

# **Intrauterine Influences on Obesity and Insulin Resistance in Pre-pubertal Children**

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*"Truth lies all around us, but is only revealed to those who search for it."*

Nicolae Iorga (1871-1940)

This thesis is dedicated to my mother for her immense love, trust, support and encouragement not only through the PhD candidature years, but throughout my entire life. I have learnt from her wisdom that giving anything less than all I could give meant sacrificing a gift.

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## Abstract

Within the paradigm of developmental origins of health and disease, an intrauterine environment that stimulates fetal overnutrition has been found to contribute to the risk of subsequent obesity in the offspring. There is compelling epidemiological evidence for a positive association between maternal obesity prior to pregnancy, gestational diabetes (GD) or excessive gestational weight gain, and the development of childhood obesity (as measured by body mass index, BMI). However, the evidence is limited and inconsistent with respect to more specific measures of adiposity (body composition or fat pattern) and insulin resistance in children. Furthermore, the long-term effects of maternal borderline gestational glucose intolerance (BGGI) on the offspring have not been considered.

Therefore, I sought to examine whether maternal obesity prior to pregnancy, gestational glucose intolerance across the entire spectrum, and gestational weight gain have deleterious effects on the development of obesity (both global and specific measures of adiposity) and insulin resistance in pre-pubertal children. These associations are particularly important from a public health perspective as, once identified, they may point towards potential windows for prevention of childhood obesity and related metabolic disorders.

This project entailed a follow-up of an existing representative, prospective birth cohort study (Generation 1 Study, n=557) in Adelaide, South Australia, recruited during 1998-2000. At the 9-10 year follow-up, rigorous anthropometric measurements were conducted in 443 children (80% of the original cohort), of whom 163 consented to provide a fasting blood sample for the estimation of insulin resistance based on homeostasis model assessment (HOMA-IR). Information on intrauterine exposures and confounders was collected from the antenatal interviews and hospital records. Maternal age, parity, smoking, pregnancy-induced hypertension, and education at the time of pregnancy were considered as potential confounders for all the associations of interest, and child current BMI z-score as a potential mediator on the pathway between the intrauterine exposures and child insulin resistance. Data were analysed using multiple linear regression and generalized linear models.

Maternal pre-pregnancy BMI was positively associated with all three obesity-related measures considered in the 9-10 year-old children (BMI z-score, percentage body fat estimated by bioelectrical impedance analysis, and waist-to-height ratio); these relationships were robust to adjustment for potential confounders (adjusted coefficients for each one kg/m<sup>2</sup> increase in maternal pre-pregnancy BMI were 0.08 (95% confidence interval 0.06, 0.10) for child BMI z-score, 0.44 (95% CI 0.31, 0.58) for percentage body fat and 0.002 (95% CI 0.002, 0.003) for waist-to-height ratio). There was no association between maternal pre-pregnancy BMI and HOMA-IR in children (with or without adjustment); however, when child current BMI z-score was included as a mediating variable, the relationship between maternal pre-pregnancy BMI and child HOMA-IR was inverse and significant (adjusted change in child HOMA-IR for each one kg/m<sup>2</sup> increase in maternal pre-pregnancy BMI was -0.83% (95% CI -1.63, -0.02)).

Intrauterine exposure to glucose intolerance during pregnancy (either BGGI or GD) was not associated with any of the three obesity-related measures in children at 9-10 years. Children of mothers who developed GD during the index pregnancy had a higher HOMA-IR; this relationship was robust to adjustment for potential confounders (adjusted change in child HOMA-IR if exposed to maternal GD was 42.9% (95% CI 20.9, 68.9)) and partly mediated by child current BMI z-score. No association was found between exposure to maternal BGGI and child HOMA-IR (with or without confounder adjustment); however, when child current BMI z-score was added as a potential mediator, exposure to BGGI was associated with a reduction in child HOMA-IR (adjusted change in child HOMA-IR if exposed to maternal BGGI was -17.9% (95% CI -29.9, -3.96)).

There were no significant associations between maternal gestational weight gain and any of the outcome measures of interest in unadjusted models. However, adjustment for pre-pregnancy BMI led to a positive association between gestational weight gain and child BMI z-score (adjusted changes in child BMI z-score for each one kg increase in maternal gestational weight gain was 0.032 (95% CI 0.007, 0.057)). Gestational weight gain was not associated with child insulin resistance, and this did not change when child current BMI z-score was included as a potential mediator on the pathway between gestational weight gain and child insulin resistance.

Potential two-way interactions between the main exposures were investigated in relation to all outcomes of interest. Two significant interactions were identified: maternal pre-pregnancy BMI and glucose tolerance status, and maternal pre-pregnancy BMI and gestational weight gain, with a synergistic effect on child waist-to-height ratio.

These results suggest that childhood obesity and insulin resistance have origins, at least in part, in intrauterine life, particularly in relation to maternal obesity at the time of pregnancy and GD. Further research to differentiate between genetic, environmental and intrauterine programming is recommended. That said, maternal pre-pregnancy BMI was the strongest predictor of child BMI z-score, while GD appeared to have an independent effect on child insulin resistance, and both clinical and public health actions to address these maternal factors are warranted for a range of reasons.



## Declaration

I, Oana Maftei certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

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Oana Maftei

Date: 21 December 2011

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## Abbreviations and acronyms

%BF	percentage body fat
ACHOIS	Australasian Carbohydrate Intolerance Study in Pregnancy
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
ADIPS	Australasian Diabetes in Pregnancy Society
ALSPAC	Avon Longitudinal Study of Parents and Children
BGGI	borderline gestational glucose intolerance
BIA	bioelectrical impedance analysis
BMI	body mass index
BW	birth weight
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CT	computed tomography
DXA	dual energy X-ray absorptiometry
EPOCH	Exploring Perinatal Outcomes among Children
FFM	fat-free mass
FGIR	fasting glucose-to-insulin ratio
FM	fat mass
FSIVGTT	frequently sampled intravenous glucose tolerance test
FTO	fat mass and obesity associated gene
GD	gestational diabetes
GLM	generalised linear model
GWG	gestational weight gain
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA1c	haemoglobin A1c
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
IGF	insulin-like growth factor
IGT	impaired glucose intolerance
IL	interleukin

IOM	Institute of Medicine
IOTF	International Obesity Task Force
IQR	interquartile range
IR	insulin resistance
LDL	low-density lipoprotein
LMS	lambda-mu-sigma
MRI	magnetic resonance imaging
NDDG	National Diabetes Data Group
NGT	normal glucose tolerance
NZSSD	New Zealand Society for the Study of Diabetes
OGCT	oral glucose challenge test
OGTT	oral glucose tolerance test
OR	odds ratio
PAR	population attributable risk
PCOS	polycystic ovarian syndrome
QUICKI	quantitative insulin sensitivity check index
r	Pearson's correlation coefficient
RCT	randomised clinical trial
RR	relative risk
SD	standard deviation
SES	socio-economic status
SFT	skinfold thickness
TBW	total body water
TNF	tumour necrosis factor
TAFE	Training and Further Education
WHO	World Health Organization
WHtR	waist-to-height ratio

## Conference presentations

1. **Maftai O**, Whitrow MJ, Moore VM, Davies MJ. *Intrauterine influences on offspring obesity in prepubertal children* - oral presentation, 7<sup>th</sup> World Congress on Developmental Origins of Health and Disease, Portland, Oregon, USA, 18-21 September 2011
2. **Maftai O**, Whitrow MJ, Moore VM, Davies MJ. *Intrauterine influences on insulin resistance in prepubertal children* - oral presentation (ranked in top 10%), 7<sup>th</sup> World Congress on Developmental Origins of Health and Disease, Portland, Oregon, USA, 18-21 September 2011
3. **Maftai O**, Whitrow MJ, Moore VM, Davies MJ. *Insulin resistance in prepubertal children in relation to intrauterine exposure to overnutrition* - oral e-poster presentation, 52<sup>nd</sup> Annual Meeting of the European Society for Paediatric Research, Newcastle, UK, 14-17 October 2011