda	2014–2015	3127	0.98 (0.97 to 1.00)	0.99 (0.97 to 1.00)
Sierra Leone	2013	4569	0.94 (0.88 to 0.99)	0.93 (0.89 to 0.99)
Zambia	2014–2015	5013	0.98 (0.95 to 1.01)	1.00 (0.96 to 1.03)
Chad	2014–2015	6493	0.95 (0.89 to 1.01)	0.96 (0.90 to 1.03)
Angola	2015–2016	5738	0.99 (0.94 to 1.05)	0.97 (0.92 to 1.02)
Tanzania	2015–2016	4153	0.97 (0.94 to 1.00)	0.96 (0.93 to 1.00)
Zimbabwe	2015	2330	0.98 (0.95 to 1.01)	0.98 (0.95 to 1.01)
Malawi	2015–2016	6561	0.99 (0.96 to 1.01)	0.98 (0.96 to 1.01)
Lesotho	2014	1368	0.96 (0.88 to 1.04)	0.98 (0.92 to 1.04)
Kenya	2014	3762	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.02)
Uganda	2016	5892	0.98 (0.96 to 1.00)	0.98 (0.96 to 1.00)
South Africa	2016	1358	0.93 (0.86 to 1.00)	0.96 (0.89 to 1.03)

*Adjusted for pregnancy planning, birth weight, region of residence, sex of child, mother's age at birth, mother's education, number of antenatal visits, birth order, maternal tobacco use, place of delivery, types of residence (rural/urban), distance to health facility, mother's occupation and household wealth.
Congo Bra, Congo-Brazzaville; Congo DR, Democratic Republic of the Congo; DHS, Demographic and Health Surveys; PR, prevalence ratio.

Strengths and limitations of this study

The strength of the present study include the use of nationally representative data on a large number of countries (n=33 countries) over a long time period (2010-2017/2018). As the small number of previous studies on caesarean section and breastfeeding are from countries outside the African continent, the present study provides insight into the link between caesarean section and breastfeeding in low-income and middle-income countries in sub-Saharan Africa. This is important because caesarean section rate is increasing in low-income and middle-income countries, and early initiation of breastfeeding may be compromised when mothers undergo caesarean section due to several factors such as mothers' emotional health and restricted mobility in the early days after the surgery. Moreover, in addition to the within-country adjusted analyses of nationally representative surveys data, we have also summarised our findings in a meta-analysis,

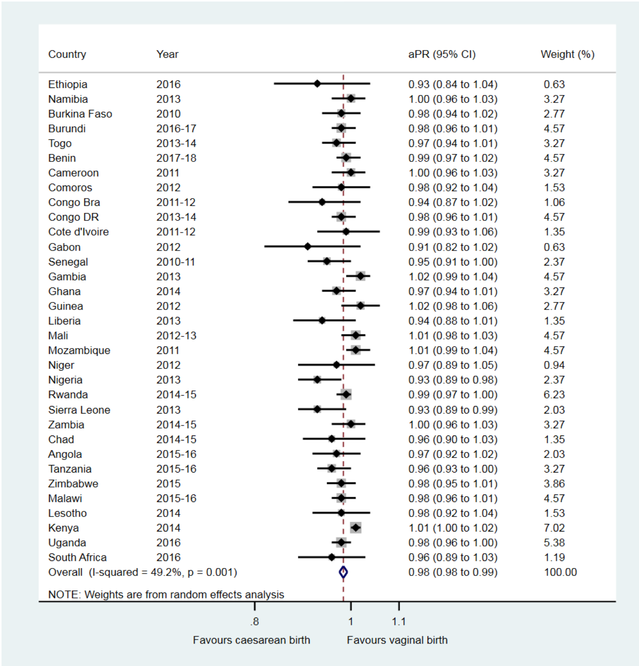

Figure 4 Association between caesarean birth and children ever breastfed in sub-Saharan Africa. aPR, adjusted prevalence ratio; Congo Bra, Congo-Brazzaville; Congo DR, Democratic Republic of the Congo.

combining data analysed individually to provide a consolidated effect estimate of the impact of caesarean section on breastfeeding indicators in sub-Saharan Africa.

We acknowledge the following limitations of this study. First, despite the high-quality of DHS data in low-income and middle-income countries, the ascertainment of breastfeeding practice depends on retrospective maternal reports, which is at risk of misreporting. Nevertheless, a study in Mexico[40] showed that the reliability of retrospective maternal reports of any breastfeeding practice was high (intraclass correlation coefficient=0.94). Furthermore, a review of 10 studies from developed and developing countries suggested a less than 3-year maternal recall period of any breastfeeding and breastfeeding duration is valid and reliable but did not include any study specifically assessing early initiation of breastfeeding.[41] On the other hand, the proportion of children exclusively breastfed may be overestimated because exclusive breastfeeding under 6 months is ascertained based on ‘previous day recall period’, and some children who are given other liquids irregularly may not have received other liquids or solid foods before the survey day.[11] A study from South Africa also revealed that maternal recall of exclusive breastfeeding is limited in accuracy when compared with the ‘objective stable isotope method’ for assessing exclusive breastfeeding.[42] Furthermore, DHS in developing countries are prone to incomplete and inconsistent reporting. Nonetheless, to overcome this problem, the DHS Program performs extensive data editing, including imputation of incomplete dates[43] and make the final edited data files accessible to data users worldwide.

Second, DHS data do not distinguish whether the caesarean section was medically indicated or not. This would be useful to study in the future as it would be important to know whether delayed initiation of breastfeeding occurs in non-medically indicated caesarean birth, as this could be addressed in institutional settings. It may be more challenging to address delayed initiation of breastfeeding among medically indicated emergency caesarean section if mothers or neonates are too sick to commence breastfeeding. However, mothers should be supported to start early expression of breast milk to establish and maintain an adequate milk supply when the newborn is too ill to breastfeed, or if the obstetric complication prevents mother from breastfeeding directly. Third, as DHS lack data on income and expenditures to measure socioeconomic position (SEP) of the household, we have used wealth index as measure of relative SEP of the household. While previous studies suggests that asset-based index is resistant to most economic shocks and is less variable in response to income and expenditure fluctuations, the wealth index can be considered to be a more stable measure of SEP than consumption expenditure in low-income and middle-income countries.[44 45]

Finally, heterogeneity associated with pooled estimates for ‘early initiation of breastfeeding’ among caesarean versus vaginally born infants is high and the source/s of heterogeneity remain unclear after subgroups analyses performed to explore why the effect estimates differ. Although we cannot be sure about the source of heterogeneity, the clinical presentation of mothers and newborn during the perinatal period may be considered as one possible source. For example, for women who delivered by emergency caesarean section after severe obstetric complication, initiation of breastfeeding with an hour may be very difficult or impossible, while for women with less labour complication delivered by emergency caesarean section or planned caesarean section, initiation of breastfeeding within 1 hour after birth may be a possibility. These scenarios may suggest clinical heterogeneity between the analyses performed in each country because of the clinical difference (eg, due to confounding by indication) between countries data analysed. It has previously been suggested that clinical heterogeneity (ie, clinical deference between studies or trials) should be explored.[46]

CONCLUSIONS

Caesarean section had a negative influence on early initiation of breastfeeding but showed little association with exclusive breastfeeding under 6 months and children ever breastfed among infants born after caesarean section versus vaginal birth in sub-Saharan Africa. Health interventions to promote and support women to initiate and maintain breastfeeding after caesarean birth should be considered.

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Chapter 7: Associations between Apgar scores and children's educational outcomes at eight years of age

7.1 Preface

This chapter contains the fourth of the five studies contributing to this thesis. This study was published in *The Australian and New Zealand Journal of Obstetrics and Gynaecology* in 2020.

In Chapter 5 and 6, the influence of obstetrical interventions during childbirth (more specifically caesarean section) on neonatal health and breastfeeding were identified. Others have shown that pre-labour caesarean section was found to reduce the postnatal rise in cortisol, a hormone that prepare the foetus for birth and supports the multi-organ extra-uterine transition.[63] Caesarean section may, therefore, influence neonatal survival during the transition from foetal to neonatal life.[196] The relative success of a newborn making the transition at birth could immediately be gauged by Apgar score, which is an overall measure of a baby's vitality at one and five minutes after birth.[158,162] As bad experiences *in utero,* and poor conditions existing during childbirth may influence the normal transition, it is also thought that these poor conditions may predispose to poor cognitive performance at later-life.

In Chapter 7, the link between the transition at birth as measured by one-and five-minute Apgar scores and children's educational outcomes at eight years of age was examined using high-income country datasets. This is because there are no readily-available datasets with Apgar scores from births in most LMICs, including Ethiopia nor are there data linkage platforms to link perinatal data with school outcomes in LMICs. Using high-quality whole-of-population linked administrative data from South Australia, this chapter (Study 4) presents the results of novel analysis regarding the associations between Apgar scores of 0-5, 6, 7, 8 and 9 (compared with 10) and children's educational outcomes as measured by the National Assessment Program—Literacy and Numeracy (NAPLAN) tests at eight years of age.

7.2 Publication

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Name of Principal Author (Candidate)	Engida Yisma		
Contribution to the Paper	Contributed to the design of the study, performed statistical analysis, interpreted the data, and drafted the 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	4-Aug-2020

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.

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ORIGINAL ARTICLE

Associations between Apgar scores and children's educational outcomes at eight years of age

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Background: Low Apgar scores are associated with neonatal morbidity and mortality, but effects of Apgar scores of 0–5, 6, 7, 8 and 9 (compared with 10) on longer-term neurodevelopmental outcomes are less clear.

Aim: To examine the associations between Apgar scores of 0–5, 6, 7, 8 and 9 (compared with 10) and children's educational outcomes as measured by the Australian National Assessment Program—Literacy and Numeracy (NAPLAN) tests at age eight.

Materials and Methods: We merged perinatal data including all children born in South Australia from 1999 to 2008 with school assessment data (NAPLAN). School assessments included five learning areas (domains)—reading, writing, spelling, grammar and numeracy. Each domain was categorised according to performing at or below National Minimum Standards (≤NMS). Effects were estimated using Augmented Inverse Probability Weighting (AIPW) accounting for a range of maternal, perinatal and sociodemographic characteristics.

Results: Risk differences comparing five-minute Apgar scores of 0–5 with Apgar scores of 10 for children performing ≤NMS for each domain were: reading (0.07 (95% CI −0.16 to 0.29)), writing (0.27 (95% CI −0.14 to 0.68)), spelling (0.15 (95% CI −0.10 to 0.40)), grammar (0.04 (95% CI −0.21 to 0.29)) and numeracy (0.21 (95% CI −0.04 to 0.45)). Risk differences for children performing ≤NMS were also evident when Apgar score of 6 was compared with Apgar score of 10.

Conclusions: Children with five-minute Apgar scores of 0–5 and 6, compared with Apgar score of 10, are at higher risk of scoring at/below the NMS on the NAPLAN assessments at eight years.

KEYWORDS

Apgar score, cognition, epidemiology, school assessment

INTRODUCTION

The Apgar score was introduced in the early 1950s by Dr Virginia Apgar as an overall measure of a baby's vitality at one minute after birth.[1] For decades, the Apgar score has been routinely reported at one and five minutes after birth. The Apgar score comprises five physiological signs—heart rate, respiratory effort, reflex irritability, muscle tone and skin colour. A rating of 0, 1 or 2 is given for each sign, reflecting whether it was absent, present but not adequate, or normal.[2,3] These result in a total score that ranges from 0 to 10.

Apgar scores can also be used as a physiological indicator of how well a newborn is making the transition from *in utero* to the *ex utero* environment.[4] For example, the skin colour is evaluated to determine the perfusion of the skin with oxygenated blood; heart rate reflects the success in the delivery of oxygen to organs; reflex irritability can be used as a marker for nervous system integration; muscle tone represents the locomotor capacity of the newborn; and respiratory rate represents pulmonary function, which facilitates the neuro-feedback-mediated effort to breathe.[4]

Although Apgar scores are useful to predict neonatal survival,[3] as originally intended, there are several factors that could influence Apgar scores. For example, factors such as maternal sedation or anaesthesia, congenital malformations, trauma, gestational age, infections and low birth weight often affect Apgar scores.[2,5] The health status of newborns may be misclassified because some components of the Apgar score such as skin colour, muscle tone and reflex irritability are partially subjective by nature—that is, the scores are affected by newborn assessment skill (inter-observer variability) and the context of the delivery.[2,4]

There is controversy regarding the use of the Apgar score alone as evidence about the diagnostic information and/or as a determining factor to initiate resuscitation.[2] For instance, according to the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 'Apgar score alone cannot be considered to be evidence of or a consequence of asphyxia'.[2] As neonatal resuscitation should be initiated before one minute of birth, the Apgar score is no longer used as a valuable determinant to initiate resuscitation in contemporary clinical practice, but it can be used to evaluate the effectiveness of resuscitation.[2,4] These limitations may make the interpretation of 'what the Apgar score is measuring' or even 'what low Apgar score is a risk for' unclear.[5] However, since there is no other better marker that provides a useful clinical shorthand or a mechanism to record fetal-to-neonatal transition, the Apgar score continues to be used in routine clinical practice. Few studies have attempted to link the transition at birth as measured by the Apgar scores and cognitive outcomes in later life.[6-9]

We undertook this study to examine whether five-minute Apgar scores of 0–5, 6, 7, 8 and 9 (compared with 10) among singleton infants without malformations who were delivered at 37 weeks of gestation or later with vertex presentation was associated with children's educational outcomes at eight years of age.

MATERIALS AND METHODS

Data source

This study utilised data from the South Australian Early Childhood Data Project (SAECDP). The SAECDP is an established project that involves linking government administrative data from state and federal sources. We have merged the perinatal and the National Assessment Program—Literacy and Numeracy (NAPLAN) datasets using de-identified linkage keys generated by an independent data linkage agency (SA-NT DataLink). Ethics approval was provided by the South Australian Department for Health and Ageing (HREC/13/SAH/106/AM08).

Inclusion and exclusion criteria

We included live-born singleton infants without malformations who were delivered at 37 weeks of gestation or later with vertex presentation in South Australia from 1999 to 2008 and have undertaken year 3 NAPLAN. The study excluded infants with birth weight <2500 g or those with no information on five-minute Apgar score. Infants born before 37 weeks' completed gestation or those with birth weight <2500 g were excluded from analysis because these are known conditions that affect both Apgar scores and children's educational outcomes.

Exposure

The South Australian Supplementary Birth Record captures the total Apgar scores measured at one and five minutes after birth. Scores for individual Apgar components were not available. The exposed group comprised infants with a range of five-minute Apgar scores (i.e., 0–5, 6, 7, 8 and 9) while the unexposed group comprised infants with Apgar score of 10.

Outcome

In Australia, children's educational outcomes are assessed by standardised NAPLAN tests at years 3, 5, 7 and 9. The NAPLAN test scores at year 3 (~eight years of age) were used in this study to maximise the eligible study population in South Australia.

NAPLAN has five test domains including reading, writing, spelling, grammar and numeracy. For each domain, NAPLAN results are reported as both direct scores (range from zero to 1000) and grouped into proficiency bands (range from one to six, for year 3). The proficiency bands are used to identify children's educational outcomes relative to the National Minimum Standard (NMS), which is band 2 for year 3. Consistent with national reporting of NAPLAN scores, we report results where NAPLAN was categorised into children performing ≤NMS (≤band 2) and >NMS (bands 3–6, for year 3). However, our data did not include NAPLAN scores from private schools which accounted for about 34% of the population of year 3 students in South Australia from 2008 to 2015.[10]

Confounding

We identified potential confounding based on *a priori* subject matter and expert knowledge, and through the use of Directed Acyclic Graphs (Fig. S1). The potential confounders included method of delivery (normal spontaneous, forceps, lower segment caesarean section (elective), lower segment caesarean section (emergency)), maternal smoking during second half of pregnancy (yes/no), gestational diabetes (yes/no), pregnancy hypertension (yes/no), intrauterine growth restriction (yes/no), gestational age (in weeks), birth weight for gestational age z-score, mother's age at birth (in years), index of relative socioeconomic disadvantage, types of antenatal care (hospital-based, private obstetrical, general practitioner, other), number of antenatal visits (≤7, 8–12, ≥13), maternal occupation, maternal ethnicity (Caucasian, Aboriginal or Torres Strait Islander, others), Australian Remoteness Index for Areas (city, inner regional, outer regional, remote and very remote), mother had a partner (yes/no), maternal analgesia use for labour (yes/no), maternal anaesthesia use for delivery (yes/no), and infant gender (male/female). Birthweight for gestational age *z*-scores were calculated based on Australian national birthweight percentiles by gender and gestational age.[11]

Statistical analysis

In order to examine the association between five-minute Apgar scores and children's educational outcomes, we calculated multi-valued[12] average treatment effects or risk differences of Apgar scores of 0–5, 6, 7, 8 and 9 (compared with 10) on whether a child met the NMS on the NAPLAN tests using augmented inverse probability weighted (AIPW) estimator.[13] The AIPW estimator is also called double-robust estimator.[14,15] The AIPW estimator was chosen over traditional regression because it delivers a marginal rather than a conditional estimate, and it fits regression models for both the exposure (Apgar) and outcome (NAPLAN) providing a doubly robust property if either the regression model for the outcome or the exposure is correctly specified.[14]

As part of our *a priori* statistical analysis plan, we undertook a negative control outcome[16] analysis to examine the potential for unmeasured confounding. We used 'family possession of school card' as a negative control outcome—where no association or an association of much smaller magnitude would be expected for the association between five-minute Apgar score and the negative control outcome. The estimate of the associations between Apgar scores and children's educational outcomes, and Apgar scores and possession of school card were compared. If the associations are of similar magnitude, this suggests that any association between Apgar scores and children's educational outcomes were more likely to be due to residual confounding.

Furthermore, as Apgar score is also captured at one minute in the perinatal database, the above analyses were repeated to estimate the association between one-minute Apgar scores and children's educational outcomes at eight years of age for the purpose of completeness. It has been suggested that the five-minute Apgar is a better predictor of neonatal survival than the one-minute Apgar score.[17]

As missing information is minimal (<3%) for variables used in our analyses, we performed complete case analyses. All analyses were conducted using STATA/SE version 15.1 (StataCorp, College Station, TX, USA).

RESULTS

Figure 1 shows the flow of the participants within this study, starting at singleton live births born with vertex presentations in South Australia from 1999 to 2008, and the proportion successfully linked to school assessments. The numbers differ by each NAPLAN domain because some children did not sit all tests (eg, if they were absent on a particular day due to illness). The timing of the assessments also affects the linkage to perinatal data. For instance, only children in the perinatal database who attended grade 3 during the period from 2008 to 2015 (when NAPLANs were collected) were able to be linked.

Perinatal and sociodemographic characteristics of the mothers and infants according to five-minute Apgar scores are shown in Table 1. Apgar scores <7 at five minutes were more common in infants of mothers who delivered by emergency caesarean section or ventouse, delivered at 37 weeks and ≥41 weeks gestation, smoked during pregnancy, who are Aboriginal or Torres Strait Islander or living in more disadvantaged areas, and who were given analgesia or anaesthesia during labour and delivery.

Table 2 shows the comparison of the proportion of children's educational outcomes at/below the NMS according to a range of five-minute Apgar scores. For example, for Apgar scores of ≤5 vs 10, the proportion of children performing at/below the NMS for each NAPLAN domain were compared as follows: reading (23.62%) and (20.01%), writing (13.91%) and (11.95%), spelling (24.81%) and (20.37%), grammar (21.85%) and (19.30%), and numeracy (27.24%) and (22.29%). We have also reported the results based on Apgar scores of <7 vs Apgar scores of 7–10 for children performing ≤NMS for each NAPLAN domain in Table S1.

Table 3 shows the association across a range of five-minute Apgar score values and children's educational outcomes at eight years of age. For example, infants with Apgar scores of ≤5 had at/below NMS reading (risk difference (RD) = 0.07 (−0.16 to 0.29)), writing (RD = 0.27 (−0.14 to 0.68)), spelling (RD = 0.15 (−0.10 to 0.40)), grammar (RD = 0.04 (−0.21 to 0.29)) and numeracy (RD = 0.21 (−0.04 to 0.45)) scores, compared with Apgar score of 10. The negative control outcome analysis results of the association between a range of five-minute Apgar score values and children's possession of school card can be accessed in Table S2.

The pattern of results is also the same when all analyses were repeated using one-minute Apgar score (Tables S3–S5).

DISCUSSION

Main findings

Our study examined the association between Apgar scores and children's educational outcomes at around age eight years. The primary adjusted analysis indicated that Apgar scores of ≤5 and Apgar score of 6, compared with Apgar score of 10, were more likely to be associated with scoring ≤NMS on each domain of NAPLAN assessments. The sensitivity analysis performed using the negative control outcome to examine the extent to which the association between a range of Apgar score values and children's

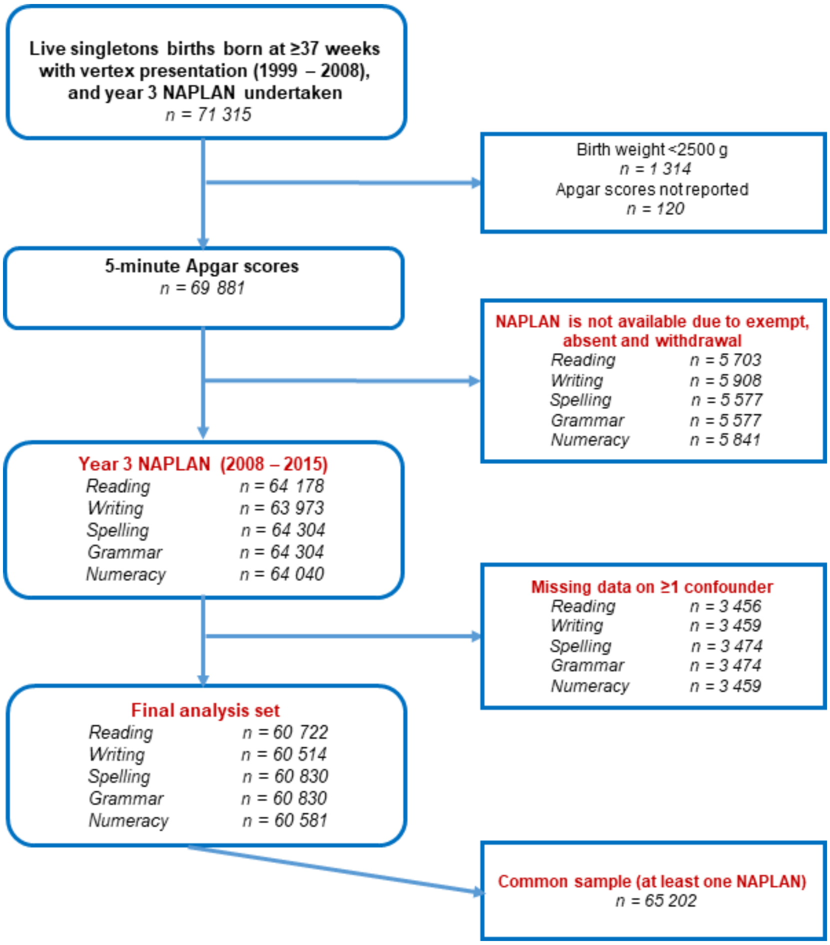

FIGURE 1 The flowchart of the study population. NAPLAN, National Assessment Program—Literacy and Numeracy.

educational outcomes is likely generated by confounding helped in the interpretation of our findings. For example, the point estimate for Apgar scores of ≤5 vs 10 and the negative control outcome (family possession of school card) was much smaller in magnitude than the estimate for the five-minute Apgar scores of ≤5 vs 10 and children's educational outcomes. Thus, a possible interpretation of our results is that residual confounding does not explain away the association between Apgar scores of ≤5 vs 10 and children's educational outcomes.

Comparison with previous findings

The majority of the available evidence regarding the association between Apgar scores and IQ comes from studies conducted by linking birth data with routine IQ test results at conscription around age 18.[6,8,9] One of these studies conducted by Seidman *et al.*,[6] showed no association between low Apgar scores and IQ at 18 years while another study by Ehrenstein *et al*.[8] showed modest association between five-minute Apgar scores <7 and low cognitive function (prevalence ratio, 1.33; 95% CI 0.94–1.88). Consistent with our study, all of the previous studies involved linking the perinatal data with school results or IQ tests in later life. Furthermore, almost all previous studies examined the association between five-minute Apgar scores dichotomised at <7 and cognition or school outcomes later in life.[6,8,9,18] However, in our study, we examined the associations between the five-minute Apgar scores of ≤ 5, 6, 7, 8 and 9 (compared with 10) and children's educational outcomes.

In the present study, both the crude comparison of the percentage of children performing at/below the NMS and the AIPW analysis together with the negative control outcome analysis suggest that, compared with Apgar score of 10, infants with Apgar scores of ≤5 and Apgar score of 6 were associated with scoring at or below the NMS on each NAPLAN assessment. The associations were more consistently evident for writing and numeracy domains. These findings may warrant the need for more immediate intensive follow-up of infants born with Apgar scores below 6, and the need for educational support at school age.

Strengths and limitations of this study

The strength of the present study included the use of whole-of-population perinatal data and a standardised NAPLAN test data. Moreover, we have improved the scientific rigour of this study by using AIPW estimator and negative control outcome analyses. We have also examined the associations between one-minute

TABLE 1 Maternal, sociodemographic, and birth characteristics according to five-minute Apgar scores: term singleton live births in South Australia, 1999–2008 (*N* = 65 202†)

Characteristics	Apgar scores at five minutes <7	Apgar scores at five minutes 7–10
Method of delivery		
Normal spontaneous	348 (53.5%)	41 243 (63.9%)
Forceps	40 (6.2%)	3192 (4.9%)
LSCS (elective)	33 (5.1%)	7018 (10.9%)
LSCS (emergency)	127 (19.5%)	8628 (13.4%)
Ventouse	102 (15.7%)	4471 (6.9%)
Smoked during second half of pregnancy (*n* = 63 541)		
No	479 (76.2%)	48 605 (77.3%)
Yes	150 (23.8%)	14 307 (22.7%)
Maternal asthma		
No	616 (94.8%)	60 075 (93.1%)
Yes	34 (5.2%)	4477 (6.9%)
Gestational diabetes		
No	621 (95.5%)	62 219 (96.4%)
Yes	29 (4.5%)	2333 (3.6%)
Pregnancy hypertension (all types)		
No	581 (89.4%)	59 845 (92.7%)
Yes	69 (10.6%)	4707 (7.3%)
Suspected intrauterine growth restriction		
No	642 (98.8%)	63 327 (98.1%)
Yes	8 (1.2%)	1225 (1.9%)
BWGA *z*-score, mean (SD)	0.0 (1.1)	0.0 (1.0)
Gestational age (in weeks)		
37	40 (6.2%)	3410 (5.3%)
38	99 (15.2%)	11 746 (18.2%)
39	115 (17.7%)	13 912 (21.6%)
40	259 (39.8%)	25 726 (39.9%)
41+	137 (21.1%)	9758 (15.1%)
Types of antenatal care (*n* = 65 059)		
Hospital-based	311 (48.0%)	28 101 (43.6%)
Private obstetrician	107 (16.5%)	16 367 (25.4%)
General practitioner	164 (25.3%)	14 388 (22.3%)
Other (eg, none, home birth, midwife)	66 (10.2%)	5555 (8.6%)
Number of antenatal visits		
≤7	64 (9.8%)	6222 (9.6%)
8–12	392 (60.3%)	40 572 (62.9%)
≥13	194 (29.8%)	17 758 (27.5%)
Maternal ethnicity (*n* = 65 201)		
Caucasian	598 (92.0%)	59 626 (92.4%)
Aboriginal or Torres Strait Islander	22 (3.4%)	1736 (2.7%)
Others	30 (4.6%)	3189 (4.9%)

(Continues)

TABLE 1 (Continued)

Characteristics	Apgar scores at five minutes <7	Apgar scores at five minutes 7–10
Maternal occupation (63 296)		
Managers	43 (6.8%)	4225 (6.7%)
Professionals	51 (8.1%)	5726 (9.1%)
Para-professionals	29 (4.6%)	3013 (4.8%)
Tradespersons	21 (3.3%)	2243 (3.6%)
Clerks	80 (12.7%)	8154 (13.0%)
Salespersons	121 (19.2%)	10 135 (16.2%)
Machine operators and labourers	52 (8.3%)	3287 (5.2%)
Students	24 (3.8%)	2048 (3.3%)
Home duties	159 (25.2%)	19 404 (31.0%)
Unemployed, pensioners, other	50 (7.9%)	4431 (7.1%)
Australian Remoteness Index for Areas (*n* = 64 194)		
City	430 (66.2%)	44 083 (68.3%)
Inner regional	59 (9.1%)	6319 (9.8%)
Outer regional	122 (18.8%)	10 899 (16.9%)
Remote and very remote	39 (6.0%)	3243 (5.0%)
Mother had partner (*n* = 65 186)		
No	119 (18.3%)	10 000 (15.5%)
Yes	531 (81.7%)	54 536 (84.5%)
Maternal age at birth (years), mean (SD)	27.9 (5.9)	28.6 (5.7)
IRSAD (*n* = 65 120)		
Most disadvantaged	125 (19.3%)	11 537 (17.9%)
2	78 (12.0%)	6067 (9.4%)
3	71 (10.9%)	6483 (10.1%)
4	100 (15.4%)	8158 (12.7%)
5	60 (9.2%)	6440 (10.0%)
6	39 (6.0%)	4617 (7.2%)
7	48 (7.4%)	5695 (8.8%)
8	55 (8.5%)	6329 (9.8%)
9	47 (7.2%)	5551 (8.6%)
Most advantaged	26 (4.0%)	3594 (5.6%)
Maternal analgesia use for labour		
No	130 (20.0%)	18 992 (29.4%)
Yes	520 (80.0%)	45 560 (70.6%)
Maternal anaesthesia use for delivery		
No	275 (42.3%)	29 260 (45.3%)
Yes	375 (57.7%)	35 292 (54.7%)
Infant gender (*n* = 65 201)		
Male	383 (58.9%)	33 015 (51.1%)
Female	267 (41.1%)	31 536 (48.9%)

BWGA, birthweight for gestational age; IRSD, Index of Relative Socioeconomic Disadvantage; LSCS, lower segment caesarean section. †The total size of population included in this table is based on at least one National Assessment Program—Literacy and Numeracy domain recorded in the database.

TABLE 2 Proportion of children performing at or below the NMS according to a range of five-minute Apgar score values (i.e., 0–5, 6, 7, 8, 9 and 10)

Domain	*N*	Apgar ≤ 5 ≤NMS/total (%)	Apgar 6 ≤ NMS/ total (%)	Apgar 7 ≤ NMS/ total (%)	Apgar 8 ≤ NMS/ total (%)	Apgar 9 ≤ NMS/ total (%)	Apgar 10 ≤ NMS/ total (%)
Reading	60 722	64/271 (23.62%)	74/333 (22.22%)	179/952 (18.80%)	721/3365 (21.43%)	7823/39 780 (19.67%)	3206/16 021 (20.01%)
Writing	60 514	37/266 (13.91%)	47/327 (14.37%)	121/945 (12.80%)	460/3350 (13.73%)	4880/39 678 (12.30%)	1905/15 948 (11.95%)
Spelling	60 830	67/270 (24.81%)	82/331 (24.77%)	206/952 (21.64%)	762/3375 (22.58%)	8199/39 880 (20.56%)	3264/16 022 (20.37%)
Grammar	60 830	59/270 (21.85%)	76/331 (22.96%)	184/952 (19.33%)	702/3375 (20.80%)	7673/39 880 (19.24%)	3093/16 022 (19.30%)
Numeracy	60 581	73/268 (27.24%)	86/333 (25.83%)	205/941 (21.79%)	771/3358 (22.96%)	8811/39 686 (22.20%)	3566/15 995 (22.29%)

NMS, National Minimum Standard.

TABLE 3 Risk differences comparing 5-minute Apgar scores of 0–5, 6, 7, 8 and 9 (compared with 10) for children performing at or below the NMS for each National Assessment Program—Literacy and Numeracy domain

Five-minute Apgar scores	Reading *n* = 60 722 RD† (95% CI)	Writing *n* = 60 514 RD (95% CI)	Spelling *n* = 60 830 RD (95% CI)	Grammar *n* = 60 830 RD (95% CI)	Numeracy *n* = 60 581 RD (95% CI)
0–5 vs 10	0.07 (−0.16, 0.29)	0.27 (−0.14, 0.68)	0.15 (−0.10, 0.40)	0.04 (−0.21, 0.29)	0.21 (−0.04, 0.45)
6 vs 10	0.16 (−0.07, 0.39)	0.20 (−0.13, 0.52)	0.18 (−0.05, 0.40)	0.14 (−0.08, 0.35)	0.12 (−0.10, 0.34)
7 vs 10	−0.05 (−0.19, 0.08)	0.03 (−0.15, 0.22)	0.02 (−0.11, 0.16)	0.01 (−0.13, 0.15)	0.00 (−0.13, 0.13)
8 vs 10	0.04 (−0.03, 0.12)	0.10 (0.00, 0.21)	0.09 (0.02, 0.17)	0.05 (−0.03, 0.13)	0.03 (−0.04, 0.10)
9 vs 10	0.00 (−0.04, 0.03)	0.03 (−0.02, 0.08)	0.02 (−0.02, 0.05)	0.01 (−0.03, 0.04)	0.01 (−0.02, 0.05)
10	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)

CI, confidence interval; NMS, National Minimum Standard; RD, risk difference.
†RD calculated from augmented inverse probability weighted analysis (adjusted for a number of confounders listed in Methods section) showing the proportion of children performing ≤ NMS on each assessment for children with five-minute Apgar scores.

Apgar scores and children's school outcome by conducting similar analyses.

The study has some potential limitations. First, misclassification of the condition of newborns as measured by Apgar scores could result from the partially subjective nature of Apgar scores—that is, due to inter-observer variability[19] and the context of the delivery.[5] However, the misclassification of the Apgar scores would occur independent of the child's NAPLAN outcome. Second, although Apgar scores have been used worldwide to describe the status of newborns after birth, both obstetrics and paediatrics professional associations[2] emphasised the limitations of use of Apgar scores to predict long-term outcomes, including neurologic outcome. Nonetheless, there is no better summary measure of fetal or neonatal condition, which accurately predicts long-term outcomes that has been developed and widely implemented.[5,20,21] Third, scores for individual Apgar components were not available.

Finally, our data only included NAPLAN scores from public schools. However, the majority (more than two-thirds) of year 3 students were enrolled in public schools in South Australia from 2008 to 2015.[10] So in this case, our estimate would be biased if the associations between Apgar score and NAPLAN were vastly different among private school attenders and led to a different estimate if the total target population had been available. However, we cannot see any reason for this to be the case.

In conclusion, we found that, compared with Apgar score of 10, the five-minute Apgar scores of ≤5 and 6 have negative associations with scoring ≤NMS across all NAPLAN domains.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Proposed Directed Acyclic Graphs (DAGs) describing the associations between Apgar scores and children's educational outcomes.

Table S1. Proportion of children performing at or below the National Minimum Standards (NMS) according to five-minute Apgar scores and risk differences comparing Apgar scores of <7 with scores of 7–10 for children performing at or below the NMS for each National Assessment Program—Literacy and Numeracy (NAPLAN) domain.

Table S2. Risk differences comparing a range of five-minute Apgar scores (ie, 0–5, 6, 7, 8 and 9) (compared with 10) for children having school card according to National Assessment Program—Literacy and Numeracy (NAPLAN) domains.

Table S3. Proportion of children performing at or below the National Minimum Standards (NMS) according to one-minute Apgar scores and risk differences comparing Apgar scores of <7 with scores of 7–10 for children performing at or below NMS for each domain.

Table S4. Proportion of children having school card according to one-minute Apgar score and risk differences comparing Apgar scores of <7 with scores of 7–10 for children having school card.

Table S5. Risk differences comparing a range of one-minute Apgar score values (ie 0–5, 6, 7, 8 and 9) (compared with 10) for children performing at or below the National Minimum Standards (NMS) for each domain.

Chapter 8: Elective labour induction versus expectant management in women and children's educational outcomes at eight years of age

8.1 Preface

This chapter contains the final of a series of five studies contributing to this thesis. This study was published in *Ultrasound in Obstetrics and Gynecology* in 2020.

In Chapters 5, 6 and 7, the association between obstetrical interventions during childbirth (caesarean section and Apgar score) and short-term and long-term outcomes, including neonatal mortality, breastfeeding and children's educational outcomes were examined. These studies revealed that obstetrical interventions during childbirth have an influence on neonatal mortality, breastfeeding and children's educational outcomes at later age. In this chapter, the focus is to estimate whether elective induction of labour at 39 weeks of gestation (the most common intervention during labour) as compared with expectant management affects children's educational outcomes at eight years of age.

As no previous study investigated the longer-term neurodevelopmental effect of elective induction of labour at 39 weeks, this chapter (Study 5) provides the first contribution to the ongoing scientific discourse on the effect of elective induction of labour at 39 weeks and longer-term neurodevelopmental outcomes in children.

8.2 Publication

Yisma E, Mol BW, Lynch JW, Murthy NM, Smithers LG. Labour induction versus expectant management in women and children's educational outcomes at eight years of age. *Ultrasound Obstet Gynecol* 2020. https://doi.org/10.1002/uog.23141

8.2.1 Statement of authorship

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Principal Author

Name of Principal Author (Candidate)	Engida Yisma		
Contribution to the Paper	Contributed to the design of the study, performed statistical analysis, interpreted the data, and drafted the 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	4-Aug-2020

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.

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Elective labor induction *vs* expectant management in women and children's educational outcomes at 8 years of age

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Short title: Elective labour induction and children's educational outcomes

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Keywords: Elective induction of labour, expectant management, school assessment, cognition, epidemiology

Contribution

What are the novel findings of this work?

Using innovative data linkage of the whole-of-population administrative perinatal data and the National Assessment Program—Literacy and Numeracy data from South Australia, we found that elective induction of labour at 39 weeks of gestation, compared with expectant management, did not affect children's educational outcomes at eight years of age.

What are the clinical implications of this work?

The findings of this study provide the first presentation of the effect of elective induction of labour at 39 weeks of gestation as compared with expectant management on children's educational outcomes.

Abstract

Objective

To estimate the effect of elective induction of labour at 39 weeks of gestation on children's educational outcomes as measured by the Australian National Assessment Program—Literacy and Numeracy (NAPLAN) tests at year 3 (~8 years of age), compared with expectant management.

Methods

We merged perinatal data, including information regarding all infants in South Australia from 1999 to 2008, with children's school assessment data (i.e., NAPLAN data). The study population included all singleton births born without malformations at 39-42 weeks of gestation in vertex presentation. Children had to have undertaken year-3 NAPLAN (~8 years of age). We excluded births from women who had a contraindication to vaginal delivery and with conditions possibly justifying elective delivery before 39 weeks of gestation. Our outcome of interest was children's educational outcomes as measured by NAPLAN. The NAPLAN included five learning domains (reading, writing, spelling, grammar and numeracy). Each domain was categorised according to performing at or below versus above the National Minimum Standards (NMS). Average Treatment Effects (ATEs) of elective induction of labour at 39 weeks for children performing at/below the NMS for each domain were estimated using Augmented Inverse Probability Weighted (AIPW) estimator accounting for potential confounders.

Results

Among 53,843 children born at 39-42 weeks with vertex presentation from 1999-2008 and those who were expected to participate in year 3 NAPLAN from 2008-2015, a total of 31,120 children had at least one year 3 NAPLAN domain. Of these (i.e., 31,120 children), 1,353 children were delivered after elective induction of labour at 39 weeks while 29,767 children were born following expectant management. The ATEs (mean differences) comparing elective induction of labour at 39 weeks with expectant management for children scoring at/below the NMS on each domain were: reading (0.01 (95% CI -0.02 to 0.03)), writing (0.02 (95% CI 0.00 to 0.04)), spelling (0.01 (95% CI -0.01 to 0.04)), grammar (0.02 (95% CI -0.01 to 0.04)) and numeracy (0.03 (95% CI -0.00 to 0.05)).

Conclusion

Elective induction of labour at 39 weeks of gestation did not affect children's standardised literacy and numeracy testing outcomes at eight years of age when compared with expectant management.

Introduction

It has been recommended that non-medically indicated deliveries such as deliveries following elective induction of labour should be avoided for women who are below 39 weeks of gestation because they are associated with adverse short- and long-term outcomes.[1] Conversely, due to the increased risk of perinatal morbidity and mortality associated with late-term and post-term pregnancies, it has been suggested that deliveries following non-medically indicated induction of labour should be considered from 41 weeks of gestation.[2,3]

However, elective induction of labour has been considered as unsafe when the gestational age is between 39 and 40 weeks because of the belief that it is associated with increased risk of caesarean delivery and adverse perinatal outcomes than spontaneous labour. This assumption was made based on observational studies[4-9] in which women who were induced were compared with women in spontaneous labour at the same gestational age. It is known that the comparison of induction of labour with spontaneous labour at the same gestational age is inappropriate because spontaneous labour is not a definite alternative to induction of labour.[10] In clinical practice, women and obstetric care providers are required to choose either induction of labour or expectant management, which comprises the onset of spontaneous labour, medically-indicated induction or caesarean at a later date.

Several studies[11-17] have found that elective induction of labour at 39 weeks reduces adverse perinatal outcomes, including caesarean delivery. However, there has been limited research reported on the link between labour induction at 39 weeks and children's educational outcomes.[18] We speculate on two potential mechanisms linking elective labour induction and children's educational outcomes. First, the risk of special educational need, compared to children born at 40 weeks, increased among children born from 37–39 weeks gestation.[19] Second, it is thought that labour induction increases stress and the presence of adverse prenatal and perinatal stress may result in epigenetic modification of gene expression, which may permanently change neuroendocrine and behavioural responses in children's later life.[20]

We undertook this study to examine whether elective induction of labour at 39 weeks, compared with expectant management, had an effect on children's educational outcomes at eight years.

Materials and Methods

Data source

This study utilised data from the South Australian Early Childhood Data Project (SAECDP). The SAECDP is an established project that involves linking government administrative data from state and federal sources. We have merged the perinatal data and the National Assessment Program—Literacy and Numeracy (NAPLAN) datasets using de-identified linkage keys generated by an independent data linkage agency (SA-NT DataLink). The ethics approval was provided by the South Australian Department for Health and Ageing (HREC/13/SAH/106/AM08).

Eligibility criteria

Of the total 285,063 children in South Australia who were born from 1999 to 2013, we included all births at 39-42 weeks of gestation in vertex presentation, which were live singletons without malformations from 1999-2008 and children who were expected to participate in year 3 NAPLAN from 2008-2015 (N= 53,843). The study excluded births from women who had contraindication to vaginal delivery (previous caesarean births), who had elective caesarean delivery, and women who were with conditions possibly justifying elective delivery prior to 39 weeks of gestation[21]—these include pregnancy hypertension, gestational diabetes, suspected foetal-growth restriction, or disorders associated with antepartum haemorrhage such as placenta previa. As the aim of our study was to compare elective induction of labour at 39 weeks with expectant management, births following spontaneous or medically-indicated deliveries at 39 weeks were excluded.

All students in year 3 were expected to participate in NAPLAN testing. However, the SAECDP did not include NAPLAN scores from students attending private schools as these have not been made available for linkage. Private school attendance accounted for about 34% of the population of year 3 students in South Australia from 2008 to 2015.[22] Moreover, some students from public school did not take NAPLAN due to exempt, absent and withdrawal. We excluded children with no NAPLAN score due to exempt, absent and withdrawal from

2008-2015. Consequently, a total of 31,120 children who had at least one NAPLAN domain met the inclusion criteria.

Exposure

In South Australia, as the perinatal database included information about onset of labour, reason for induction of labour, and gestational age at birth, the exposure variable was computed from these three variables. The exposed group comprised births following elective induction of labour at 39 weeks of gestation. The control (unexposed) group comprised births following expectant management—that is, deliveries following spontaneous labour and elective induction of labour or medically-indicated induction or caesarean from 40-42 weeks of gestation. Gestational age (at birth) dating was determined predominately based on early dating ultrasound. However, in the small number of women when dating ultrasound was not available, gestational age was determined from the first day of the last menstrual period and estimates at birth.

Outcome

In South Australia and other jurisdictions, children's educational outcomes are assessed by standardized NAPLAN tests at years 3, 5, 7 and 9. The NAPLAN test scores at year 3 (~8 years of age) were used in this study to maximize the eligible study population in South Australia. The NAPLAN has five test domains including reading, writing, spelling, grammar and numeracy. For each domain, NAPLAN results are reported as both direct scores (range from 0 to 1000) and grouped into proficiency bands (range from 1 to 6, for year 3). The proficiency bands are used to identify children's educational outcomes relative to the National Minimum Standard (NMS), which is band 2 for year 3. Consistent with the national reporting of NAPLAN scores, we report results where NAPLAN was categorised into children performing at or below the NMS (≤ band 2) versus above the NMS (bands 3–6). Moreover, we also categorised the NAPLAN scores into children scoring band 1 versus bands 2–6 for the purpose of comparison.

Confounding

We identified the potential confounding based on *a priori* subject matter and expert knowledge. The potential confounders in this study included maternal smoking during the second half of pregnancy (yes/no), birth weight for gestational age z-score, mother's age at birth (in years), index of relative socioeconomic disadvantage, types of antenatal care (hospital-based, private obstetrical, general practitioner, other), number of antenatal visits (≤7, 8-12, ≥13), maternal occupation, maternal ethnicity (Caucasian, Aboriginal or Torres Strait Islander, others), Australian remoteness index for areas (city, inner regional, outer regional, remote and very remote), mother had a partner (yes/no), and infant sex (male/female). Birthweight for gestational age z-scores were calculated based on the Australian national birthweight percentiles by sex and gestational age.[23]

Statistical analysis

In order to estimate the effect of induction of labour at 39 weeks and children's educational outcomes, we calculated the Average Treatment Effects (ATEs) of elective induction of labour at 39 weeks of gestation compared with expectant management on whether a child met the NMS on each NAPLAN domain using Augmented Inverse Probability Weighted (AIPW) estimator.[24] The AIPW estimator is also called a doubly-robust estimator.[25,26] The AIPW estimator was chosen over traditional regression because it delivers a marginal rather than a conditional estimate, and it fits regression models for both the exposure (elective induction of labour) and the outcome (NAPLAN) providing a doubly-robust property if either the regression model for the outcome or the exposure is correctly specified.[25]

In this study, the AIPW estimator fits a logistic regression model for the exposure conditional on each confounder listed above to estimate propensity scores for each individual. The propensity scores were used to weight the observed data. The AIPW also fits a logistic regression model for the outcome conditional on all confounders for each category of the exposure to obtain predicted outcomes for each individual. After estimating the propensity scores and predicted outcomes, the AIPW estimator combines the estimated values along with observed values to calculate the doubly robust estimates of outcomes for each level of exposure for each individual.[25] Finally, the mean of the estimates of outcome under exposed (elective induction of labour) and control (expectant management) was calculated. These estimated means were used to calculate ATE, which is a mean difference in outcome among exposed and control groups. As our outcome (children's educational outcomes) was binary, the ATE calculated using the combined doubly robust estimate is equivalent to population proportion of children performing at or below the NMS on each NAPLAN domain.

All analyses were conducted using STATA/SE version 15. (StataCorp, College Station, TX, USA).

Results

Figure 1 shows the flow of the participants within this study, starting at singleton live births with vertex presentations at 39-42 weeks of gestation in South Australia from 1999 to 2008, and the proportion of children merged to school assessments data (NAPLAN) from 2008 to 2015. A total of 31,120 children—1,353 were delivered after elective induction of labour at 39 weeks and 29,767 were born following expectant management—who had at least one NAPLAN domain at eight years of age were merged. The total number of births differ according to each NAPLAN domain because some children did not sit all tests (e.g., if they were absent on a particular day due to illness). The timing of the assessments also affects the linkage to perinatal data. For instance, only children in the perinatal database who attended grade three during the period from 2008 to 2015 (when NAPLANs were collected) were merged and included in this study.

Perinatal and sociodemographic characteristics of the mothers and infants according to elective induction of labour at 39 weeks versus expectant management are shown in **Table 1**. The proportion of spontaneous vaginal delivery was higher among women who were electively induced at 39 weeks than women who were expectantly managed. Elective induction of labour at 39 weeks of gestation was more common in women who did not smoke during pregnancy, who attended antenatal care with private obstetrician, who had 8-12 antenatal visits, and who are Caucasian or living in a city. The proportion of elective induction of labour at 39 weeks was also higher in women who had partner. The average age of women who underwent elective induction of labour at 39 weeks was higher compared with those who were expectantly managed (**Table 1**).

Table 2 shows the proportion of children's educational outcomes at or below the NMS according to elective induction of labour at 39 weeks versus expectant management as well as the results from the AIPW estimator analysis. For instance, the proportion of children performing at/below the NMS for each NAPLAN according to elective induction of labour at 39 weeks versus expectant management were compared as follows: reading (17.61%) and

(18.93%), writing (11.61%) and (11.56%), spelling (18.61%) and (19.74%), grammar (18.30%) and (18.58%), and numeracy (21.46%) and (21.23%).

The ATEs (as calculated from the AIPW estimator analysis) comparing elective induction of labour at 39 weeks with expectant management for children scoring at or below the NMS on NAPLAN domain ranged from 0.01 (95% CI -0.02 to 0.03) for reading to 0.03 (95% CI 0.00 to 0.05) for numeracy (**Table 2**).

The pattern of the results is also the same when similar analyses were conducted for children scoring band 1 versus bands 2–6 (**Supplementary Table S1**).

Discussion

In the current study, using the whole-of-population perinatal data including information regarding infants in South Australia born from 1999 to 2008 and year 3 NAPLAN data, we compared births following elective induction of labour at 39 weeks of gestation with expectant management to examine children's educational outcome at around age eight years. Our estimates suggest that elective induction of labour at 39 weeks, compared with expectant management, had little to no effect on performing at or below the NMS for each NAPLAN domain.

Previous systematic reviews and meta-analyses, randomized control trials and observational studies of elective induction of labour at 39 weeks of gestation have exclusively reported on short-term perinatal outcomes, including caesarean delivery.[11-17] These previous studies have shown that elective induction of labour at 39 weeks, compared with expectant management, had lower rates of maternal and neonatal morbidity, lower rates of caesarean section, and fewer stillbirths. The underlying biological mechanism that provides the possible explanation for the improved perinatal outcomes following elective induction of labour at 39 weeks may be related to the prevention of the impact of placental insufficiency and excess foetal growth. For example, elective induction of labour at 39 weeks of gestation may lower rates of stillbirth as the placenta is able to perfuse the foetus before and during labour. It was hypothesised that placental insufficiency is the underlying mechanism for unexplained term stillbirth.[27] On the other hand, it has been demonstrated that foetal macrosomia (birth weight $\geq$4500 g) is associated with prolonged labour, cephalo-pelvic disproportion and shoulder dystocia.[28] Elective induction of labour at 39 weeks may reduce the risk of adverse perinatal outcomes by preventing excess foetal growth as the gestational age increases.

Despite the large amount of evidence regarding the short-term outcome of elective induction of labour at 39 weeks, there is limited evidence regarding the longer-term neurodevelopmental effects of induction of labour at 39 weeks of gestation. A 2020 study conducted by Werner *et al*[18] in Rhode Island, USA to evaluate educational outcomes among children born by induction of labour at 39 or 40 weeks versus children born following expectant management found that induction of labour at term is not associated with poorer third-grade reading and math test scores. However, the study did not distinguish whether the induction of labour was elective or not. The current study was, however, the first to examine the effect of elective induction of labour at 39 weeks on children's educational outcomes. We found that elective induction of labour at 39 weeks had little to no effect on standardised NAPLAN tests at around age 8 years. The current study provides the first contribution to the ongoing scientific discourse on the effect of elective induction of labour at 39 weeks of gestation and longer-term neurodevelopmental outcomes.

The strength of the present study included the use of the whole-of-population perinatal data and a standardised NAPLAN test data. Our data comprised information regarding the reason of induction of labour, which helped us identify the elective and medically-indicated induction of labour. Moreover, we have improved the scientific rigour of the current study by using AIPW estimator in order to balance a broad range of sociodemographic and perinatal factors associated with both the exposure (elective induction of labour at 39 weeks) and the outcome (children's educational outcomes).

The study has some limitations. The first limitation could be regarding information on gestational age, which was only available in weeks in our perinatal dataset. There may be errors in the gestational age dating, resulting in misclassification of our exposure. However, the misclassification of the exposure would occur independent of the children's NAPLAN outcome but may bias estimates to the null. The other limitation of this study was that our data only included NAPLAN scores from public schools, which is representative of the student population from public schools in South Australia. Nevertheless, it has been emphasised by a number of authors that representativeness is not a prerequisite for causal inference.[29,30] Moreover, as the majority (more than two-thirds) of year 3 students were enrolled in public schools in South Australia from 2008 to 2015,[22] our estimate regarding the effect of elective induction of labour on children's educational outcomes is unlikely to be biased. The only way our estimate would be biased was if the association between elective induction of labour and NAPLAN was vastly different among private school attenders, and led to a different estimate if the total target population had been available. However, we cannot see any reason for this to be the case.

In conclusion, elective induction of labour at 39 weeks of gestation compared with expectant management did not affect the proportion of children scoring at or below the NMS on standardised NAPLAN tests at eight years of age.

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Legends

Figure 1. The flowchart of the study population. NAPLAN, National Assessment Program—Literacy and Numeracy.

Supplementary Material

Table S1. Proportion of children performing at Band 1 according to elective induction of labour at 39 weeks versus expectant management and

ATEs comparing elective induction of labour at 39 weeks with expectant management for children performing at Band 1 for each NAPLAN

domain

Table 1. Maternal, sociodemographic, and birth characteristics according to elective induction of labour at 39 weeks and expectant management at 40, 41 and 42 weeks: live singleton births in South Australia, 1999-2008 (N=31,120†)

	Elective induction of labour (N=1353)	**Expectant-Management (N= 29767)**
Method of delivery		
Normal spontaneous	1052 (77.8%)	21630 (72.7%)
Forceps	60 (4.4%)	1731 (5.8%)
Emergency caesarean section	158 (11.7%)	3970 (13.3%)
Ventouse	83 (6.1%)	2436 (8.2%)
Smoked second half of pregnancy (n= 30,349)		
No	1058 (80.0%)	22683 (78.1%)
Yes	265 (20.0%)	6343 (21.9%)
BWGA z-score, mean (SD)	0.2 (1.0)	0.0 (1.0)
Types of antenatal care (n= 31,068)		
Hospital-based	460 (34.0%)	12035 (40.5%)
Private obstetrician	650 (48.0%)	6592 (22.2%)
General practitioner	208 (15.4%)	7780 (26.2%)
Other (e.g. none, home birth, midwife)	35 (2.6%)	3308 (11.1%)
Number of antenatal visits		
<=7	88 (6.5%)	2170 (7.3%)
8-12	901 (66.6%)	18727 (62.9%)
>=13	364 (26.9%)	8870 (29.8%)
Maternal ethnicity (n= 31,119)		
Caucasian	1286 (95.0%)	27854 (93.6%)
Aboriginal or Torres Strait Islander	33 (2.4%)	651 (2.2%)
Others	34 (2.5%)	1261 (4.2%)
Maternal occupation (n= 30,305)		
Managers	99 (7.5%)	2014 (6.9%)
Professionals	143 (10.9%)	2706 (9.3%)
Para-professionals	76 (5.8%)	1373 (4.7%)
Tradespersons	43 (3.3%)	1057 (3.6%)
Clerks	201 (15.3%)	3899 (13.5%)
Salespersons	189 (14.4%)	5008 (17.3%)
Machine operators and labourers	40 (3.0%)	1591 (5.5%)
Students	19 (1.4%)	1026 (3.5%)
Home duties	448 (34.0%)	8192 (28.3%)
Unemployed, other	59 (4.5%)	2122 (7.3%)

Australian Remoteness Index for Areas (n= 31,116)		
City	955 (70.6%)	19657 (66.0%)
Inner regional	107 (7.9%)	3166 (10.6%)
Outer regional	232 (17.1%)	5305 (17.8%)
Remote and very remote	59 (4.4%)	1635 (5.5%)
Mother had partner (n= 31,114)		
No	166 (12.3%)	4665 (15.7%)
Yes	1187 (87.7%)	25096 (84.3%)
Maternal age at birth (years), mean (SD)	29.6 (5.5)	28.1 (5.7)
IRSAD (n= 31,078)		
Most disadvantaged	197 (14.6%)	5249 (17.7%)
2	102 (7.5%)	2829 (9.5%)
3	142 (10.5%)	3057 (10.3%)
4	158 (11.7%)	3725 (12.5%)
5	141 (10.4%)	2949 (9.9%)
6	83 (6.1%)	2208 (7.4%)
7	121 (9.0%)	2583 (8.7%)
8	178 (13.2%)	2838 (9.5%)
9	153 (11.3%)	2568 (8.6%)
Most advantaged	76 (5.6%)	1721 (5.8%)
Infant sex		
Male	666 (49.2%)	15135 (50.8%)
Female	687 (50.8%)	14632 (49.2%)

Abbreviations: BWGA, birthweight for gestational age; IRSD, Index of Relative Socioeconomic Disadvantage

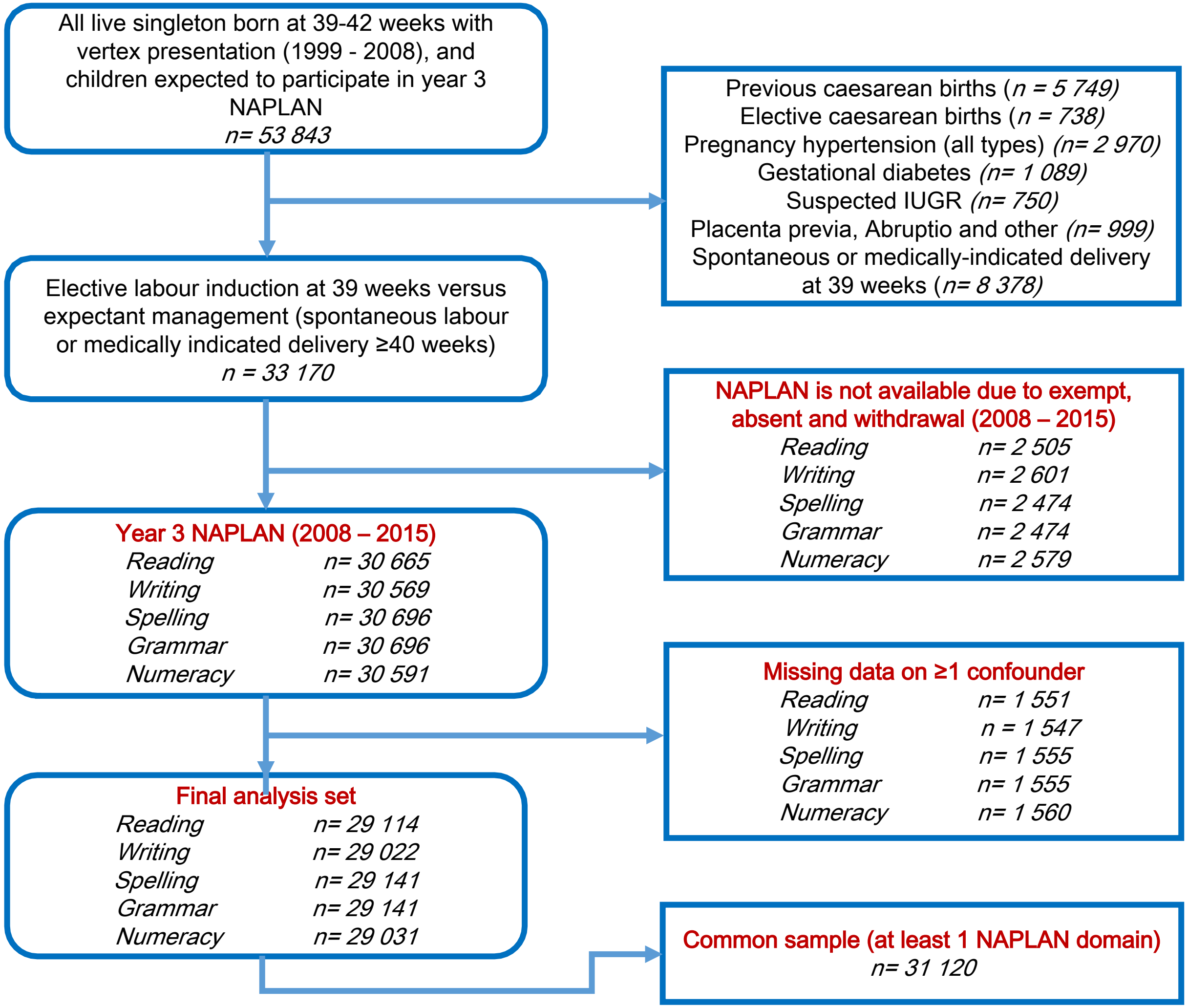
†The total sample size included in this table is based on at least one NAPLAN domain recorded in the database.

Table 2. Proportion of children performing at or below the NMS according to elective induction of labour at 39 weeks versus expectant management and ATEs comparing elective induction of labour at 39 weeks with expectant management for children performing at or below the NMS for each NAPLAN domain

Domain	Total sample (N)	Elective labour induction ≤NMS/total (%)	Expectant management ≤NMS/total (%)	ATE[†]	95% CI	P
Reading	29,114	223/1,266 (17.61%)	5271/27,848 (18.93%)	0.01	-0.02, 0.03	0.524
Writing	29,022	140/1,264 (11.61%)	3209/27,758 (11.56%)	0.02	0.00, 0.04	0.101
Spelling	29,141	236/1,268 (18.61%)	5502/27,873 (19.74%)	0.01	-0.01, 0.04	0.308
Grammar	29,141	232/1,268 (18.30%)	5178/27,873 (18.58%)	0.02	-0.01, 0.04	0.178
Numeracy	29,031	273/1,272 (21.46%)	5892/27,759 (21.23%)	0.03	-0.00, 0.05	0.053

Abbreviations: ATE, Average Treatment Effect; CI, confidence interval; NMS, National Minimum Standard.

[†]ATE calculated from augmented inverse probability weighted analysis adjusted for maternal smoking during the second half of pregnancy, birth weight for gestational age z-score, mother's age at birth, index of relative socioeconomic disadvantage, types of antenatal care, number of antenatal visits, maternal occupation, maternal ethnicity, Australian remoteness index for areas, mother had a partner, and infant sex.


All live singleton born at 39-42 weeks with vertex presentation (1999 - 2008), and children expected to participate in year 3 NAPLAN
n= 53 843
Previous caesarean births (n = 5 749)
Elective caesarean births (n = 738)
Pregnancy hypertension (all types) (n= 2 970)
Gestational diabetes (n= 1 089)
Suspected IUGR (n= 750)
Placenta previa, Abruptio and other (n= 999)
Spontaneous or medically-indicated delivery at 39 weeks (n= 8 378)
Elective labour induction at 39 weeks versus expectant management (spontaneous labour or medically indicated delivery ≥40 weeks)
n = 33 170
NAPLAN is not available due to exempt, absent and withdrawal (2008 – 2015)
Reading n= 2 505
Writing n= 2 601
Spelling n= 2 474
Grammar n= 2 474
Numeracy n= 2 579
Year 3 NAPLAN (2008 – 2015)
Reading n= 30 665
Writing n= 30 569
Spelling n= 30 696
Grammar n= 30 696
Numeracy n= 30 591
Missing data on ≥1 confounder
Reading n= 1 551
Writing n = 1 547
Spelling n= 1 555
Grammar n= 1 555
Numeracy n= 1 560
Final analysis set
Reading n= 29 114
Writing n= 29 022
Spelling n= 29 141
Grammar n= 29 141
Numeracy n= 29 031
Common sample (at least 1 NAPLAN domain)
n= 31 120

Chapter 9: Discussion and conclusions

The discussion of specific results of the five studies was detailed in previous chapters. In this chapter, I summarise the overall research and provide a general discussion. The main objective of the thesis was to examine the effect of obstetrical interventions during labour and birth on maternal and child outcomes, including breastfeeding, neonatal mortality and children's educational outcomes. The uniqueness of the current thesis is that it utilised high-quality data from low-, middle- and high-income countries, and applied advanced epidemiological data analysis methods that are designed to improve causal inference.[190-194] In this final chapter, key findings and contributions of each study are presented, strengths and limitations are discussed, as well as implications and concluding remarks are provided.

9.1 Key findings and contributions

Caesarean section rates and sociodemographic characteristics in Ethiopia

In Study 1, it was found that the caesarean section rate in Ethiopia in 2016 was more than double the rate in 2000. As detailed in Chapter 4, Study 1 also highlighted that there were substantial regional and socioeconomic disparities in caesarean section rates in Ethiopia. For instance, among the administrative regions of Ethiopia, Somali state had the lowest rate and Addis Ababa had the highest in 2016. The rates among urban women were about twelve times higher than those among rural women in 2016. The caesarean section rate among births in the richest quintiles of household wealth was about 14 times more than for births among women in the poorest quintiles of household wealth in 2016. Furthermore, the risk of caesarean delivery was about 78% higher for women who gave birth in private sector than women who gave birth in public health facilities.

The increase in the national caesarean section rates seen in Ethiopia was partly attributable to an increase in the proportion of deliveries occurring within health facilities. The proportion of health facility deliveries in Ethiopia in 2016 was more than five times the proportion of health facility births in 2000.[116] Moreover, urban women, women from the richest quintiles of household wealth and private healthcare facilities were the major contributors to the national increase in caesarean section rates in Ethiopia. The large disparities in the caesarean section rate according to sociodemographic characteristics suggests unequal access to emergency caesarean section, particularly for poor and rural women in Ethiopia. This means that if there are obstetric complications during labour and birth, poorer and rural women and their newborns are at higher risk for adverse birth outcomes. Boerma *et al.*[5] in their 2018 study defined the population level caesarean section use thresholds of less than 10% as an indicator of poor access (underuse), and reported that access to caesarean section remains a challenge in many low-income countries, particularly for poor women.

Caesarean section and neonatal mortality in Ethiopia

In Study 2, the temporal association between caesarean section and neonatal mortality was examined using both individual-and aggregate-level data from 2000 to 2016 in Ethiopia. Study 2 found that the association between caesarean birth and neonatal death had changed over time. For instance, the adjusted prevalence ratios (aPR) for neonatal death among neonates born via caesarean section versus vaginal birth increased from 0.95 (95% CI: 0.29 to 3.19) to 2.81 (95% CI: 1.11 to 7.13) from 2000 to 2016, respectively. These differences in associations were attributable to changes in patterns of the underlying indications for caesarean intervention which may be aggravated by contextual factors such as unequal access, infrastructural, structural and health workforce constraints. The changing association between caesarean birth and neonatal death may reflect a maturing of the health system and a secular shift in the characteristics of Ethiopian women undergoing caesarean section after complicated labour or severe foetal compromise. Hence, caesarean birth in Ethiopia may not prevent neonatal deaths because the foetus has already experienced complications that mean neonatal death is difficult to prevent.

There have been a number of studies that reported on the association between caesarean section and neonatal mortality.[35-44,49-51] However, a review of the literature revealed that these previous studies relied on reporting only the magnitude and direction of the association between caesarean section and neonatal mortality and did not provide an interpretation of the associations by considering contextual factors such as unequal access, infrastructural, structural and health workforce constraints that could play a role in the association between caesarean section and neonatal mortality. As detailed in Chapter 5, Study 2 was guided by the 'Three Delays Model' to facilitate the interpretation of the association between caesarean section and neonatal mortality by considering these contextual factors in Ethiopia. It is clear that in addition to reporting the magnitude of associations, the ability to provide an interpretation of what the associations mean using the 'Three Delays Model' constitutes a major advance in the literature. This is because Study 2 was the first study to examine the temporal association between caesarean birth and neonatal mortality as well as to interpret the association between caesarean birth and neonatal mortality both empirically and theoretically.

Caesarean section and breastfeeding in sub-Saharan Africa

In Study 3, it was found that the within-country aPR for early initiation of breastfeeding and exclusive breastfeeding under 6 months was variable across the 33 countries in sub-Saharan Africa, but not for children ever breastfed. Furthermore, as detailed in Chapter 6, the meta-analyses, which summarised the magnitude of these within-country effect estimates (aPR), showed that caesarean section was associated with a 46% reduction in the prevalence of early initiation of breastfeeding, while there was little difference in exclusive breastfeeding under 6 months, and for children ever breastfed.

Unlike other studies that investigated the relationship between caesarean section and breastfeeding, Study 3 is unique in a number of ways. First, it utilised standard definitions of breastfeeding outcomes recommended by agencies such as the WHO. Second, it utilised high-quality nationally representative data collected using standardised methodology and identical core questionnaire in large number of countries (33 countries) in sub-Saharan Africa over a long time period (2010-2017/2018). Third, it employed similar analytical methodology, in which adjustment for similar potential confounders for each of the 33 countries was made, for three different breastfeeding outcomes (early initiation of breastfeeding, exclusive breastfeeding under 6 months and children ever breastfed). Finally, the study summarised the magnitudes of the 33 within-country effects for the three breastfeeding outcomes in an overall estimate using random-effects meta-analysis. Given these, Study 3 provides high-quality public health evidence regarding the link between caesarean section and breastfeeding indicators from the perspective of LMICs in sub-Saharan Africa.

Apgar scores and children’s educational outcomes

In Study 4, as each value of the Apgar score may indicate different physiological conditions, it was aimed at examining the associations between one- and five-minute Apgar scores of 0-5, 6, 7, 8 and 9 (compared with 10) and children's educational outcomes at eight years of age. As detailed in Chapter 7, Study 4 found that children with five-minute Apgar scores of 0-5 and 6, compared with children with Apgar score of 10, were at higher risk of scoring at/below the NMS on NAPLAN assessments at eight years of age. However, the potential mechanisms by which Apgar scores of below 6 could affect children's educational outcomes remain unclear. One possible explanation is that low Apgar scores may co-occur with markers of hypoxia and hypoxic–ischemic encephalopathy,[172] and prenatal diseases, including the effects of gene polymorphisms and these may predispose to poor cognitive function in later life.[170] Another possibility is that mild prolonged partial hypoxic injury to the brain at birth may cause low Apgar scores that may be sufficient to cause neuronal damage and affect cognition at later age.[170]

An important contribution of Study 4 to the ongoing scientific discourse is that it investigated the link between a range of Apgar score values (i.e., Apgar score of 0-5, 6, 7, 8 and 9 (compared with 10)) and children's educational outcomes at eight years of age. It has been suggested that Apgar score could perform better when it is used as a quasi-continuous measure rather than the use of Apgar scores by grouping at familiar cut-points (<7 or <4) for research purposes. For example, Bovbjerg *et al.* in their 2019 study conducted to determine the optimal cut-point for five-minute Apgar score concluded that 'a dichotomized [dichotomised] Apgar score is not an effective proxy outcome for research purposes.'[163] This is because the false-positive and false-negative rates were found to be above the required levels of accuracy. Moreover, a 2020 commentary by Frey[197] suggests that an Apgar score of

7-10 may not be considered as ‘normal’ and suggested that anything less than a perfect Apgar score of 10 may be a cause for concern.

Labour induction versus expectant management and children’s educational outcomes

Study 5 aimed at estimating the effect of elective induction of labour at 39 weeks of gestation on children’s educational outcomes as measured by NAPLAN tests at age eight years, compared with expectant management. A good deal is already known about the beneficial effects of induction of labour at 39 weeks of gestation as compared with expectant management on short-term perinatal outcomes, including caesarean delivery.[19-25] However, a review of literature revealed no study regarding the effect of elective induction of labour at 39 weeks of gestation versus expectant management on longer-term neurodevelopmental outcomes in children’s later life. Hence, Study 5 estimated the effect of elective induction of labour at 39 weeks of gestation as compared to expectant management on children’s educational outcomes at age eight years. This is important because a 2010 study by MacKay and colleagues[111] found that the risk of special educational need, compared to children born at 40 weeks, increased among children born from 37–39 weeks gestation.

As detailed in Chapter 8, Study 5 showed that elective induction of labour at 39 weeks of gestation compared with expectant management was not associated with the proportion of children scoring at or below the NMS on each NAPLAN domain (reading, writing, spelling, grammar and numeracy) at eight years of age. The findings of this study provide the first presentation of the effect of induction of labour at 39 weeks of gestation as compared with expectant management on children’s educational outcomes at eight years of age.

9.2 Strengths and limitations

Strengths

This thesis had several strengths. First, the thesis brings together a range of issues relevant to clinical obstetric and public health practice during labour and birth, breastfeeding, neonatal health and children's educational outcomes spanning low-, middle-, and high-income country contexts.

Second, the thesis utilised two different high-quality data sources, encompassing data from low-, middle-, and high-income country settings. The two data sources included the DHS from 33 LMICs in sub-Saharan Africa and the SAECDP from Australia (high-income country). The DHS data are among the most valid and reliable interviewer-led surveys that are representative at both local and national levels in LMICs. The DHS study design, sampling and methodology were standardised and replicable with quality assurance measures. The SAECDP is an established project that encompasses high quality whole-of-population linked administrative data from state and federal sources in South Australia. The use of these two different data sources allowed this thesis to examine the five research questions across diverse health system resource settings.

Finally, this thesis has applied the best practice approach in designing and analysing observational data to enhance causal inference. For instance, a qualitative *a priori* assumptions regarding the underlying biologic mechanisms between exposures, outcomes and potential confounders were encoded using DAGs before performing any statistical analyses. This is consistent with the best practice to identify confounding and other biases in contemporary epidemiology. Moreover, advanced statistical methods such as AIPW was used, which is consistent with the best practice using a potential outcomes approach, focused on achieving exchangeability between the exposed and unexposed, to analysing observational data.[191-193] Sensitivity analyses via negative control outcome were also conducted to examine the potential for residual confounding.[194]

Limitations

In Chapters 4-8, the limitations of each study have been discussed. In this section, I discuss the overall limitations and potential areas for future research.

Even though two of the three studies that utilised DHS data examined the effect of caesarean section on neonatal mortality and breastfeeding, it was not possible to examine the link between caesarean section and longer-term outcomes such as neurodevelopmental outcomes. This is because the DHS did not collect data on longer-term outcomes, including children's school assessments. However, the effect of caesarean section on children's school achievement has already been conducted using the SAECDP data previously.[157] Furthermore, the effect of instrumental delivery, as a possible obstetrical intervention during childbirth, on longer-term neurodevelopmental outcome in children's later life using SAECDP data was not included in this thesis. However, this has already been examined using similar data (SAECDP) in South Australia by Hsieh *et al*.[198] in 2019.

Although this thesis has advantage of using data from two sources (DHS and SAECDP) to help examine the effect of obstetrical interventions during labour and birth on short-and long-term outcomes across diverse health system resource settings, there are some concerns regarding these data sources. For instance, the DHS data were cross-sectional surveys, which relied on face-to-face interviews by trained interviewers (data collectors). Therefore, information on obstetric interventions during labour and birth (exposures) and outcomes (e.g., breastfeeding practices) were entirely dependent up on retrospective maternal reports and this may be subject to response bias, incomplete and inconsistent reporting. However, in order to overcome such problems, 'The DHS Program' performs extensive data editing operations, including imputation of incomplete dates of events (e.g., date of birth of each child and date of birth of the mother).[199] Moreover, prior to the implementation of the DHS, the survey questionnaires were pretested in both urban and rural clusters in each country. The results of the pilot survey were used to modify the survey questionnaire by the DHS implementing agencies.

Unlike the DHS data, the SAECDP data, which were collected on the entire population in South Australia, contain information on longer-term outcomes (e.g., ~8-year-old children's school assessments data). However, as the SAECDP data were collected by government departments largely for government purposes, it lacks the nuances of self-report and may not contain data on topics that the DHS usually collect. The combined use of the household-based surveys and linked administrative government database in this thesis, however, could be considered as a better approach to capture the available data in public health research because the limitations and advantages of these data sources may balance each other.

As it was highlighted in Study 1, caesarean section rate was defined as the number of caesarean births over the total number of live births expressed as a percentage, by adopting the definition used in the existing literature.[45] However, it has been suggested that a better measure of caesarean section rate is when it includes the proportion of all births, including stillbirths.[5] As such data were not available for present research, it would be important to include this when defining caesarean section rate in future research. In Study 2, the interpretation of the association between caesarean birth and neonatal mortality was provided in view of contextual factors in Ethiopia using the ‘Three Delays Model’. However, this interpretation may not reflect the context of other LMICs because the base rate of caesarean delivery is very low in Ethiopia. Thus, it would be important to explore the association between caesarean birth and neonatal mortality within the context of other LMICs in Africa or elsewhere in future research. In Study 3, delayed initiation of breastfeeding following caesarean birth was found using DHS data from 33 countries in sub-Saharan Africa. However, as it is difficult to distinguish whether the caesarean section was medically indicated or not from the DHS data, it would be useful to study in future whether delayed initiation of breastfeeding occurs in non-medically indicated caesarean births. This is important because adverse health outcomes related to non-medically indicated caesarean births could be addressed in institutional settings. Studies 4 and 5 have examined the effects of obstetrical interventions (Apgar score and elective labour induction) using data from high-income country context. Further research is required to add to knowledge about the effect of obstetrical interventions, more specifically Apgar score and labour induction, on neurodevelopmental outcomes in children’s later life in LMICs in sub-Saharan Africa, where there is no evidence.

9.3 Implications

This thesis has a number of implications. First, the findings of each study in this thesis add to a growing body of evidence regarding the effect of obstetrical interventions during labour and birth on short- and long-term outcomes. This is important from clinical medicine and public health perspectives because it has documented the effects of obstetrical interventions during labour and birth on breastfeeding, neonatal mortality and children’s educational outcomes across diverse health system resource settings.

Second, the application of the 'Three Delays Model' in Study 2 to understand and interpret the increased risk of neonatal mortality following caesarean birth within the context of Ethiopia may guide investments in health services and help provide context-specific interventions. For instance, in resource constrained areas, neonatal mortality can be reduced by increasing timely access to caesarean section and timely decisions for caesarean delivery via increasing health service coverage, improving infrastructure, increasing the number of skilled birth attendants, improving quality of care and increasing awareness about the importance of antenatal care and health facility delivery among women.

Third, given the increase in rate of caesarean section continues to be a major public health concern, evidence regarding the links between caesarean section and both short- and long-term outcomes would be relevant to inform public health policy for intervention. For instance, in Study 3, it was found that caesarean section has a negative influence on early initiation of breastfeeding in 33 sub-Saharan African countries. Interventions that help support and promote early initiation of breastfeeding such as immediate or early skin-to-skin contact, parent education, and hand expression of breast milk (to establish and maintain adequate milk supply) would be important.[200] Moreover, in Study 4, it was found that children with five-minute Apgar scores of 0–5 and 6, compared with Apgar score of 10, are at higher risk of scoring at/below the NMS on the NAPLAN assessments at eight years. These findings could be translated into real-world impacts and could be applied in each nation's context. For example, a more immediate intensive follow-up of babies born with Apgar scores below 6, and educational support at school age would be important to improve children's health and neurodevelopment.

Finally, this thesis suggests some implications for future research. For instance, in Study 1, the disproportionately increased use of caesarean section among richest and urban women in Ethiopia were found. Thus, further work is needed to understand why caesarean section is increasingly used among wealthier and urban women in low-income countries, especially in sub-Saharan Africa to provide a more concrete basis for interventions towards appropriate use of caesarean section for the benefit of mothers and their babies.

9.4 Concluding remarks

The findings from this thesis present a comprehensive analyses of the effect of obstetrical interventions during labour and birth on breastfeeding, neonatal mortality and children's educational outcomes at eight years of age by utilising data from low-, middle-, and high-income countries. The findings of Study 1 highlighted that there were large disparities in caesarean section use in Ethiopia, demonstrating unequal access. The results from Studies 2, 3 and 4 suggest that obstetrical interventions during labour and birth (caesarean section and Apgar score) have an influence on neonatal mortality, breastfeeding and children's educational outcomes at later age. However, the findings of Study 5 suggest that elective induction of labour at 39 weeks of gestation as compared with expectant management did not affect children's educational outcomes at eight years of age.

Appendices

Appendix A: Online Supplementary Material for Study 1

Appendix A contains the published version of the online supplementary material for Study 1:

Yisma E, Smithers LG, Lynch JW, Mol BW. Cesarean section in Ethiopia: prevalence and sociodemographic characteristics. *J Matern Fetal Neonatal Med 2019*; **32**(7): 1130-1135.

Table 4a. Log-Poisson regression analysis showing prevalence ratios for caesarean section in relation to sociodemographic characteristics using Ethiopia DHS 2011

	Unadjusted PR (95% CI) (N=1,571)	Adjusted PR[a] (95% CI) (N=1,571)
Types of residence		
Urban	1	1
Rural	0.74 (0.47, 1.19)	0.97 (0.53, 1.77)
Region		
Tigray	1	1
Afar	1.19 (0.69, 2.07)	1.23 (0.68, 2.23)
Amhara	0.50 (0.23, 1.08)	0.49 (0.23, 1.04)
Oromia	0.26 (0.12, 0.56)	0.26 (0.12, 0.56)
Somali	0.36 (0.14, 0.91)	0.5 (0.20, 1.28)
Benishangul-Gumuz	0.57 (0.28, 1.16)	0.58 (0.28, 1.21)
SNNP	0.79 (0.44, 1.40)	0.75 (0.42, 1.33)
Gambela	1.27 (0.81, 1.99)	1.52 (0.91, 2.53)
Harari	0.87 (0.55, 1.36)	0.90 (0.56, 1.43)
Addis Ababa	1.06 (0.72, 1.55)	0.95 (0.61, 1.49)
Dire Dawa	0.62 (0.39, 0.99)	0.69 (0.42, 1.12)
Mother's age at birth		
<20	1	
20-34	1.11 (0.63, 1.95)	1.45 (0.80, 2.61)
35-49	1.49 (0.61, 3.64)	2.69 (1.07, 6.75)
Mother's education		
No education	1	1
Primary	1.83 (1.00, 3.34)	1.68 (0.88, 3.20)
Secondary	2.35 (1.27, 4.35)	1.91 (1.00, 3.63)
Higher	2.03 (1.03, 4.00)	1.81 (0.86, 3.79)
Place of delivery		
Public	1	1
Private	1.42 (0.90, 2.26)	1.18 (0.82, 1.71)
Birth order		
1	1	1
2-3	0.59 (0.39, 0.88)	0.59 (0.38, 0.90)
4+	0.57 (0.29, 1.13)	0.60 (0.28, 1.27)
Sex of child		
Male	1	1
Female	(0.52, 1.19)	(0.57, 1.29)
Wealth quantile		
Poorest	1	
Poorer	2.62 (0.83, 8.29)	3.18 (0.97, 10.41)

Middle	3.17 (1.19, 8.46)	3.67 (1.44, 9.34)
Richer	1.12 (0.38, 3.28)	1.36 (0.47, 3.89)
Richest	2.47 (1.14, 5.35)	1.69 (0.73, 3.91)

Notes: In this table, it is assumed that women who did not give birth in health facility did not receive a caesarean section.

[a]Mutually adjusted.

Abbreviations: PR, prevalence ratio; CI, confidence interval.

Table 4b. Log-Poisson regression analysis showing prevalence ratios for caesarean section in relation to sociodemographic characteristics using Ethiopia DHS 2005

	Unadjusted PR (95% CI) (N=997)	Adjusted PR[a] (95% CI) (N=997)
Types of residence		
Urban	1	1
Rural	0.64 (0.40, 1.02)	0.73 (0.36, 1.48)
Region		
Tigray	1	1
Afar	1.09 (0.27, 4.34)	0.94 (0.25, 3.52)
Amhara	1.30 (0.52, 3.25)	1.10 (0.44, 2.76)
Oromia	1.20 (0.50, 2.87)	1.36 (0.55, 3.34)
Somali	1.39 (0.45, 4.30)	1.16 (0.34, 3.96)
Benishangul-Gumz	0.22 (0.03, 1.74)	0.25 (0.03, 1.88)
SNNP	1.84 (0.82, 4.15)	2.49 (1.08, 5.74)
Gambela	0.77 (0.30, 1.98)	1.15 (0.42, 3.15)
Harari	0.74 (0.32, 1.72)	0.62 (0.27, 1.45)
Addis Ababa	1.45 (0.68, 3.08)	1.05 (0.49, 2.25)
Dire Dawa	0.95 (0.41, 2.24)	0.79 (0.33, 1.89)
Mother's age at birth		
<20	1	1
20-34	1.17 (0.68, 2.03)	1.31 (0.75, 2.26)
35-49	0.89 (0.38, 2.11)	1.44 (0.56, 3.73)
Mother's education		
No education	1	1
Primary	0.64 (0.32, 1.28)	0.49 (0.24, 1.02)
Secondary	1.48 (0.91, 2.39)	0.98 (0.52, 1.85)
Higher	1.66 (0.86, 3.21)	1.24 (0.57, 2.70)
Place of delivery		
Public	1	1
Private	1.04 (0.54, 2.00)	1.13 (0.60, 2.12)
Birth order		
1	1	1

2-3	0.77 (0.51, 1.17)	0.75 (0.50, 1.13)
4+	0.52 (0.27, 0.97)	0.43 (0.21, 0.86)
Sex of child		
Male	1	1
Female	1.04 (0.70, 1.56)	0.96 (0.66, 1.40)
Wealth quantile		
Poorest	1	1
Poorer	4.87 (0.64, 36.84)	4.85 (0.62, 38.11)
Middle	1.98 (0.24, 16.28)	1.38 (0.16, 12.10)
Richer	2.53 (0.36, 17.78)	2.41 (0.33, 17.58)
Richest	4.62 (0.74, 28.75)	3.04 (0.42, 22.23)

Notes: In this table, it is assumed that women who did not give birth in health facility did not receive a caesarean section.

[a]Mutually adjusted.

Abbreviations: PR, prevalence ratio; CI, confidence interval.

Table 4c. Log-Poisson regression analysis showing prevalence ratios for caesarean section in relation to sociodemographic characteristics using Ethiopia DHS 2000.

	Unadjusted PR (95% CI) (n=1,041)	Adjusted PR[a] (95% CI) (n=1,041)
Types of residence		
Urban	1	1
Rural	0.59 (0.31, 1.14)	0.88 (0.40, 1.94)
Region		
Tigray	1	1
Afar	3.47 (1.07, 11.22)	2.63 (0.68, 10.18)
Amhara	0.31 (0.05, 1.73)	0.49 (0.07, 3.39)
Oromia	1.58 (0.48, 5.20)	1.41 (0.36, 5.45)
Somali	2.11 (0.58, 7.73)	2.54 (0.54, 11.80)
Benishangul-Gumz	2.40 (0.72, 8.01)	2.77 (0.68, 11.32)
SNNP	1.22 (0.35, 4.34)	1.53 (0.37, 6.33)
Gambela	0.69 (0.19, 2.53)	0.70 (0.16, 3.02)
Harari	1.11 (0.36, 3.39)	0.87 (0.23, 3.28)
Addis Ababa	1.02 (0.35, 2.98)	0.77 (0.21, 2.82)
Dire Dawa	0.65 (0.19, 2.18)	0.57 (0.14, 2.33)
Mother’s age at birth		
<20	1	1
20-34	0.80 (0.41, 1.58)	1.14 (0.59, 2.22)

35-49	0.18 (0.07, 0.51)	1.28 (0.35, 4.71)
Mother's education		
No education	1	1
Primary	2.31 (1.00, 5.36)	1.91 (0.93, 3.92)
Secondary	3.76 (1.78, 7.95)	2.31 (1.12, 4.76)
Higher	4.27 (1.56, 11.71)	2.63 (0.75, 9.28)
Place of delivery		
Public	1	1
Private	0.55 (0.21, 1.43)	0.56 (0.19, 1.64)
Birth order		
1	1	1
2-3	0.38 (0.20, 0.74)	0.41 (0.20, 0.84)
4+	0.09 (0.04, 0.22)	0.10 (0.04, 0.30)
Sex of child		
Male	1	1
Female	0.69 (0.42, 1.15)	0.74 (0.46, 1.19)
Wealth quantile		
Poorest	1	1
Poor	1.44 (0.15, 14.24)	2.30 (0.23, 22.54)
Middle	0.95 (0.10, 8.87)	0.61 (0.05, 7.45)
Richer	0.72 (0.08, 6.33)	0.49 (0.05, 5.05)
Richest	1.75 (0.26, 12.02)	0.95 (0.10, 8.69)

Notes: In this table, it is assumed that women who did not give birth in health facility did not receive a caesarean section.

[a]Mutually adjusted.

Abbreviations: PR, prevalence ratio; CI, confidence interval.

Appendix B: Online Supplementary Material for Study 2

Appendix B contains the published version (pdf) of the online supplementary material for Study 2:

Yisma E, Mol BW, Lynch JW, Smithers LG. The changing temporal association between caesarean birth and neonatal death in Ethiopia: secondary analysis of nationally representative surveys. *BMJ Open* 2019; 9(10):e027235.

SUPPLEMENTARY MATERIAL

This file includes supplementary analyses that complement the main findings and pictures that describe the ‘Three Delays Model’ and the Ethiopian health system structure cited in the full text of the article.

Yisma E, *et al. BMJ Open* 2019; 9:e027235. doi: 10.1136/bmjopen-2018-027235

Table A1. Crude and multivariable-adjusted prevalence ratios for neonatal death associated with 'timing of decision to conduct caesarean section' versus vaginal delivery, Ethiopian DHS, 2016

	Prevalence ratio (95%CI) for neonatal death
Unadjusted (n= 10 641)	
Vaginal delivery	1 [*Ref.*]
Caesarean section decided before onset of labour	4.21 (1.34 to 13.19)
Caesarean section decided after onset of labour	2.31 (0.84 to 6.41)
Adjusted[a] (n=10 641)	
Vaginal delivery	1 [*Ref.*]
Caesarean section decided before onset of labour	3.79 (1.03 to 13.93)
Caesarean section decided after onset of labour	2.26 (0.75 to 6.82)

[a]Adjusted for place of delivery, type of residence (urban/rural), sex of child, size of baby at birth, mother's age at birth, mother's education, birth order, household wealth.

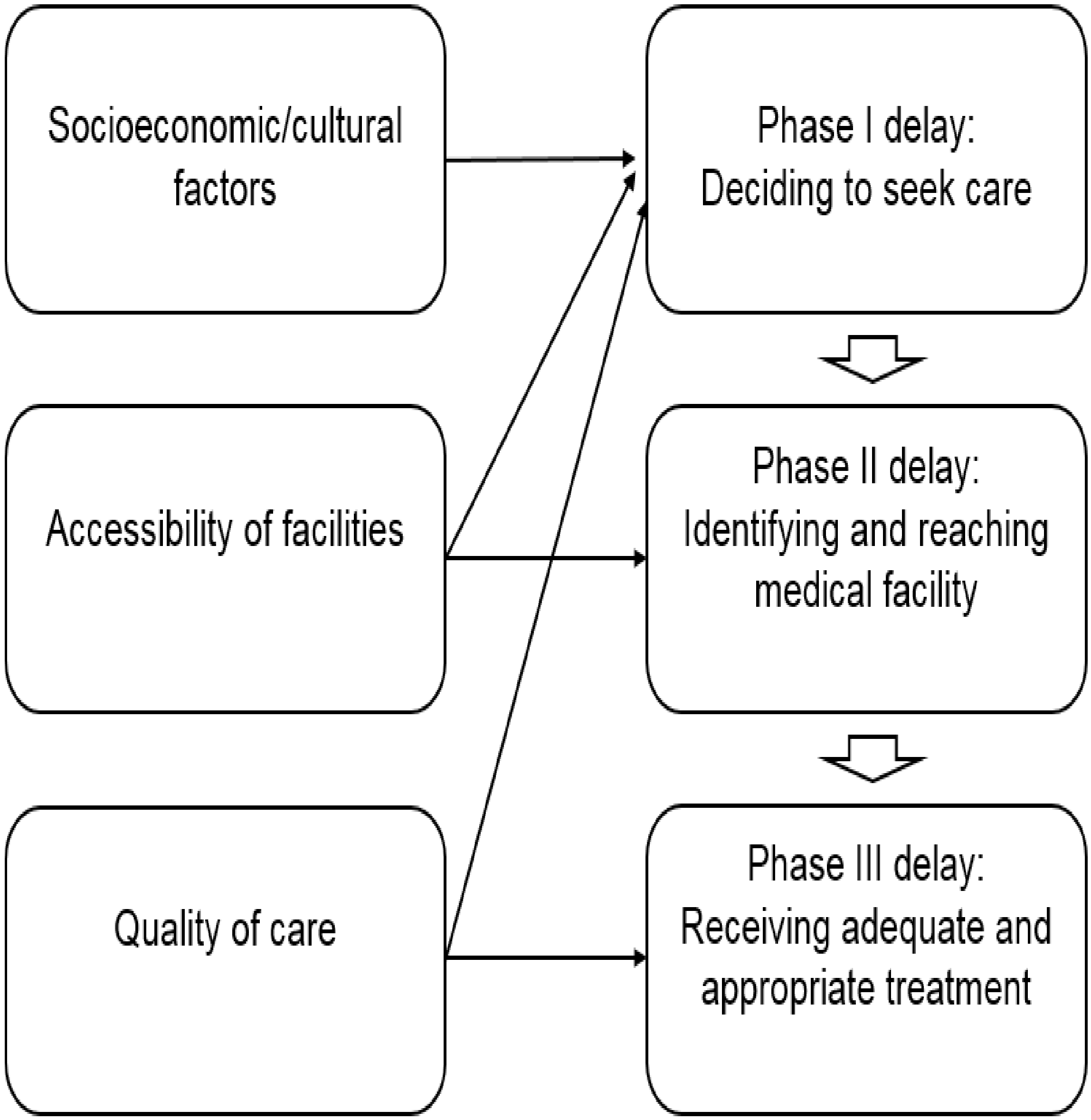
NB: 'Timing of decision to conduct caesarean section'—caesarean section that was planned before the onset of labour pains and caesarean section that was decided after the onset of labour pains—was used as a proxy to 'types of caesarean section'.

Yisma E, *et al. BMJ Open* 2019; 9:e027235. doi: 10.1136/bmjopen-2018-027235

Table A2. Trends in proportion of neonatal deaths in the 5 years before each of the surveys according to residence and region, Ethiopia DHS 2000, 2005, 2011 and 2016

	Survey year								
	2000 %	Number of births	**2005** %	Number of births	**2011** %	Number of births	**2016** %	Number of births	Absolute change %
Residence									
Urban	4.4	1 277	4.4	815	3.9	1528	3.4	1 216	-1.0
Rural	4.8	10 983	3.9	10348	3.7	10344	2.8	9 807	-2.0
Region									
Tigray	5.3	788	2.7	698	4.1	753	2.7	716	-2.6
Affar	2.9	126	2.9	107	1.9	121	2.6	114	-0.3
Amhara	4.8	3 202	5.2	2621	4.5	2656	3.2	2 072	-1.6
Oromia	5.3	4 999	3.8	4411	3.4	5014	2.8	4 851	-2.5
Somali	3.8	142	3.0	477	2.9	364	4.1	508	+0.3
Benishangul-Gumuz	6.3	124	3.8	105	4.8	140	2.9	122	-3.4
SNNPR	4.0	2 602	3.4	2500	3.5	2494	2.5	2 296	-1.5
Gambela	5.3	29	2.4	31	3.6	40	2.8	27	-2.5
Harari	3.7	25	2.2	22	4.1	29	3.1	26	-0.6
Addis Ababa	2.8	182	2.9	153	2.2	222	2.1	244	-0.7
Dire Dawa	3.7	40	2.7	37	1.6	39	3.0	47	-0.7
Total	4.8	12 260	3.9	11 163	3.7	11 872	2.9	11 023	-2.0

Yisma E, *et al. BMJ Open* 2019; 9:e027235. doi: 10.1136/bmjopen-2018-027235



Source: *Soc Sci Med*, 1994; **38**(8): 1091-110.[1]

Figure A1. The ‘Three Delays Model’

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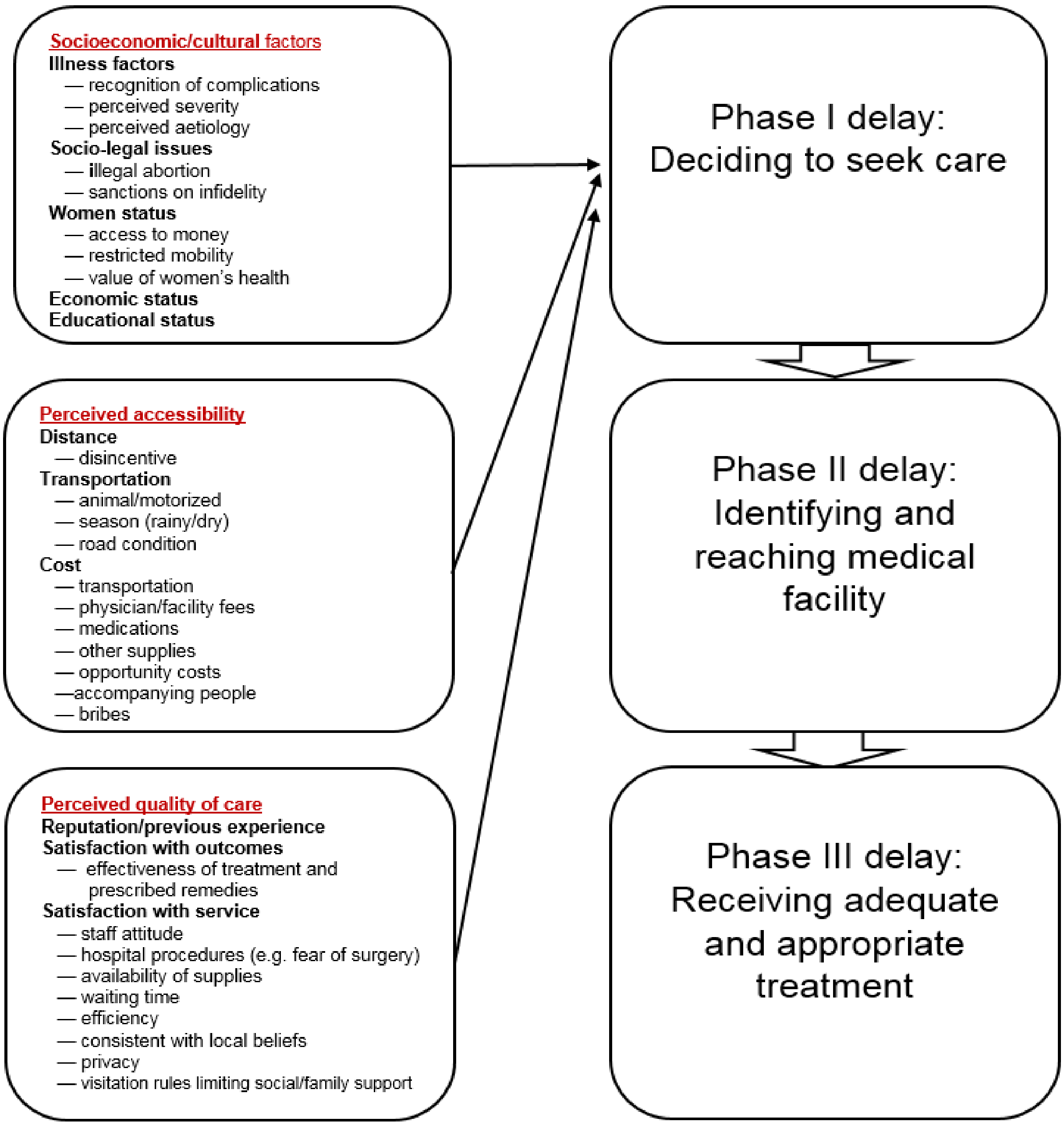

Source: Soc Sci Med, 1994; ***38****(8): 1091-110.*[1]

Figure A2. Phase I delay, detail

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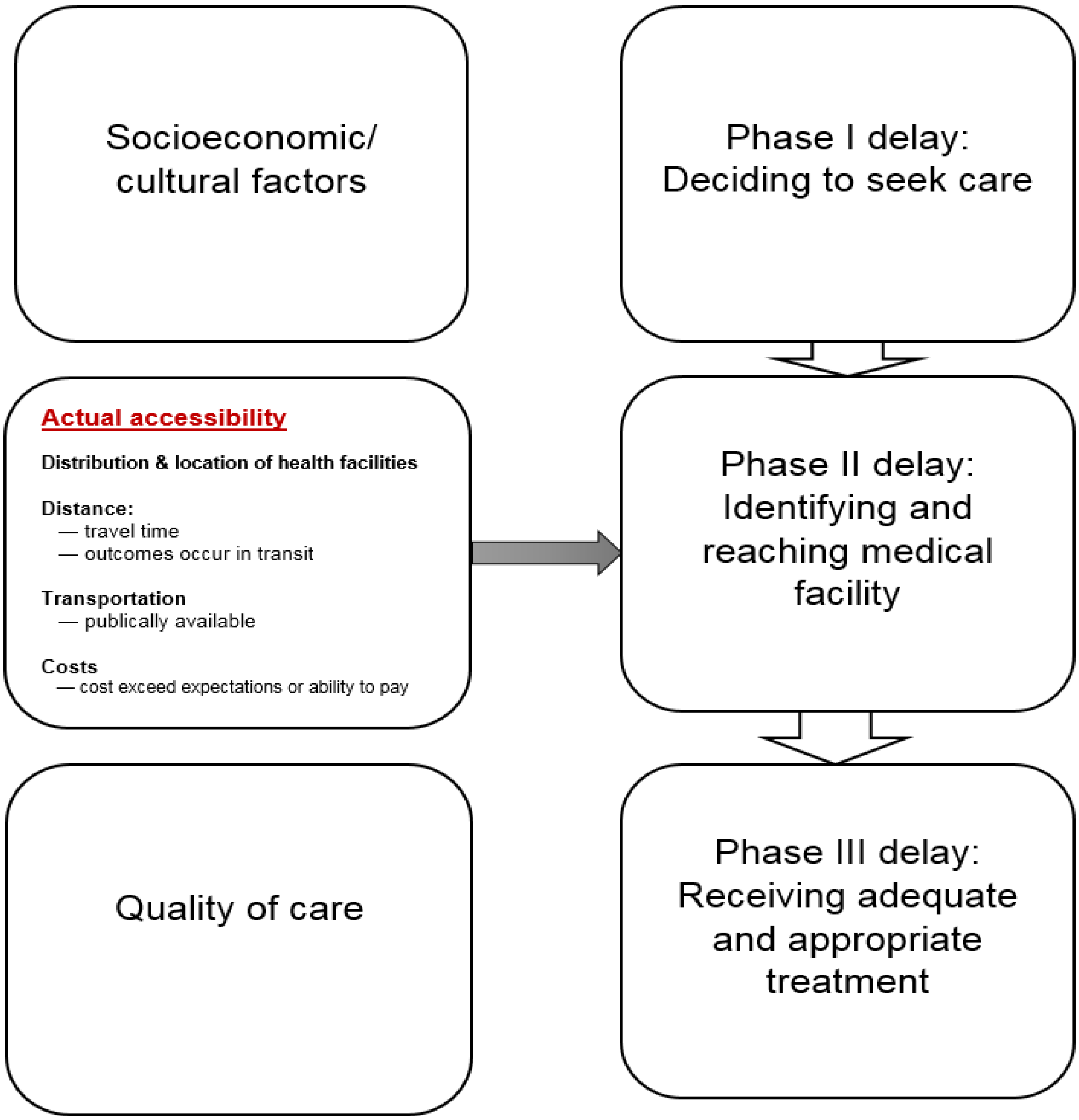
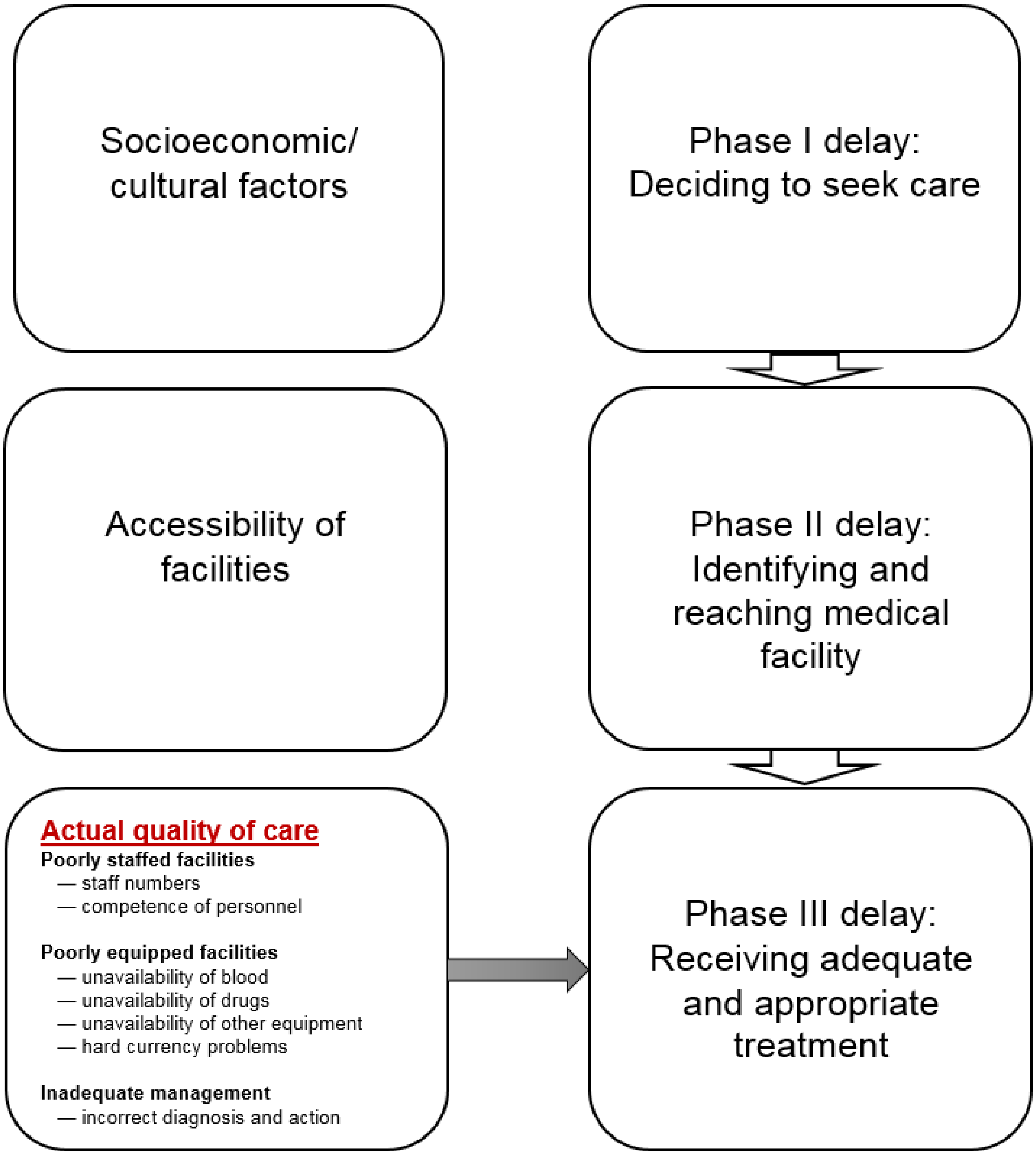


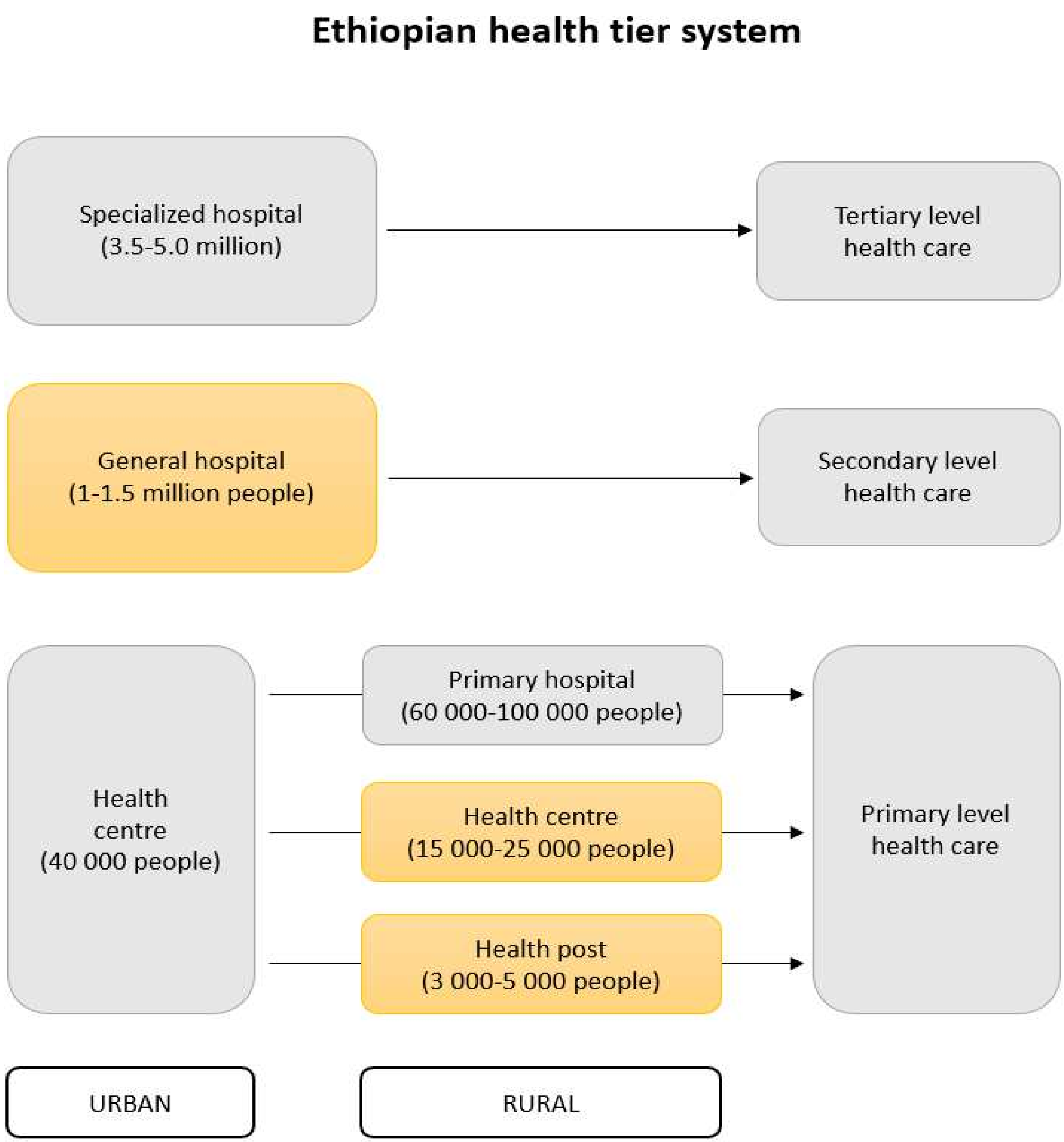
Source: *Soc Sci Med*, 1994; **38**(8): 1091-110.[1]

Figure A3. Phase II delay, detail



Source: *Soc Sci Med*, 1994; **38**(8): 1091-110.[1]

Figure A4. Phase III delay, detail



Source: Ethiopian Health Sector Transformation Plan, 2015,[2] and World Health Organization, 2017. [3]

Figure A5. Ethiopian health system structure

References

1. Thaddeus S, Maine D. Too far to walk: maternal mortality in context. *Soc Sci Med* 1994; **38**(8): 1091-110.

2. Ministry of Health. Health Sector Transformation Plan. Addis Ababa: Federal Democratic Republic of Ethiopia; 2015.

3. WHO. Primary health care systems (PRIMASYS): case study from Ethiopia, abridged version. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

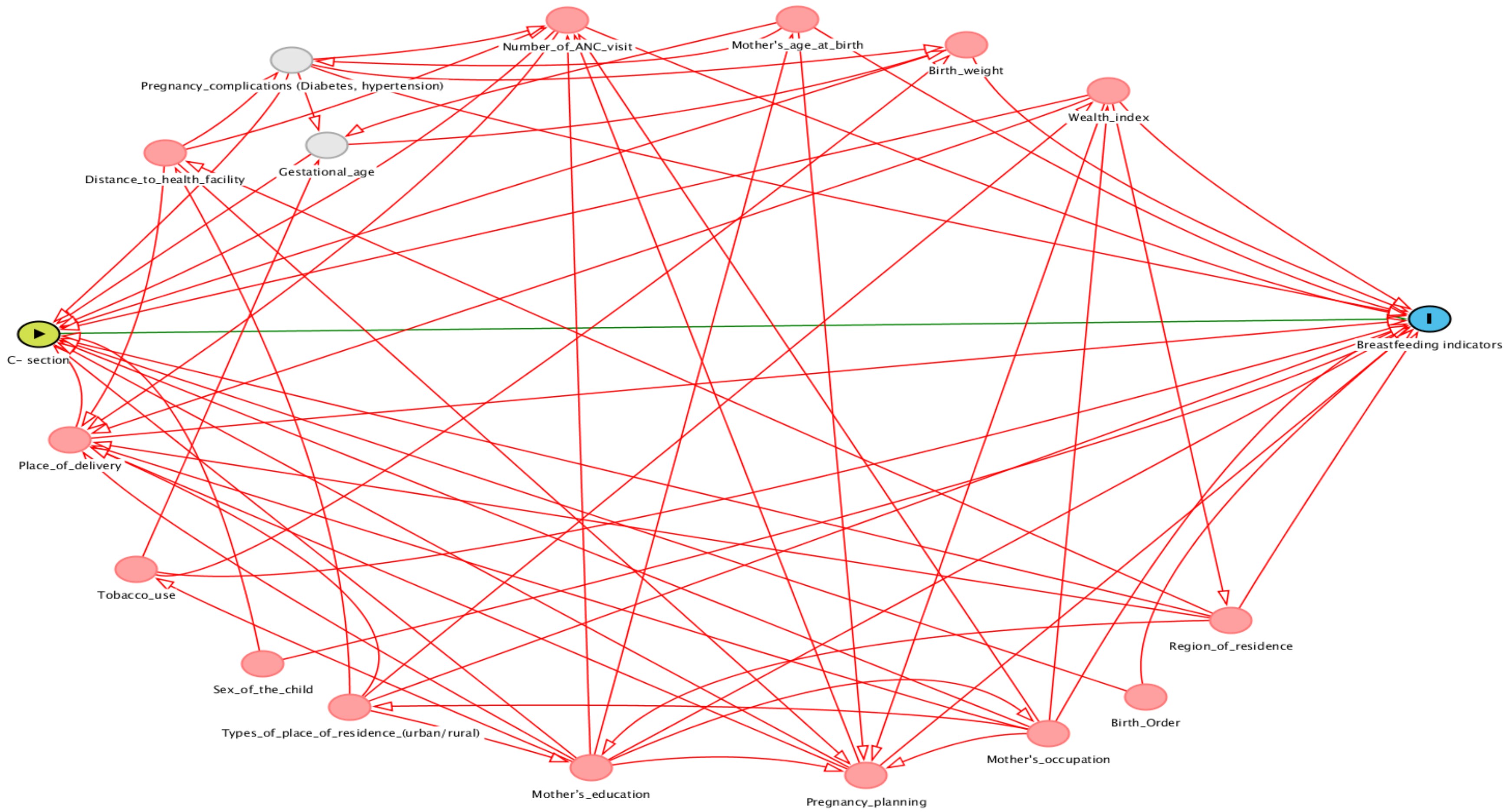
Yisma E, *et al. BMJ Open* 2019; 9:e027235. doi: 10.1136/bmjopen-2018-027235

Appendix C. Online Supplementary Material for Study 3

Appendix C contains the published version (pdf) of the online supplementary material for Study 3:

Yisma E, Mol BW, Lynch JW, Smithers LG. Impact of caesarean section on breastfeeding indicators: within-country and meta-analyses of nationally representative data from 33 countries in sub-Saharan Africa**.** *BMJ Open* 2019; **9**(9): e027497.

Web-appendix 1. Proposed Directed Acyclic Graphs (DAGs) describing the association between caesarean birth and breastfeeding



Web-appendix 2. DAGs model code

The following **DAGs code** can used to generate the proposed DAGs in this study online at [http://www.dagitty.net/.](http://www.dagitty.net/)

Birth_Order 1 @0.558,0.687

Birth_weight 1 @0.490,0.099

Breastfeeding%20indicators O @0.677,0.369

C-%20section E @0.135,0.342

Distance_to_health_facility 1 @0.187,0.197

Gestational_age U @0.248,0.190

Mother%E2%80%99s_education 1 @0.348,0.751

Mother's_age_at_birth 1 @0.426,0.076

Mother's_occupation 1 @0.521,0.720

Number_of_ANC_visit 1 @0.339,0.077

Place_of_delivery 1 @0.151,0.455

Pregnancy_complications%20(Diabetes%2C%20hypertension) U @0.235,0.113

Pregnancy_planning 1 @0.452,0.758

Region_of_residence 1 @0.590,0.618

Sex_of_the_child 1 @0.224,0.657

Tobacco_use 1 @0.176,0.572

Types_of_place_of_residence_(urban%2Frural) 1 @0.257,0.696

Wealth_index 1 @0.544,0.141

Birth_Order Breastfeeding%20indicators @0.548,0.572 C-%20section

Birth_weight Breastfeeding%20indicators @0.511,0.205 C-%20section

C-%20section Breastfeeding%20indicators @0.667,0.361

Distance_to_health_facility Number_of_ANC_visit @0.251,0.161 Place_of_delivery @0.183,0.353 Pregnancy_complications%20(Diabetes%2C%20hypertension) @0.211,0.169 Pregnancy_planning

Gestational_age Birth_weight @0.389,0.174 C-%20section

Mother%E2%80%99s_education Breastfeeding%20indicators C-%20section Mother's_age_at_birth Mother's_occupation @0.475,0.620 Number_of_ANC_visit Place_of_delivery @0.177,0.528 Pregnancy_planning @0.404,0.732 Tobacco_use @0.208,0.612

Mother's_age_at_birth Breastfeeding%20indicators @0.581,0.298 Gestational_age @0.270,0.161 Pregnancy_complications%20(Diabetes%2C%20hypertension) @0.393,0.130 Pregnancy_planning

Mother's_occupation Breastfeeding%20indicators @0.595,0.409 C-%20section Number_of_ANC_visit Place_of_delivery @0.473,0.694 Pregnancy_planning @0.490,0.720 Types_of_place_of_residence_(urban%2Frural) @0.461,0.690 Wealth_index

Yisma E, *et al. BMJ Open* 2019; 9:e027497. doi: 10.1136/bmjopen-2018-027497

Number_of_ANC_visit Breastfeeding%20indicators @0.584,0.316 C-%20section @0.269,0.235 Place_of_delivery @0.296,0.228

Place_of_delivery Breastfeeding%20indicators C-%20section @0.160,0.403

Pregnancy_complications%20(Diabetes%2C%20hypertension) Birth_weight @0.302,0.151 Breastfeeding%20indicators @0.315,0.182 C-%20section @0.229,0.168 Gestational_age Number_of_ANC_visit @0.303,0.103

Pregnancy_planning Breastfeeding%20indicators C-%20section Number_of_ANC_visit Place_of_delivery

Region_of_residence Breastfeeding%20indicators @0.612,0.533 C-%20section Distance_to_health_facility Mother%E2%80%99s_education @0.385,0.628 Place_of_delivery

Sex_of_the_child Breastfeeding%20indicators @0.567,0.461 C-%20section @0.198,0.372

Tobacco_use Birth_weight @0.220,0.603 Breastfeeding%20indicators @0.270,0.609 Gestational_age

Types_of_place_of_residence_(urban%2Frural) Breastfeeding%20indicators Distance_to_health_facility @0.257,0.485 Mother%E2%80%99s_education @0.300,0.718 Place_of_delivery @0.294,0.602 Wealth_index

Wealth_index Breastfeeding%20indicators @0.572,0.218 C-%20section Place_of_delivery @0.519,0.167 Pregnancy_planning Region_of_residence

Sex_of_the_child Breastfeeding @0.635,0.256 C-%20section @0.198,0.372

Tobacco_use Birth_weight @0.220,0.603 Breastfeeding Gestational_age

Wealth_index Breastfeeding C-%20section Place_of_delivery Pregnancy_planning Region_of_residence

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Web-appendix 3. Description of variables in Directed Acyclic Graphs (DAGs)—*a priori*

Pregnancy planning---- Women who are planning to conceive often take antenatal care and more likely to undergo C-section if pregnancy complication occurs. Besides, they may take better care of themselves and their newborns, which in turn may affect breastfeeding practice.

Birth order--- C-section rates are higher among the first births and breastfeeding practice is low among first births. Breastfeeding practice is high among second or more births because of previous infant feeding experiences among mothers.

Tobacco use--- Previous studies found that smokers are less likely to begin or persist with breastfeeding compared to non-smokers. Moreover, due to the greater dose of nicotine that will be delivered to the newborn through the breastmilk, the infant will spent less time in active sleep.[1] Tobacco smoking will also affect caesarean section mediated through birth weight and gestational age.

Place of delivery--- Antenatal care and place of delivery may contribute to mother's breastfeeding practice. Interventions about breastfeeding through health education will promote breastfeeding practice. On the hand, caesarean birth rates are higher in private health institutions than other health facilities.[2]

Number of antenatal care visits---Previous studies have demonstrated that antenatal care has an effect on women's breastfeeding practices. Women who had the recommended antenatal care visits during pregnancy might know signs of pregnancy complication and this may, in turn, affect caesarean section.

Mother's education--- Educated mothers are more likely to practice breastfeeding[3] and also to undergo caesarean section if obstetric complications occur. On the other hand, previous studies showed that caesarean births are higher among educated women.

Region of residence---Both exposure (caesarean section) and outcome (breastfeeding indicators) may display geographic variations mediated through sociodemographic, socioeconomic, behavioural, ethnic, cultural, and other factors.

Sex of child--- Due to sex preferences, women may more likely undergo caesarean section to save the life of the newborn when pregnancy complication occurs. It has been shown that sex of child impacts breastfeeding as a result of different factors including, sex preference, and cultural beliefs surrounding gender.

Household wealth --- Both exposure and outcome may display household wealth variations not only directly but also mediated through other factors such as place of childbirth.

Birth weight--- Birth weight affects caesarean section rates. It is highly recommended that low birth weight infants should be put to the breast as soon as possible after birth and should be exclusively breastfed until six months of life. Birth weight is also affected by gestational age, pregnancy complications and maternal tobacco use.

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Mother's age at birth---is a risk factor for some caesarean births, maternal age may also affect breastfeeding practice. For example, despite inconsistent findings, some studies found that early cessation of breastfeeding was common among younger mothers and another study concluded primiparous mothers in late child-bearing aged 35 years or older are at the greatest risk of exclusive breastfeeding.[4]

Pregnancy complications (Gestational diabetes mellitus, all types of hypertension in pregnancy and others) ----Because of both exposure and outcome may display variations based on factors related to pregnancy complications directly or mediated through other factors like birth weight and gestational age, it can be assumed that these factors are important confounders of the association between caesarean section and breastfeeding.

Gestational age---It has been demonstrated that caesarean sections are usually performed at early term "37-39" and infants born at these period have lower odds of being breastfed compared to infants born after 40 weeks gestation.

Distance to health facility---Long distance to health facilities may delay access to emergency caesarean section and may also aggravate the obstetric complication encountered by mothers leading to bad outcome. On the other hand, severe obstetric complications may prevent mother from breastfeeding and healthcare providers should provide breastfeeding support (e.g., how to express breastmilk in order to initiate and maintain breastfeeding) to establish and maintain breastfeeding. Distance to health facility also affects number antenatal care visits, place of delivery, and pregnancy planning (because access to health services is limited for women who live far away from health facilities).

Web-appendix 4. Description of how variables in the current study are defined

Exposure

Delivery by caesarean section: Whether the singleton last born child was born by caesarean section.

Outcome

Breastfeeding indicators:-

(1) **Early initiation of breastfeeding:** Proportion of children born in the past 2 years before the survey who were put to the breast within one hour of birth. "This indicator is based on historic recall and the numerator and denominator include both living and deceased children who were born within the past 2 years."[5]

(2) **Exclusive breastfeeding under 6 months**: Proportion of infants 0–5 months of age who are fed exclusively with breast milk. DHS use this definition to calculate exclusive breastfeeding under 6 months and the numerator in the calculation of 'exclusive breastfeeding under 6 months' involves "infants 0–5 months of age who received only breast milk during the previous day while the denominator is total number of 'infants 0–5 months of age'. This indicator is based on 'recall of the previous day' and includes living infants who are residing with mothers.[5]

(3) **Children ever breastfed**: Proportion of children born in the last two years who reported to have been breastfed. "This indicator is based on historic recall. The numerator and denominator include both living and deceased children who were born within the past 2 years before the survey."[5]

Variables used to eliminate or minimize confounding

Wealth quintiles: It was derived from an index (generated through principal component analysis) based on ownership of a range of assets (e.g., car, refrigerator and television), housing characteristics (e.g., material of dwelling floor and roof and main cooking fuel) and access to basic services (e.g., electricity supply, source of drinking water and sanitation facilities), etc. depending on the specific questions asked in each country. The index was standardized to a mean of 0 and a standard deviation of 1 and higher scores refer to greater wealth. DHS categorizes household wealth index into 'wealth quintiles'.

Number of antenatal visits: Women were asked whether they had received antenatal consultation from a health professional (doctor, nurse, or midwife) during the prenatal period. They were also asked the total number of antenatal visits during pregnancy. The variable used in this study reflects the number of visits reported by women who had received at least one antenatal consultation from a health professional. If women received antenatal care from a non-health professional, it was coded as zero in the 'number of antenatal visits' variable.

Birth order: The order in which a child was born.

Birth weight: All DHS in low-and middle-income countries collect information on baby's size at birth based on mother's perception by asking question, "was the newborn very large, larger than average, average, smaller than average or very small?" This is because the majority of births in these countries occur at home and birth weight is not available to be included. Previous studies conducted using DHS in low-and middle-income countries have shown that about 75% mothers are able to correctly report baby size at birth.[6-9] In reference to these studies and due to lack of information on actual birthweight data, we used mother's recall of baby's size at birth as 'proxy to birth weight'.[10] We then computed a categorical variable "low birth weight" (very small or smaller than average) and 'normal birth weight' (average, larger than average, very large).

Mother's education: Mother's highest education level attended which is standardized and categorized as: No education, Primary, Secondary, and Higher for each country in low-and middle-income countries.

Mother's occupation: The standardized mother's occupation groups (with some country-specific variations) include: professional, technical and managerial; clerical; sales or services; skilled manual; unskilled manual; household domestic; agricultural— own land; agricultural—family land; agricultural— rented land; agricultural—other; or other.

Distance to health facility: DHS collect information regarding problems faced by women of reproductive age (15-49 years) in accessing health care to obtain medical advice or treatment for themselves when they are sick were gathered. It consisted of four questions: distance to health facility (big problem/not big problem); getting money for treatment (big problem/not big problem); getting permission to go for treatment (big problem/not big problem); and not wanting to go alone (big problem/not big problem). Thus, we have used distance to health facility (big problem/not big problem) as a proxy to 'actual distance' in this study.

Other variables include: Pregnancy planning (yes/no), region of residence (categories include country-specific administrative areas/regions/provinces), sex of child (male/female), mother's age at birth (in years), maternal tobacco use (yes/no), place of delivery (public sector, private sector, home, and other), and types of residence (urban/rural).

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Web-appendix 5. Sample STATA code from Kenya DHS 2014 to generate 'exclusive breastfeeding under 6 months' variable.

Sample: Live singleton last-born children in the past 2 years and living with their mothers

```
* age in months (age)
gen age = v008-b3
* drop if too old or not alive
keep if age<24 & b5==1

* recode age into groups
recode age (0/1=1 "0-1")(2/3=2 "2-3")(4/5=3 "4-5")(6/8=4 "6-8")(9/11=5 "9-11")(12/17=6 "12-17")(18/23=7
"18-23")(24/59=.), gen(child_age)

* tab all living children born in the last 2 years
tab child_age
tab child_age [iw=v005/1000000]

* keep only those children living with mother
keep if b9==0

* ... and keep the last born of those
drop if _n > 0 & caseid == caseid[_n-1]

* check the denominator
tab child_age
tab child_age [iw=v005/1000000]

* Breastfeeding status
gen water=0
gen liquids=0
gen milk=0
gen solids=0
gen breast=0

* Water
replace water=1 if (v409>=1 & v409<=7)

* Other non-milk liquids
replace liquids=1 if v410>=1 & v410<=7
replace liquids=1 if v412c>=1 & v412c<=7
replace liquids=1 if v413>=1 & v413<=7

* Powdered or tinned milk, formula, fresh milk
replace milk=1 if v411>=1 & v411<=7
replace milk=1 if v411a>=1 & v411a<=7

* Solid food
replace solids=1 if v412a>=1 & v412a<=7
replace solids=1  if v414e>=1 & v414e<=7
replace solids=1 if v414f>=1 & v414f<=7
replace solids=1 if v414g>=1 & v414g<=7
replace solids=1 if v414h>=1 & v414h<=7
replace solids=1 if v414i>=1 & v414i<=7
replace solids=1 if v414j>=1 & v414j<=7
replace solids=1 if v414k>=1 & v414k<=7
replace solids=1 if v414l>=1 & v414l<=7
replace solids=1 if v414m>=1 & v414m<=7
replace solids=1 if v414n>=1 & v414n<=7
```


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```
replace solids=1 if v414o>=1 & v414o<=7
replace solids=1 if v414p>=1 & v414p<=7
replace solids=1 if v414s>=1 & v414s<=7
replace solids=1 if v414v>=1 & v414v<=7

* Still breastfeeding
replace breast=1 if m4==95
tab1 water liquids milk solids breast

* Compute column variables used in DHS final reports
gen feeding=1
replace feeding=2 if water==1
replace feeding=3 if liquids==1
replace feeding=4 if milk==1
replace feeding=5 if solids==1
replace feeding=0 if breast==0
tab feeding,m

label define feeding 0 "Not breastfeeding" 1 "Exclusive breastfeeding" 2 "+Water" 3 "+Liquids" 4 "+Other
Milk" 5 "+Solids"
label val feeding feeding

tab child_age feeding [iweight=v005/1000000], row

*Compute ‘exclusive breastfeeding under 6 months’ (exfeeding) variable
gen exfeeding=.
replace exfeeding=1 if age<6 & feeding==1
replace exfeeding=0 if age<6 & feeding!=1
label define exfeeding 1 "Exclusive breastfeeding" 0 "no exclusive breastfeeding"
label val exfeeding exfeeding
lab var exfeeding "Exclusive breastfeeding under 6 months"
```


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Web-appendix 6, Figures A-C. Subgroup analyses for the association between caesarean section and early initiation of breastfeeding in sub-Saharan Africa

We have conducted subgroup random-effects meta-analyses to explore potential sources of heterogeneity in the association between caesarean section and early initiation of breastfeeding in sub-Saharan Africa. For this purpose, we have defined the following subgroups *a priori*: (1) categorising the countries by region (according to United Nations geoscheme); (2) by rate of caesarean section categories (<5%, 5-15%, and >15%)[11]; and (3) by prevalence of early initiation of breastfeeding categories (≤50% and >50%). Although we have conducted the subgroup analyses, the source/s of the heterogeneity remains unclear. The forest plots from our subgroup investigations are displayed in **Figures A-C**.

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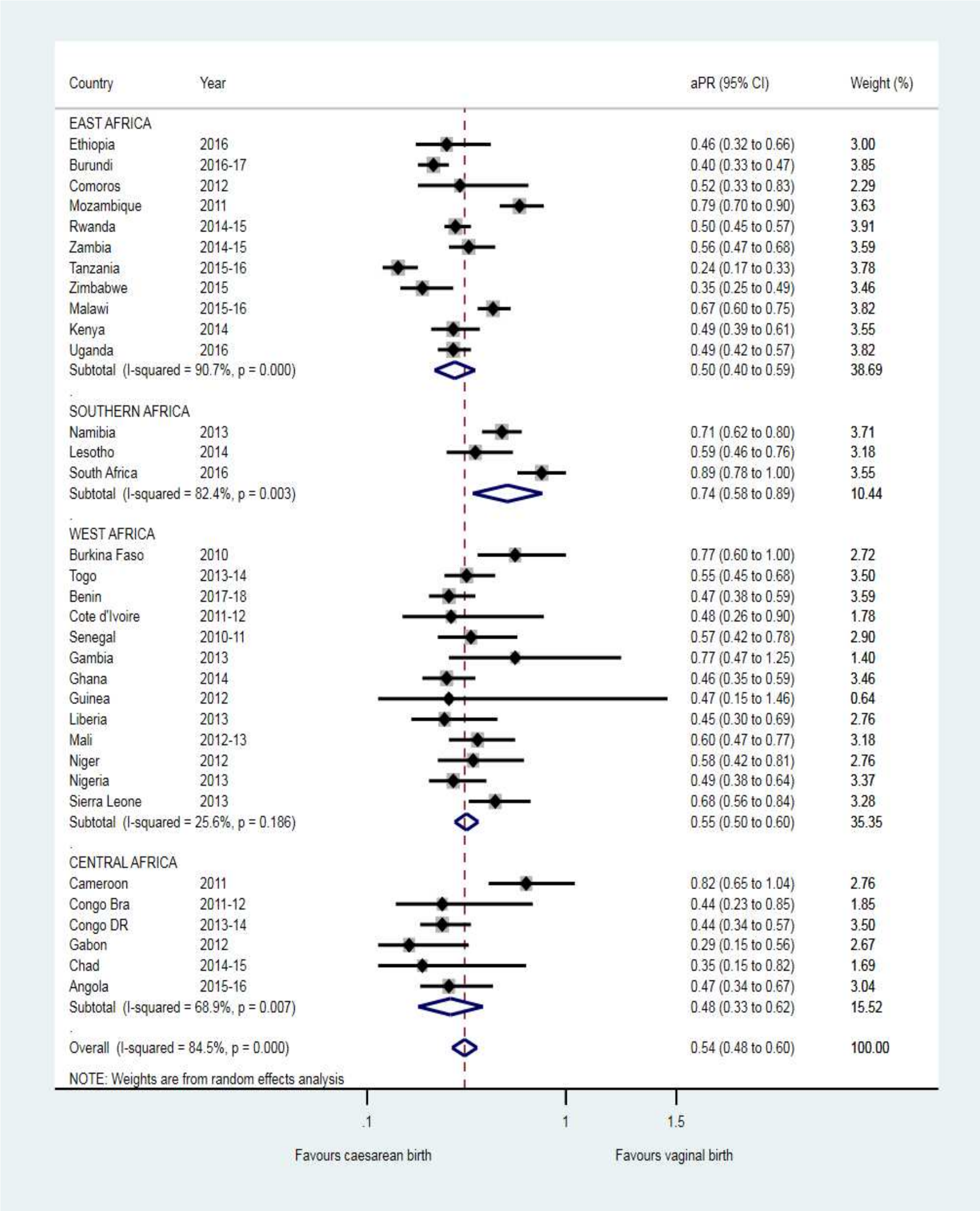

Figure A. Subgroup analyses for the association between caesarean section and early initiation of breastfeeding in sub-Saharan Africa stratified by geographic regions

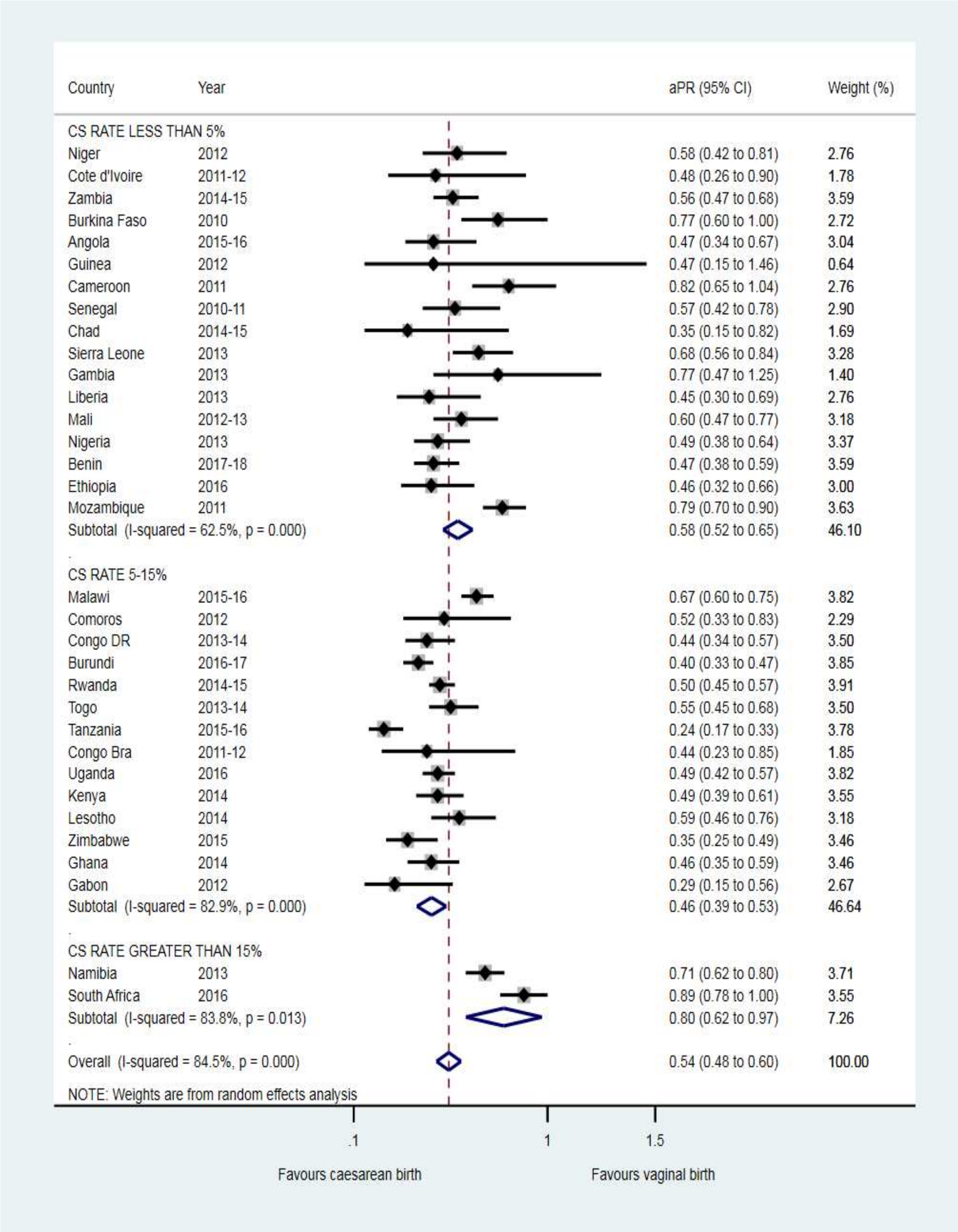

Figure B. Subgroup analyses for the association between caesarean section and early initiation of breastfeeding in sub-Saharan Africa stratified by caesarean section rates

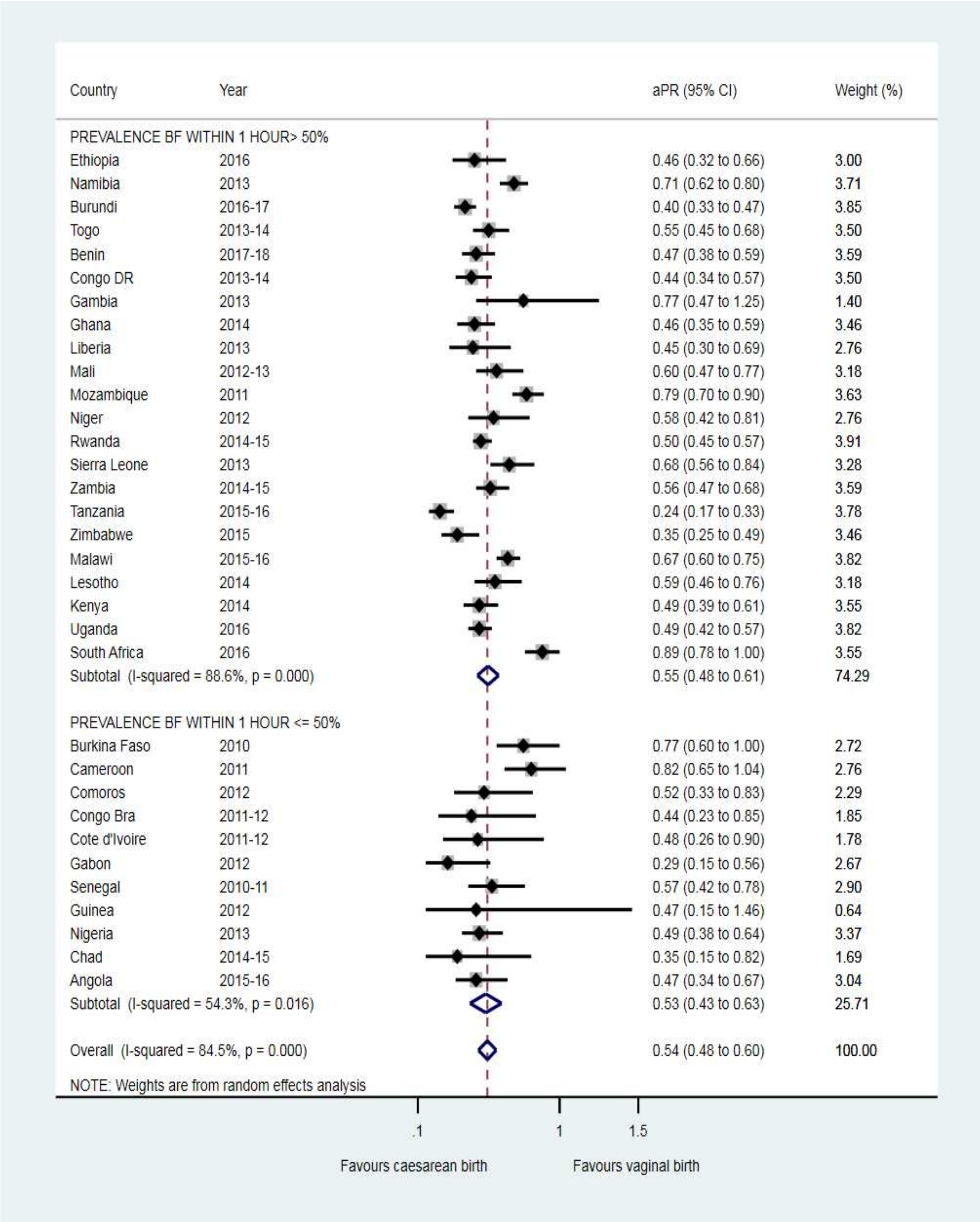

Figure C. Subgroup analyses for the association between caesarean section and early initiation of breastfeeding in sub-Saharan Africa stratified by prevalence of early initiation of breastfeeding

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Appendix D: Online Supplementary Material for Study 4

Appendix D includes supplementary information and analyses that complement Study 4.

Yisma E, Mol BW, Lynch JW, Murthy NM, Smithers LG. Associations between Apgar scores and children's educational outcomes at eight years of age. *Aust N Z J Obstet Gynaecol* 2020; 1–7.

Figure S1. Proposed Directed Acyclic Graphs (DAGs) describing the associations between Apgar scores and children's educational outcomes

Table S1. Proportion of children performing at or below the NMS according to 5-minute Apgar scores and risk differences comparing Apgar scores of <7 with scores of 7-10 for children performing at or below the NMS for each NAPLAN domain

Table S2. Risk differences comparing a range of 5-minute Apgar scores (i.e., 0-5, 6, 7, 8 and 9 (compared with 10) for children having school card according to NAPLAN domains

Table S3. Proportion of children performing at or below the NMS according to 1-minute Apgar scores and risk differences comparing Apgar scores of <7 with scores of 7-10 for children performing at or below NMS for each domain

Table S4. Proportion of children having school card according to 1-minute Apgar score and risk differences comparing Apgar scores of <7 with scores of 7-10 for children having school card

Table S5. Risk differences comparing a range of 1-minute Apgar score values (i.e., 0-5, 6, 7, 8 and 9 (compared with 10) for children performing at or below the NMS for each domain

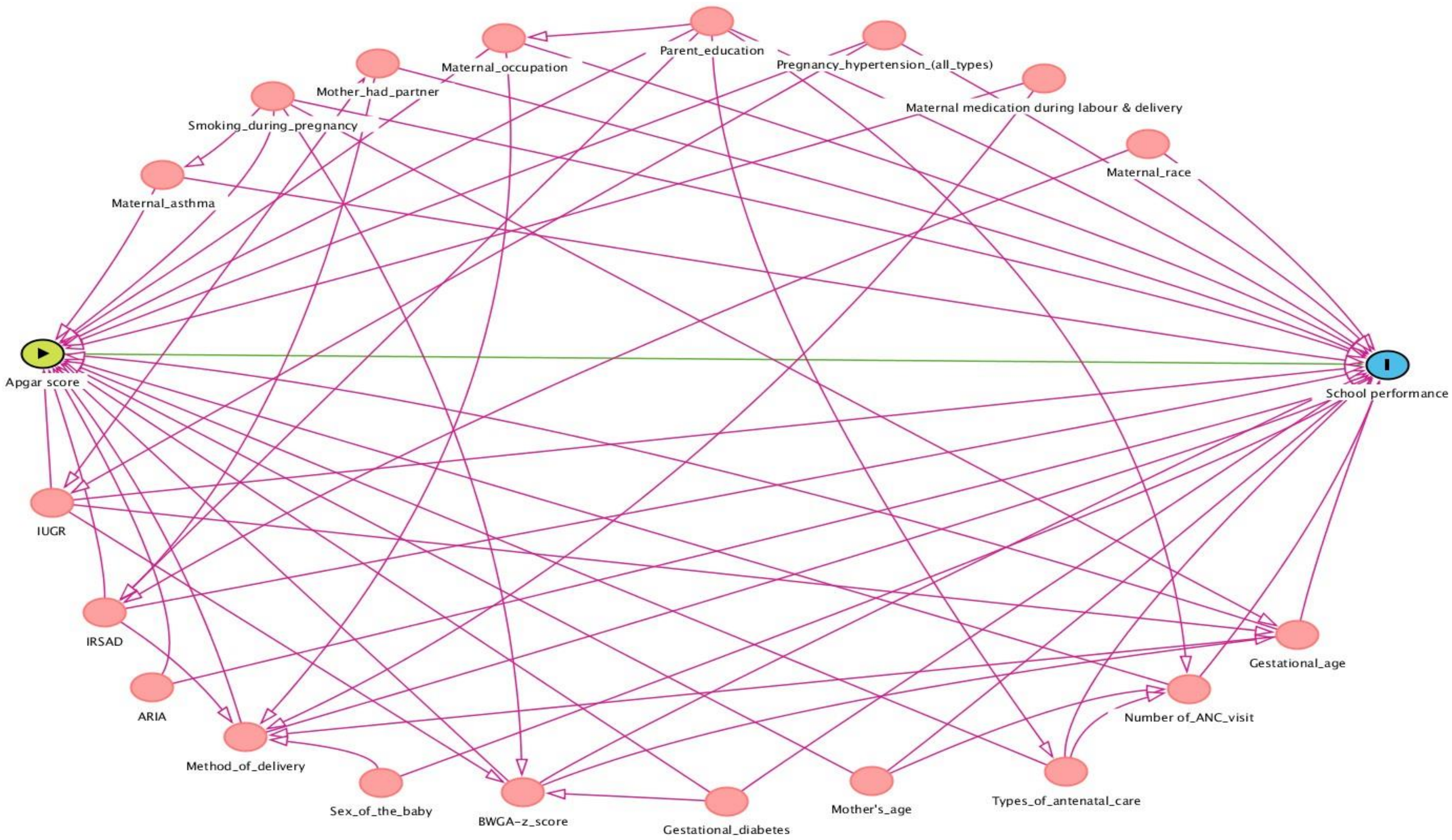

Figure S1. Proposed Directed Acyclic Graphs (DAGs) describing the associations between Apgar scores and children's educational outcomes

Table S1. Proportion of children performing at or below the NMS according to 5-minute Apgar scores and risk differences comparing Apgar scores of <7 with scores of 7-10 for children performing at or below the NMS for each NAPLAN domain

Domain	N	Apgar <7 ≤NMS/total (%)	Apgar 7-10 ≤NMS/total (%)	RD‡	95% CI	P
Reading	60,722	138/604 (22.85%)	11929/60118 (19.84%)	0.02	-0.01, 0.05	0.283
Writing	60,514	84/593 (14.17%)	7366/59921 (12.29%)	0.02	-0.01, 0.05	0.127
Spelling	60,830	149/601 (24.79%)	12431/60229 (20.64%)	0.03	0.00, 0.06	0.078
Grammar	60,830	135/601 (22.46%)	11652/60229 (19.35%)	0.01	-0.02, 0.05	0.351
Numeracy	60,581	159/601 (26.46%)	13353/59980 (22.26%)	0.03	-0.00, 0.07	0.080

Abbreviations: RD, risk difference; NMS, National Minimum Standard; CI, confidence interval.

‡RD calculated from augmented inverse probability weighted analysis (adjusted for a number of confounders listed in methods section) of the proportion of children performing ≤NMS on each assessment for children with low versus normal 5-minute Apgar score.

Table S2. Risk differences comparing a range of 5-minute Apgar scores (i.e., 0-5, 6, 7, 8 and 9 (compared with 10) for children having school card according to NAPLAN domains

5-minute Apgar scores	**School card—Reading** *n=60,722* **RD[‡] (95%CI)**	**School card—Writing** *n=60,514* **RD (95%CI)**	**School card—Spelling** *n=60,830* **RD (95%CI)**	**School card—Grammar** *n=60,830* **RD (95%CI)**	**School card—Numeracy** *n=60,581* **RD (95%CI)**
0-5 vs 10	0.02 (-0.24, 0.27)	0.01 (-0.25, 0.27)	0.02 (-0.24, 0.27)	0.02 (-0.24, 0.27)	0.02 (-0.24, 0.28)
6 vs 10	0.3 (0.08, 0.52)	0.25 (0.03, 0.47)	0.25 (0.03, 0.46)	0.25 (0.03, 0.46)	0.28 (0.06, 0.49)
7 vs 10	0.08 (-0.05, 0.22)	0.06 (-0.07, 0.19)	0.05 (-0.08, 0.18)	0.05 (-0.08, 0.18)	0.07 (-0.06, 0.2)
8 vs 10	0.09 (0.02, 0.17)	0.09 (0.02, 0.16)	0.09 (0.02, 0.16)	0.09 (0.02, 0.16)	0.09 (0.02, 0.16)
9 vs 10	0.00 (-0.03, 0.03)	-0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.04)
10	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)

Abbreviations: RD, Risk difference; NMS, National Minimum Standard; CI, confidence interval.

[‡]**RD** calculated from augmented inverse probability weighted analysis (adjusted for a number of confounders listed in methods section) showing the proportion of children performing ≤NMS on each assessment for children with Apgar scores at 5 minutes.

Associations between 1-minute Apgar scores and children's educational outcomes at 8 years of age

Table S3. Proportion of children performing at or below the NMS according to 1-minute Apgar scores and risk differences comparing Apgar scores of <7 with scores of 7-10 for children performing at or below the NMS for each domain

NAPLAN domain	N	Apgar <7 ≤NMS/total (%)	Apgar 7-10 ≤NMS/total (%)	RD‡	95% CI	P
Reading	60,700	1508/7127 (21.16%)	10554/53573 (19.70%)	0.01	-0.00, 0.02	0.281
Writing	60,490	967/7099 (13.62%)	6481/53391 (12.14%)	0.01	0.00, 0.02	0.045
Spelling	60,806	1641/7157 (22.93%)	10934/53649 (20.38%)	0.02	0.01, 0.03	0.001
Grammar	60,806	1476/7157 (20.62%)	10304/53649 (19.21%)	0.01	-0.00, 0.02	0.216
Numeracy	60,557	1647/7112 (23.16%)	11851/53445 (22.17%)	0.00	-0.01, 0.02	0.357

Abbreviations: RD, risk difference; NMS, National Minimum Standard; CI, confidence interval.

‡ **RD** calculated from augmented inverse probability weighted analysis (adjusted for a number of confounders listed in methods section) of the percentage of children performing ≤NMS on each assessment for children with low compared with normal Apgar score at 1 minute.

Table S4. Proportion of children having school card according to 1-minute Apgar scores and risk differences comparing Apgar scores of <7 with scores of 7-10 for children having school card

School card[§]	N	Apgar <7 School card/total (%)	Apgar 7-10 School card/total (%)	RD[‡]	95% CI	P
Reading—school card	60,700	1590/7127 (22.31%)	11344/53573 (21.17%)	0.01	0.00, 0.02	0.042
Writing—school card	60,490	1578/7099 (22.23%)	11283/53391 (21.13%)	0.01	0.00, 0.02	0.049
Spelling—school card	60,806	1599/7157 (23.34%)	11374/53649 (21.20%)	0.01	0.00, 0.02	0.047
Grammar—school card	60,806	1599/7157 (23.34%)	11374/53649 (21.20%)	0.01	0.00, 0.02	0.047
Numeracy—school card	60,557	1576/7112 (22.16%)	11351/53445 (21.17%)	0.01	-0.00, 0.02	0.069

Abbreviations: RD, risk difference; CI, confidence interval.

[§]School card possession variable was computed for each assessment for children who had complete data on each NAPLAN domain and all the confounders.

[‡]**RD** calculated from augmented inverse propensity weighted estimator analysis (adjusted for a number of confounders listed in methods section) of the percentage of children having school card at year 3 among children with low versus normal Apgar score at 1 minute.

Table S5. Risk differences comparing a range of 1-minute Apgar score values (i.e., 0-5, 6, 7, 8 and 9 (compared with 10) for children performing at or below the NMS for each domain

1-minute Apgar scores	**Reading** *n=60,700* **RD‡ (95%CI)**	**Writing** *n=60,490* **RD (95%CI)**	**Spelling** *n=60,806* **RD (95%CI)**	**Grammar** *n=60,806* **RD (95%CI)**	**Numeracy** *n=60,557* **RD (95%CI)**
0-5 vs 10	0.15 (-0.03, 0.33)	0.15 (-0.09, 0.40)	0.18 (0.00, 0.36)	0.10 (-0.08, 0.27)	0.02 (-0.13, 0.16)
6 vs 10	0.15 (-0.03, 0.33)	0.17 (-0.08, 0.42)	0.18 (0.00, 0.36)	0.10 (-0.08, 0.28)	0.04 (-0.11, 0.19)
7 vs 10	0.15 (-0.02, 0.32)	0.15 (-0.09, 0.38)	0.14 (-0.03, 0.31)	0.10 (-0.07, 0.27)	0.03 (-0.11, 0.17)
8 vs 10	0.14 (-0.03, 0.30)	0.07 (-0.14, 0.29)	0.11 (-0.05, 0.27)	0.10 (-0.07, 0.27)	0.02 (-0.11, 0.16)
9 vs 10	0.11 (-0.05, 0.27)	0.08 (-0.14, 0.29)	0.07 (-0.08, 0.22)	0.05 (-0.11, 0.21)	0.00 (-0.13, 0.13)
10	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)

Abbreviations: ‡**RD**, calculated from augmented inverse probability weighted analysis showing the proportion of children performing ≤NMS on each assessment for children with Apgar scores at one minutes after birth. NB: Multinomial logit model was used to predict Apgar score (treatment model), using all confounders specified for outcome model (logit). In order to aid the interpretation of RDs, we have expressed the RDs as proportions (percentages) of the Potential Outcome Mean (POM) for the control (Apgar score of 10). Therefore, RDs can be interpreted as proportion as in the binary-treatment model.

Appendix E: Online Supplementary Material for Study 5

Table S1. Proportion of children performing at Band 1 according to elective induction of labour at 39 weeks versus expectant management and ATEs comparing elective induction of labour at 39 weeks with expectant management for children performing at Band 1 for each NAPLAN domain

Domain	Total sample (N)	Elective labour induction Band1/total (%)	Expectant management Band 1/total (%)	ATE†	95% CI	P
Reading	29,114	75/1,266 (5.92%)	1718/27,848 (6.17%)	0.01	-0.01, 0.03	0.321
Writing	29,022	39/1,264 (3.09%)	1105/27,758 (3.98%)	0.00	-0.02, 0.01	0.676
Spelling	29,141	62/1,268 (4.89%)	1736/27,873 (6.23%)	0.00	-0.02, 0.02	0.963
Grammar	29,141	89/1,268 (7.02%)	2161/27,873 (7.75%)	0.01	-0.01, 0.03	0.244
Numeracy	29,031	72/1,272 (5.66%)	1616/27,759 (5.82%)	0.02	-0.00, 0.03	0.089

Abbreviations: ATE, Average Treatment Effect; CI, confidence interval; NMS, National Minimum Standard.

†ATE calculated from augmented inverse probability weighted analysis adjusted for maternal smoking during the second half of pregnancy, birth weight for gestational age z-score, mother's age at birth, index of relative socioeconomic disadvantage, types of antenatal care, number of antenatal visits, maternal occupation, maternal ethnicity, Australian remoteness index for areas, mother had a partner, and infant sex.

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