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TITLE PAGE

Effect of birthweight and early pregnancy body mass index on the risk for pregnancy complications

Running title: Birthweight, body mass index and pregnancy complications

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Key points**What is already known?**

- Those born with a low birthweight may be “programmed” for vascular and metabolic disease in later life
- When such individuals are exposed to additional stresses, they may manifest vascular/metabolic diseases
- Pregnancy may act as a “second hit” for those who are programmed for future vascular and metabolic disease

What does this study add?

- Women who reported a low birthweight were at increased risk of major pregnancy complications
- This large study confirms previous evidence that for those born with a low birth weight, becoming overweight or obese further increases the risk for pregnancy complications

ABSTRACT

Objective: We investigated the influence of birthweight on the risk of pregnancy complications including preeclampsia (PE), gestational hypertension (GH), small for gestational age (SGA) pregnancy, spontaneous preterm birth (sPTB) and gestational diabetes mellitus (GDM) and assessed the effect of early pregnancy BMI on the above relationship.

Methods: 5336 nulliparous women from the SCOPE study were included. Women's birthweights were self-reported and confirmed via medical records when possible. A birthweight of 3000-3499g was considered the reference.

Results: After adjusting for confounders, birthweight <2500g was associated with increased risk of GH (aOR=2.2, 95% CI=1.3-3.7), preeclampsia (aOR=1.7, 95% CI =1.0-2.9), SGA (aOR=1.9, 95% CI=1.1-3.2) and GDM (aOR=2.4, 95% CI=1.0-5.8) compared to the referent. Women born with a birthweight <2500g and subsequently became overweight or obese were at increased risk of GH (aOR=2.2, 95% CI=1.1-4.5), preeclampsia (aOR=2.3, 95% CI=1.2-4.5) and GDM (aOR=3.2, 95% CI=1.1-9.5), compared to women who were born with a birthweight $\geq$ 2500g and remained lean.

Conclusion: Women who were born with a low birthweight are at increased risk of pregnancy complications. Those born small may have undergone "programming" in response to unfavourable intrauterine conditions. In such women, the physiological demands of pregnancy may act as a "second hit" leading to pregnancy complications.

INTRODUCTION

The intrauterine environment is recognised as a crucial determinant of later life disease susceptibility since the original theory was proposed in the 1990's (1). The fetal origins of adult disease hypothesis was first described by David Barker, who proposed that disruptions to the intrauterine environment during fetal development can 'program' for increased risks for diseases in adult life (1). Subsequent epidemiological studies confirmed this hypothesis showing strong evidence associating low birthweight with increased vulnerability to a myriad of adult life vascular and metabolic diseases including hypertension, cardiovascular disease, stroke and type 2 diabetes mellitus (1-4).

Some individuals who are "programmed" for increased disease risk develop chronic diseases despite healthy environmental and lifestyle effects which may be due to genetic predisposition, whereas others develop disease only when exposed to a "second hit" (5). These "second hits" are often adverse lifestyle factors i.e. smoking, unhealthy diets and sedentary lifestyles (5). Pregnancy is increasingly being recognised as a common "second hit" for females (5). Pregnancy is considered a physiological stress test for the female cardiovascular system which undergoes many physiological changes during pregnancy to meet the demands of the growing fetus (5). Women who successfully "pass" the test have uncomplicated pregnancies while those who "fail" may experience adverse pregnancy outcomes. Therefore, women who were born small when exposed to the "second hit" of pregnancy may experience pregnancy complications. The primary aim of this study was to examine the influence of maternal birthweight on the risk of development of pregnancy complications including preeclampsia (PE), gestational hypertension (GH), small for gestational age (SGA) pregnancy, spontaneous preterm birth (sPTB) and gestational diabetes mellitus (GDM). Those born small have a tendency to become overweight/obese in adulthood (6). Therefore, we also assessed whether maternal

overweight/obesity had an impact on the association between maternal birthweight and pregnancy complications.

MATERIALS AND METHODS

The participants of this study were women who were recruited to the SCOPE study between November 2004 and February 2011 in Adelaide, Australia, Auckland, New Zealand, Manchester, Leeds and London, United Kingdom and Cork, Ireland. The SCOPE study (www.scopestudy.net) is an international, multicenter, prospective cohort study with the aim of developing screening tests to predict preeclampsia, SGA infants and spontaneous preterm birth across different populations. Ethics approval was gained from local ethics committees of each participating center (Australia REC 1712/5/2008, New Zealand AKX/02/00/364, Manchester, Leeds and London 06/MRE01/98, Cork ECM5 (10)05/02/08) and all women provided written informed consent.

Recruitment of participants to the SCOPE study has previously been described in detail (7). In brief, participants were referred from hospital antenatal clinics, obstetricians, general practitioners, community midwives or self-referred. Nulliparous women with singleton pregnancies were recruited before 15 weeks' of gestation. Those considered at high risk of preeclampsia, SGA or preterm birth because of underlying medical conditions (including known pre-existing chronic hypertension on hypertensive medication or with a blood pressure $>160/100$ mmHg at 15 weeks of gestation), gynaecological history, three or more miscarriages or terminations of pregnancy or couples who received medical or surgical interventions which could modify pregnancy outcome were not eligible. Participants were interviewed at 15 ± 1 and 20 ± 1 weeks of gestation by SCOPE research midwives.

Recruited women were excluded from the present analyses if any of the following reasons applied: protocol violation, lost to follow up, multiple sexual partners and unsure of the identity

of the biological father of the baby and miscarriage or termination (Figure 1). At the 15 ± 1 weeks' interview, data collected included demographic information, medical history, previous obstetric history, family history of obstetric complications and medical disorders. Current pregnancy data included information on any complications during current pregnancy, diet, smoking, alcohol and the use of recreational drugs. Each woman's birthweight and the gestational age at which she was born were self-reported and confirmed from clinical records or birth registries when possible. The birthweights of 4407 out of 5327 women (82.7%) were confirmed from clinical records or birth registries. Maternal physical measurements obtained at 15 weeks of gestation included height, weight and blood pressure. All participants were followed prospectively and pregnancy outcome data and infant measurements were recorded by research midwives usually within 72 hours of birth.

Definitions of pregnancy outcomes

Gestational hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two or more measurements 6 h apart after 20 weeks of gestation. *Preeclampsia* was defined using the revised ISSHP definition of gestational hypertension or postpartum hypertension with proteinuria (24-h urinary protein 300 mg or spot urine protein : creatinine ratio ≥ 30 mg/mmol creatinine or urine dipstick protein $\geq ++$) or any multisystem complication of preeclampsia or utero-placental dysfunction as evidenced by intrauterine growth restriction (8). Multisystem complications included any of acute renal insufficiency defined as a new increase in serum creatinine concentration ≥ 100 $\mu\text{mol/L}$ antepartum or >130 $\mu\text{mol/L}$ postpartum; effects on liver, defined as raised aspartate transaminase or alanine transaminase concentration, or both, >45 IU/L and/or severe right upper quadrant or epigastric pain or liver rupture; neurological effects included eclampsia, imminent eclampsia (severe headache with hyper-reflexia and persistent visual disturbance), or cerebral haemorrhage; and

haematological effects included thrombocytopenia (platelets $<100 \times 10^9/L$), disseminated intravascular coagulation, or haemolysis. *Small for gestational age (SGA)* was defined as a birth weight below the 10th customised centile adjusted for maternal height, weight, parity and ethnicity, gestational age at delivery and infant sex. *Normotensive SGA* was defined as birth of a SGA infant where the mother did not have hypertension. *Spontaneous preterm birth (sPTB)* was defined as spontaneous preterm labour or preterm premature rupture of membranes resulting in a preterm birth at <37 weeks. *Gestational diabetes mellitus (GDM)* was defined as fasting glucose ≥ 5.1 mmol/L or a 2 h level of ≥ 8.5 mmol/L following an Oral Glucose Tolerance Test, according to the new World Health Organization classification. At the time of recruitment of participants to the SCOPE study, the screening procedures for GDM were not the same throughout the recruiting centres due to country specific guidelines. Therefore, only participants from Adelaide and Auckland were included in all the analyses for GDM. *Uncomplicated pregnancy* was defined as a pregnancy with no antenatal medical or obstetric complications and resulting in the delivery of an appropriately grown, healthy baby at ≥ 37 weeks' of gestation.

Statistics

Statistical analyses were performed using R version 2.8.0 (cran.r-project.org). The data for each pregnancy complication (preeclampsia, gestational hypertension, SGA, spontaneous preterm birth and gestational diabetes mellitus) was compared to the uncomplicated pregnancy group. Women who reported a birthweight 3000-3499g were considered the reference group as the mean birthweights across the recruiting centres were within this range. The risks for pregnancy complications for women with a birthweight $<2500g$, 2500-2999, 3500-3999 and $\geq 4000g$ were compared with the reference group. For categorical variables, Chi-square test was used to compare the groups and for continuous variables, student's *t*-test was used. Generalized

linear mixed models with Logit link was used to estimate odds ratios for each of the measures of variable of interest. For each variable, adjusted odds ratios were calculated by adding variables to the mixed model and with recruitment centres differences accounted for as a random effect. Based on previous literature, established confounders for each pregnancy complication were included in the models as follows: *for preeclampsia*, maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of preeclampsia, hypertension in first degree relative, maternal gestational age at birth, infant sex and recruitment centre; *for gestational hypertension*, maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of hypertensive disease of pregnancy, hypertension in first degree relative, maternal gestational age at birth, infant sex and recruitment centre; *for normotensive SGA pregnancy*, maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of low birthweight, maternal gestational age at birth, infant sex and recruitment centre; *for spontaneous preterm birth*, adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of sPTB, maternal gestational age at birth and infant sex and *for GDM*, maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of GDM, maternal gestational age at birth, infant sex and recruitment centre. Elevated BMI is a known risk factor for most of the above pregnancy complications. Low birthweight is known to lead to adult obesity and hence BMI is considered an effect modifier in the relationship between birthweight and pregnancy complications. Therefore, we have conducted separate analyses to assess the effect of BMI on the association between birthweight and pregnancy complications. Results are reported as number and percent [n (%)] or mean $\pm$ standard deviation (SD) as appropriate. $P < 0.05$ was considered statistically significant. A retrospective power calculation was performed and demonstrated a $>90\%$ power to detect a two-fold increase in risk of each pregnancy complication in women with a birthweight $<2500\text{g}$.

RESULTS

Of the 5690 pregnant women recruited, 5327 were eligible for this study (figure 1). Amongst them, 3200 (60.1%) had uncomplicated pregnancies, 357 (6.7%) had gestational hypertension, 347 (6.5%) had preeclampsia, 433 (8.1%) had SGA infants in the absence of any hypertensive disease of pregnancy (normotensive SGA), 216 (4.1%) had sPTB, 163 (3.1%) had GDM and 854 (26.7%) had other medical or obstetric complications (figure 1). Of the Adelaide and Auckland SCOPE cohort eligible for this study ($n = 1954$), 97 women (4.9%) had GDM (figure 1).

The characteristics of the participants according to pregnancy outcome are shown in table 1 and characteristics of the participants according to recruitment centre are shown in supplementary table 1. After adjusting for confounders, a birthweight $<2500\text{g}$ was associated with increased risk of developing preeclampsia ($\text{OR} = 1.7$, 95% $\text{CI} = 1.0 - 2.9$), gestational hypertension ($\text{OR} = 2.2$, 95% $\text{CI} = 1.3 - 3.7$), SGA pregnancy ($\text{OR} = 1.9$, 95% $\text{CI} = 1.1 - 3.2$) and GDM ($\text{OR} = 2.4$, 95% $\text{CI} = 1.0 - 5.8$) compared to the reference group (table 2).

We also evaluated whether women's BMI at 15 weeks' gestation had an impact on the association between their birthweight and risk for pregnancy complications (table 3). Women were stratified into 4 groups as follows. Group 1 (reference group), those who had a birthweight $\geq 2500\text{g}$ and remained lean ($\text{BMI} < 25 \text{ kg/m}^2$) at the 15 weeks' visit, Group 2, those who had a birthweight $\geq 2500\text{g}$ and were either overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$), Group 3, those who had a birthweight $< 2500\text{g}$ and remained lean ($\text{BMI} < 25 \text{ kg/m}^2$) and Group 4, those who had a birthweight $< 2500\text{g}$ and were either overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$). The risk for pregnancy complications for women in groups 2, 3 and 4 were compared to that for women in group 1. After adjusting for confounders, women in group 2 were at increased risk for preeclampsia and gestational hypertension, those in group 3 were at increased risk for

gestational hypertension and those in group 4 were at increased risk for preeclampsia, gestational hypertension and GDM (table 3).

DISCUSSION

The results herein for this large well defined prospective cohort shows that a woman's birthweight has an effect on her pregnancy and that this effect is modified by her BMI at 15 ± 1 weeks' gestation.

Women who reported a birthweight $<2500\text{g}$ were found to be at 1.7 times higher risk of preeclampsia compared to those who had a birthweight of $3000 - 3499\text{g}$. Women who reported a birthweight of $3500 - 3999\text{g}$ or a birthweight $\geq 4000\text{g}$ had a 40% reduced risk of preeclampsia compared to the control group. When we stratified the cohort based on the woman's birthweight and her BMI at 15 ± 1 weeks' gestation, no significant risk for preeclampsia was seen for women who had a low birthweight but remained lean. The risk of preeclampsia for those who had a normal birthweight but became overweight or obese was 1.5 times higher compared to those who had a normal birthweight and remained lean. The highest risk for preeclampsia (2.3 times increased risk) was seen for women who had a low birthweight and subsequently became overweight or obese as adults. These findings confirm the previous findings of Dempsey and colleagues (9). We have used the revised ISSHP definition of preeclampsia for our analyses which includes women who had gestational hypertension and SGA infants in the preeclampsia group. Hence the reported rate of preeclampsia in this paper is higher than that reported in previous publications from the SCOPE study.

Women who reported a low birthweight were at 2.2 times increased risk of developing gestational hypertension compared to women who had a normal birthweight. When stratified by birthweight and BMI, women who had a low birthweight but remained lean as adults were at 1.6 times increased risk of GH, those who had a normal birthweight but were overweight or

obese had 3.0 times increased risk of GH and those who had a low birthweight and were overweight or obese had 2.2 times increased risk of developing GH compared to the control group.

The causal pathways linking low birthweight with preeclampsia and gestational hypertension are yet to be confirmed but a few plausible mechanism have been proposed. Exposure to unfavourable conditions *in utero* have been shown to lead to nephron deficits and renal dysfunction by a number of mechanisms. In animal models, altered programming of nephron number is shown to be associated with glomerular hypertrophy and reduced renal vascular dilation contributing to risk of hypertension (10, 11). Maternal nutritional status during pregnancy also plays an important role in fetal programming with malnutrition having adverse effects on renal development (10). Additionally, alterations in the renin-angiotensin-aldosterone system (RAAS) including upregulation or downregulation of specific receptors, have also been implicated in the development of renal dysfunction (12). Therefore, those who are born with a low birthweight may be “programmed” *in utero* for later life hypertension. When such individuals experience added stresses including an elevated BMI or the haemodynamic burden of pregnancy, they may develop gestational hypertension or preeclampsia. (13). The mechanism of hypertensive diseases of pregnancy in women born with low birthweight could be renal-mediated via programming of the RAAS suggesting a subclass of hypertensive diseases in pregnancy.

Women with a low birth weight were at 1.9 times increased risk of delivering a SGA infant, however, when stratified according to birthweight and BMI no significant differences were seen between the groups. Fetal growth *in utero* serves as a marker of many prenatal conditions and hence birthweight is influenced by many factors. Heritability accounts for 0.2 – 0.4 for variation in birthweight and the mother’s birthweight is shown to be a stronger predictor of

offspring birthweight than the father's birthweight independent of the mother's adult size (14, 15).

Although there was a small increase in risk of sPTB for women who reported a low birthweight this association was not significant after adjusting for confounders and woman's BMI also did not have an effect. The multivariable logistic regression models showed that this was mainly due to the very strong effect of maternal smoking on the risk for sPTB. Several previous studies reported that women who were born with a birthweight <2500g have an increased risk of delivering preterm (16-20) while others found no association (21, 22). The disagreement in findings could be due to the definition of preterm birth, with some studies including all preterm births (spontaneous and medically induced), as well as due to the different confounders that have been used in statistical analyses. A previous study that assessed the influence of women's BMI on the association between their birthweight and risk for sPTB reported findings similar to ours (20).

Women who reported a birthweight <2500g were found to be at 2.4 times increased risk of GDM compared to the control group and when stratified by birthweight and BMI, those who were born with a low birthweight and became overweight or obese were at 3.2 times increased risk of GDM compared to the control group. Consistent with our findings, a previous study by Seghieri and colleagues also showed that low birthweight among women was associated with a two-fold increased risk for GDM after adjusting for age, parity, family history of diabetes and pre pregnancy BMI (23). The relationship between low birthweight and GDM can also be proposed to be linked to intrauterine programming. It has been postulated that growth restricted infants have a reduced number of pancreatic β cells leading to diminished capacity to produce insulin which can result in increased risk for diabetes (3, 23).

The link between exposure to adverse intrauterine conditions resulting in intrauterine growth restriction and obesity in adulthood was first shown in birth cohort studies of individuals

exposed to the Dutch Famine (24). Since then there has been robust evidence linking low birthweight with adult life obesity. Our findings suggest that some women who were born small when exposed to the “second hit” of pregnancy, may experience pregnancy complications.

We acknowledge that maternal birthweight in 920 (17.3%) women in our study was self-reported and hence could be influenced by recall bias. We also did not have pre-pregnancy BMI in these women and used BMI data obtained at $15 \pm$ week’s gestation. Although weight gain during the first 15 weeks of pregnancy is usually minimal, some women gain substantial weight in early pregnancy and some women lose weight during this period. Since we did not have data on pre-pregnancy BMI, we could not assess early pregnancy weight gain/loss which can influence pregnancy outcome (25). Hence we acknowledge this limitation. However, the availability of data on a large number of variables enabled us to correct for many important confounding factors.

Overall, the main finding of this study is that women who are born with a low birthweight and subsequently become overweight or obese appear to be at increased risk for developing gestational hypertension, preeclampsia and GDM. Many modifiable environmental and life style factors contribute to the risk of pregnancy complications. Further studies assessing the influence of such factors including diet and exercise on the relationship between low birthweight and pregnancy complications may yield important results on whether modifiable lifestyle factors could reduce the risk of pregnancy complications among those born small.

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Data sharing: The SCOPE study, which commenced recruitment in 2004, did not seek specific consent from participants for sharing their data publicly. However, the SCOPE Consortium Scientific Advisory Board invites applications to use the collected data via email to the chairperson, Amy Aherne at amy.aherne@ucc.ie. Applicants will be asked to complete a Research Application Form specifying details for their planned study which will then be reviewed by the SCOPE Scientific Advisory Board. The SCOPE Consortium is keen to promote collaboration among researchers and to see our unique SCOPE database and pregnancy biobank used in studies which meet our ethics and consenting process. The SCOPE consortium is a member of the International Pregnancy Collaboration (<https://pregnancyclab.tghn.org/>) and has participated in several studies involving shared data.

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Figure 1 Study Population

Includes 14 spontaneous preterm birth (SPTB) and SGA, 11 SPTB and preeclampsia, 12 sPTB and GDM. ^ Includes 18 gestational diabetes (GDM) and PE, 12 GDM and SPTB. \$ These included any pregnancy that was not completely uncomplicated but were not complicated by any of the major pregnancy complications and included those requiring admission to hospital for other significant medical or surgical conditions, antepartum haemorrhage, isolated episodes of increased blood pressure, cholestasis, chromosomal abnormalities and congenital anomalies in infant.

Table 1 Characteristics of the study population

	Uncomplicated (N = 3200)	Preeclampsia (N = 347)	P value	GH (N = 357)	P value	SGA (N = 433)	P value	sPTB (N = 216)	P value	Uncomplicated* (N = 1857)	GDM* (N = 97)	P value
Age (years)	28.8 ± 5.3	28.2 ± 5.8	0.06	28.6 ± 5.29	0.28	28.4 ± 5.7	0.11	28.5 ± 5.8	0.71	28.2 ± 5.6	29.0 ± 5.4	0.17
Ethnicity			0.5		0.03		0.27		0.02			<0.001
Caucasian	2948 (92.1%)	319 (91.9%)		338 (94.7%)		390 (90.1%)		203 (93.9%)		1667 (89.8%)	80 (82.5%)	
Polynesian	61 (1.9%)	9 (2.6%)		10 (2.8%)		9 (2.1%)		1 (0.5%)		60 (3.2%)	1 (1.0%)	
Asian	85 (2.7%)	5 (1.4%)		1 (0.28%)		11 (2.5%)		1 (0.5%)		73 (3.9%)	6 (6.2%)	
Indian	54 (1.7%)	7 (2.02%)		5 (1.4%)		10 (2.3%)		8 (3.7%)		31 (1.7%)	9 (9.3%)	
Other	52 (1.6%)	7 (2.02%)		3 (0.8%)		13 (3%)		3 (1.4%)		26 (1.4%)	1 (1.0%)	
Gravidity			0.76		0.06		0.06		<0.001			0.14
1	2508 (78.4%)	268 (77.2%)		298 (83.5%)		319 (73.7%)		150 (69.4%)		1407 (758%)	65 (67.0%)	
2	542 (16.9%)	64 (18.4%)		49 (13.7%)		93 (21.5%)		44 (20.4%)		341 (18.4%)	25 (25.9%)	
≥ 3	150 (4.7%)	15 (4.3%)		10 (2.8%)		21 (4.8%)		22 (10.2%)		109 (5.9%)	7 (7.2%)	
At 15 ± 1 weeks												
Smoking	291 (9.1%)	35 (10.1%)	0.61	32 (8.9%)	1	91 (21.02%)	<0.001	36 (16.7%)	<0.001	163 (8.8%)	8 (8.3%)	1
Body mass index (kg/m ²)	24.8 ± 4.3	27.9 ± 6.3	<0.001	27.8 ± 5.5	<0.001	25.1 ± 4.9	0.52	25.6 ± 5.4	0.1	25.0 ± 4.6	30.4 ± 6.8	<0.001
SBP (mmHg)	105 ± 10	113 ± 11	<0.001	113 ± 10	<0.001	107 ± 10	0.07	108 ± 11	0.006	106 ± 10	114 ± 13	<0.001
DBP (mmHg)	64 ± 7	70 ± 8	<0.001	70 ± 8	<0.001	65 ± 8	0.33	66 ± 8	0.02	63.5 ± 7.7	70.1 ± 9.5	<0.001
Pregnancy outcome												
Gestation at delivery (wks)	40.2 ± 1.1	38.3 ± 2.7	<0.001	39.8 ± 1.6	0.001	39.3 ± 3.2	<0.001	34.2 ± 3.4	<0.001	40.1 ± 1.2	38.5 ± 2.2	<0.001
Birthweight (g)	3591 ± 397	2934 ± 734	<0.001	3515 ± 475	0.002	2694 ± 517	<0.001	2387 ± 721	<0.001	3588 ± 398	3320 ± 657	<0.001
Birthweight centile	54 ± 25	31 ± 31	<0.001	50 ± 27	0.001	5 ± 3	<0.001	49 ± 31	0.02	54 ± 25	53 ± 32	0.6

Results are expressed as mean ± SD or N (%). All p values are for comparison of complicated pregnancy group with uncomplicated. SBP, systolic blood pressure; DBP, diastolic blood pressure

* Data from Adelaide and Auckland SCOPE cohort only

Table 2 Association between maternal weight at birth and pregnancy complications

Risk for pregnancy complications	Maternal birthweight				
	<2500g	2500-2999g	3000-3499g	3500-3999	≥4000
Uncomplicated n (%)	154 (4.8)	533 (16.7)	1281 (40.0)	934 (29.2)	298 (9.3)
Preeclampsia n (%)	30 (8.6)	78 (22.5)	150 (43.2)	67 (19.3)	22 (6.3)
OR (95% CI)	1.6 (1.0 - 2.5)	1.2 (0.9 - 1.6)	1	0.6 (0.5 - 0.8)	0.6 (0.4 - 1.0)
aOR (95% CI)	1.7 (1.0 - 2.9)	1.2 (0.9 - 1.7)	1	0.6 (0.5 - 0.9)	0.6 (0.4 - 1.0)
GH n (%)	28 (7.8)	74 (20.7)	127 (35.6)	97 (27.2)	31 (8.7)
OR (95% CI)	1.8 (1.2 - 2.9)	1.4 (1.0 - 1.9)	1	1.0 (0.8 - 1.4)	1.0 (0.7 - 1.5)
aOR (95% CI)	2.2 (1.3 - 3.7)	1.4 (1.1 - 2.0)	1	1.0 (0.8 - 1.4)	1.0 (0.6 - 1.5)
SGA n (%)	36 (8.3)	110 (25.4)	169 (39.0)	98 (22.6)	20 (4.6)
OR (95% CI)	1.7 (1.2 - 2.6)	1.5 (1.2 - 2.0)	1	0.8 (0.6 - 1.0)	0.5 (0.3 - 0.8)
aOR (95% CI)	1.9 (1.1 - 3.2)	1.6 (1.2 - 2.1)	1	0.8 (0.6 - 1.0)	0.5 (0.3 - 0.8)
sPTB n (%)	20 (9.3)	37 (17.1)	88 (40.7)	54 (25.0)	17 (7.9)
OR (95% CI)	1.8 (1.1 - 3.1)	1.0 (0.7 - 1.5)	1	0.8 (0.6 - 1.2)	0.8 (0.5 - 1.4)
aOR (95% CI)	1.3 (0.7 - 2.4)	0.9 (0.6 - 1.3)	1	0.9 (0.6 - 1.2)	0.8 (0.5 - 1.4)
*Uncomplicated n (%)	96 (5.2)	316 (17.0)	737 (39.7)	543 (29.2)	165 (8.9)
*GDM n (%)	11 (11.3)	24 (24.7)	39 (40.2)	16 (16.5)	7 (7.2)
OR (95% CI)	2.0 (1.0 - 4.1)	1.4 (0.8 - 2.3)	1	0.6 (0.3 - 1.1)	0.8 (0.4 - 1.9)
aOR (95% CI)	2.4 (1.01 - 5.8)	1.3 (0.7 - 2.3)	1	0.6 (0.3 - 1.1)	0.8 (0.3 - 1.8)

Preeclampsia adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of preeclampsia, hypertension in first degree relative, maternal gestational age at birth, infant sex and recruitment centre

Gestational hypertension (GH) adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of hypertensive disease of pregnancy, hypertension in first degree relative, maternal gestational age at birth, infant sex and recruitment centre

SGA adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of low birthweight, maternal gestational age at birth, infant sex and recruitment centre

Spontaneous preterm (sPTB) birth adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of sPTB, maternal gestational age at birth, infant sex and recruitment centre

Gestational diabetes mellitus (GDM) adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of diabetes, maternal gestational age at birth, infant sex and recruitment centre

* Data from Adelaide and Auckland SCOPE cohort only

Table 3: Risk of pregnancy complications according to maternal birthweight and BMI at 15 weeks' gestation

Risk for pregnancy	Maternal birthweight (g) / BMI (kg/m ²)			
	≥ 2500g, <25 kg/m ² (Gp 1)	≥ 2500g, ≥ 25 kg/m ² (Gp 2)	<2500g, <25 kg/m ² (Gp 3)	<2500g, ≥ 25 kg/m ² (Gp 4)
Uncomplicated n (%)	1882 (58.81)	1164 (36.38)	86 (2.69)	68 (2.12)
Preeclampsia n (%)	114 (32.85)	203 (58.5)	11 (3.17)	19 (5.48)
OR (95% CI)	1	2.9 (2.3 - 3.7)	2.1 (1.1 - 4.1)	4.6 (2.7 - 7.9)
aOR (95% CI)	1	1.5 (1.04 – 2.02)	2.0 (0.9 – 4.1)	2.3 (1.2 – 4.5)
GH n (%)	112 (31.37)	217 (60.78)	13 (3.64)	15 (4.2)
OR (95% CI)	1	3.1 (2.5 - 3.9)	2.5 (1.4 - 4.7)	3.7 (2.1 - 6.7)
aOR (95% CI)	1	1.6 (1.1 – 2.2)	3.0 (1.6 – 5.9)	2.2 (1.1 – 4.5)
SGA n (%)	109 (50.46)	87 (40.28)	9 (4.17)	11 (5.09)
OR (95% CI)	1	1.1 (0.9 - 1.4)	1.9 (1.1 - 3.1)	1.9 (1.1 - 3.3)
aOR (95% CI)	1	1.0 (0.7 – 1.4)	1.5 (0.8 - 2.8)	1.4 (0.7 – 2.9)
sPTB n (%)	234 (54.04)	163 (37.64)	20 (4.62)	16 (3.7)
OR (95% CI)	1	1.3 (0.9 - 1.7)	1.8 (0.9 - 3.7)	2.8 (1.4 - 5.4)
aOR (95% CI)	1	0.9 (0.6 – 1.4)	1.3 (0.6 – 2.8)	1.4 (0.6 – 3.2)
Uncomplicated n (%)	1049 (56.49)	712 (38.34%)	54 (2.91)	42 (2.26)
GDM n (%)	25 (25.77)	61 (62.89)	1 (1.03)	10 (10.31)
OR (95% CI)	1	3.6 (2.2 – 5.8)	0.78 (0.1 – 5.8)	9.9 (4.5 - 22.1)
aOR (95% CI)	1	0.9 (0.5 – 1.9)	0.8 (0.1 – 1.9)	3.2 (1.1 – 9.5)

Preeclampsia adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of preeclampsia, hypertension in first degree relative, maternal gestational age at birth, infant sex and recruitment centre

Gestational hypertension (GH) adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of hypertensive disease of pregnancy, hypertension in first degree relative, maternal gestational age at birth, infant sex and recruitment centre

SGA adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of low birthweight, maternal gestational age at birth, infant sex and recruitment centre

Spontaneous preterm (sPTB) birth adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of sPTB, maternal gestational age at birth, infant sex and recruitment centre

Gestational diabetes mellitus (GDM) adjusted for maternal age, smoking at 15 weeks' gestation, ethnicity, socioeconomic status, family history of diabetes, maternal gestational age at birth, infant sex and recruitment centre

* Data from Adelaide and Auckland SCOPE cohort only

Supplementary table 1 Characteristics of the study population stratified according to recruiting centre

Characteristic	Adelaide University (n=1072)	Kings College, London (n=182)	Manchester University (n=306)	University College, Cork (n=1709)	University of Auckland (n=1918)	University of Leeds (n=140)	Total (n=5327)
Age (years): Mean (SD)	23.8 (5.1)	31.1 (4.7)	28.3 (5.5)	29.8 (4.5)	30.4 (4.7)	26.1 (5.6)	28.7 (5.4)
Ethnicity: N(%)							
Caucasian	1019 (95.1)	149 (81.9)	263 (85.9)	1675 (98.0)	1644 (85.7)	128 (91.4)	4878 (91.6)
Polynesian	5 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	96 (5.0)	0 (0.0)	102 (1.9)
Asian	19 (1.8)	6 (3.3)	7 (2.3)	5 (0.3)	91 (4.7)	1 (0.7)	129 (2.4)
Indian	3 (0.3)	7 (3.8)	15 (4.9)	19 (1.1)	64 (3.3)	5 (3.6)	113 (2.1)
Other	26 (2.4)	19 (10.4)	21 (6.9)	10 (0.6)	23 (1.2)	6 (4.3)	105 (2.0)
Gravidity: N(%)							
1	790 (73.7)	126 (69.2)	220 (71.9)	1443 (84.4)	1446 (75.4)	102 (72.9)	4127 (77.5)
2	212 (19.8)	43 (23.6)	70 (22.9)	228 (13.3)	366 (19.1)	25 (17.9)	944 (17.7)
≥ 3	70 (6.5)	13 (7.1)	16 (5.2)	38 (2.2)	106 (5.5)	13 (9.3)	256 (4.8)
Woman's reported birthweight (g): Mean (SD)	3240.2 (585.1)	3251.1 (537.0)	3266.2 (531.4)	3360.6 (534.9)	3314.2 (537.7)	3277.0 (504.1)	3308.3 (547.1)
Woman's reported gestational age at delivery (weeks): Mean (SD)	39.4 (2.1)	39.6 (1.9)	39.6 (1.9)	39.9 (1.5)	39.9 (1.9)	39.8 (1.5)	39.8 (1.8)
At 15 ± 1 weeks							
Smoking: N(%)	252 (23.5)	8 (4.4)	33 (10.8)	172 (10.1)	71 (3.7)	30 (21.4)	566 (10.6)
Body mass index (kg/m ²): Mean (SD)	27.2 (6.6)	24.4 (3.8)	25.1 (4.8)	24.9 (4.2)	24.8 (4.2)	25.2 (5.1)	25.3 (4.9)
SBP (mmHg): Mean (SD)	109.7 (10.2)	104.2 (9.0)	104.5 (9.0)	105.6 (10.3)	106.7 (10.5)	110.0 (13.0)	106.8 (10.5)
DBP (mmHg): Mean (SD)	64.5 (8.0)	65.2 (7.0)	63.7 (6.8)	66.7 (7.3)	64.5 (8.2)	65.2 (8.4)	65.2 (7.8)
Pregnancy outcome							
Gestation at delivery (weeks): Mean (SD)	39.3 (2.7)	39.8 (2.4)	39.8 (2.5)	39.8 (2.0)	39.5 (2.5)	40.3 (1.8)	39.6 (2.4)
Birthweight (g): Mean (SD)	3334.8 (662.2)	3381.4 (592.1)	3340.9 (611.1)	3438.7 (567.7)	3406.4 (611.3)	3386.4 (550.4)	3397.2 (607.3)
Birthweight centile: Mean (SD)	46.1 (29.5)	45.5 (29.5)	42.7 (28.6)	48.5 (29.5)	48.4 (28.9)	38.7 (29.1)	47.3 (29.3)
PE: N(%)	108 (10.1)	7 (3.8)	12 (3.9)	104 (6.1)	101 (5.3)	15 (10.7)	347 (6.5)
GHTN: N(%)	90 (8.4)	6 (3.3)	11 (3.6)	161 (9.4)	89 (4.6)	0 (0.0)	357 (6.7)