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Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study

LME McCowan,[a] CT Roberts,[b] GA Dekker,[c] RS Taylor,[a] EHY Chan,[a] LC Kenny,[d] PN Baker,[e] R Moss-Morris,[f] LC Chappell,[g] RA North,[g] on behalf of the SCOPE consortium

[a] Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand [b] Discipline of Obstetrics and Gynaecology, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, Australia [c] Women and Children's Division, Lyell McEwin Hospital, University of Adelaide, Adelaide, Australia [d] Anu Research Centre, Department of Obstetrics and Gynaecology, University College, Cork, Ireland [e] Faculty of Medicine & Dentistry, University of Alberta, Edmonton, AB, Canada [f] School of Psychology, University of Southampton, Southampton, UK [g] Division of Reproduction and Endocrinology, St Thomas' Hospital King's College London, London, UK
Correspondence: Prof. LME McCowan, Department of Obstetrics and Gynaecology, University of Auckland, Private Bag 92019, Auckland, New Zealand. Email l.mccowan@auckland.ac.nz

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Objective To identify clinical and ultrasound variables associated with the birth of small-for-gestational-age (SGA) infants by customised centiles, subclassified according to whether their mothers were normotensive or developed hypertensive complications.

Design Prospective, multicentre cohort study.

Setting Participating centres of the Screening for Pregnancy Endpoints (SCOPE) study in Auckland, New Zealand, Adelaide, Australia, Manchester and London, UK, and Cork, Ireland.

Population The 3513 nulliparous participants of the SCOPE study.

Methods Women were interviewed at 15 ± 1 weeks, and had ultrasound growth measurements and umbilical and uterine Doppler studies at 20 ± 1 weeks. Variables associated with SGA infants were identifed using logistic regression.

Main outcome measures Small for gestational age (i.e. a birthweight of less than the tenth customised centile), normotensive-SGA and hypertensive-SGA. Comparison groups for statistical analyses were non-SGA, normotensive non-SGA and hypertensive non-SGA.

Results Among 376 (10.7%) SGA infants, 281 (74.7%) were normotensive-SGA and 95 (25.3%) were hypertensive-SGA. Independent risk factors for normotensive-SGA were low maternal birthweight, low fruit intake pre-pregnancy, cigarette smoking, increasing maternal age, daily vigorous exercise, being a tertiary student, head and abdominal circumference of less than the tenth centile and increasing uterine artery Doppler indices at the 20-week scan. Protective factors were: high green leafy vegetable intake pre-pregnancy, and rhesus-negative blood group. Risk factors for hypertensive-SGA were conception by *in vitro* fertilisation, previous early pregnancy loss and femur length of less than tenth centile at the 20-week scan.

Conclusions Risk factors for infants who are SGA by customised centiles have been identified in a cohort of healthy nulliparous women. A number of these factors are modifiable; however, further studies are needed to replicate these findings.

Keywords Birthweight, customised birthweight centile, fetal growth restriction, risk factors, small for gestational age.

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Introduction

Small-for-gestational-age (SGA) babies comprise approximately 50% of stillbirths, and survivors are at increased risk of cardiovascular disease and diabetes in adulthood.[1,2] Historically, SGA has most commonly been defined using population birthweight centiles, but the use of customised centiles has enabled the identification of small babies at higher risk of morbidity and mortality than those identified by population centiles.[3,4] Less than half of all SGA babies are identified before birth,[5] and improved antenatal identification could reduce the associated morbidity and

mortality. When customised SGA is diagnosed before birth, approximately two-thirds have abnormal umbilical and/or uterine artery Doppler indices, suggesting that these pregnancies are more likely to have placental disease and true growth restriction.[4] Whereas many publications have described risk factors for SGA babies by population centiles,[6–8] no prospective studies have reported risk factors for babies classified as SGA using customised birthweight centiles.[9]

Small for gestational age can be broadly classified into two main categories: SGA with a normotensive mother (normotensive-SGA) and SGA where the mother has hypertensive pregnancy complications (hypertensive-SGA). Our recent large study of 17,855 nulliparous women showed that the vast majority of SGA infants (81.7%) were born to normotensive women, fewer (10.7%) were born to women with gestational hypertension and the remainder (7.6%) were born to women with pre-eclampsia.[10] Previous studies of risk factors for SGA have therefore been dominated by risk factors for normotensive-SGA pregnancies, and risk factors for the subgroup of SGA pregnancies with hypertensive mothers have not previously been well characterised. The primary aims were to identify early pregnancy risk factors amongst healthy nulliparous women for:

- SGA infants by customised birthweight centiles;
- SGA infants amongst normotensive women;
- SGA infants amongst women with hypertensive complications in pregnancy.

Furthermore, we wished to determine whether these clinical risk factors would be modified by the addition of data from the 20-week ultrasound scan. Pregnancy outcomes between normotensive-SGA and hypertensive-SGA pregnancies were compared as a secondary aim.

Methods

The participants were healthy nulliparous women with singleton pregnancies recruited to the Screening for Pregnancy Endpoints (SCOPE) study between November 2004 and August 2008, in Auckland, New Zealand, Adelaide, Australia, Manchester and London, UK, and Cork, Ireland. SCOPE is a prospective, multicentre cohort study with the main aim of developing screening tests to predict pre-eclampsia, SGA infants and spontaneous preterm birth. Ethical approval was gained from local ethics committees and all women provided written informed consent.

Women were recruited to the SCOPE study at 15 ± 1 weeks of gestation. The estimated date of delivery was calculated from a certain last menstrual period (LMP) date. The estimated date of delivery was only adjusted if: (1) a scan performed before 16 weeks of gestation found a difference of ≥7 days between the scan gestation and that calculated by the LMP; or (2) a difference of ≥10 days was found between the 20-week scan gestation and that calculated from the LMP. If the LMP date was uncertain, then scan dates were used to calculate the estimated date of delivery. Those considered at high risk of pre-eclampsia, SGA or spontaneous preterm birth, because of underlying medical conditions (including known pre-existing chronic hypertension on antihypertensive medication or with a blood pressure >160/100 mmHg at 15 weeks of gestation), gynaecological history, three or more previous miscarriages or terminations of pregnancy, or who received interventions that may modify pregnancy outcome, were excluded.

Women who agreed to participate were interviewed and examined by a research midwife at 15 ± 1 and 20 ± 1 weeks of gestation, and underwent ultrasound examination at 20 ± 1 weeks of gestation. Detailed clinical data were collected at each time point, which included demographic information, socio-economic index, with a higher score indicating higher socio-economic status,[11] medical history, the woman's birthweight, previous early pregnancy losses (miscarriage or termination of pregnancy), history of infertility, duration of sexual relationship, gynaecological history, and family history of obstetric complications and medical disorders. A tertiary education student was a participant still attending university. A strong family history of pre-eclampsia was considered to be two-first-degree family members (mother and/or sister[s]) with a history of pre-eclampsia. Current pregnancy data included vaginal bleeding, hyperemesis, dietary information, folate level and low-dose multivitamin supplementation, smoking, alcohol and recreational drug use, defined as taking any of the following: marijuana, herbal highs, binge alcohol or hard drugs (cocaine, opiates, amphetamines or methylamphetamines). A high intake of green leafy vegetables was defined as three or more portions per day, and low fruit intake was defined as less than one portion per week. Psychological scales were completed, including the Perceived Stress Scale,[12] Edinburgh Postnatal Depression Scale,[13] and state version of the short-form State–Trait Anxiety Inventory.[14] Vigorous exercise was defined as daily exercise leading to heavy breathing or being out of breath.[15] Maternal physical measurements obtained at 15 weeks of gestation included blood pressure, height, weight, and arm, waist, hip and head circumferences. Maternal lipids and random glucose were also measured at 15 weeks of gestation. At the time of interview, data were entered into an internet accessed, auditable database (Medscinet^{AB}, Stockholm, Sweden).

Ultrasound examination was performed at 20 weeks of gestation, including fetal measurements (biparietal diameter, femur length, and head and abdominal circumference) and Z scores were calculated so that measurements were independent of gestational age at which the scan was performed. Doppler studies of the umbilical and uterine

arteries were performed,[16] and mean uterine resistance index (RI) was calculated from the left and right uterine RI. If only a left or right RI was available, this was used as 'mean RI' (n = 10). Women who did not have uterine or umbilical artery Doppler studies performed at 20 weeks of gestation (n = 114, 3.2%) were excluded from the analysis, which combined clinical variables collected at 15 weeks of gestation with data from the 20-week scan.

Participants were followed prospectively, with pregnancy outcome data and infant measurements recorded by research midwives, usually within 72 hours of birth. Stringent data monitoring included: (1) individually checking all data for each participant, and (2) using a customised software program to detect any systematic data-entry errors.

Outcome measures

The primary outcomes were: SGA, defined as a birthweight of less than the tenth customised centile, adjusted for maternal height, booking weight and ethnicity, as well as gestational age at delivery and sex of the infant;[17] normotensive-SGA, defined as birth of an SGA infant where the mother did not have hypertension; and hypertensive-SGA, defined as birth of an SGA infant where the mother had either gestational hypertension, pre-eclampsia and/or mild chronic hypertension.

Definitions

Gestational hypertension was defined as systolic blood pressure of ≥140 mmHg, and/or diastolic blood pressure of ≥90 mmHg, on at least two occasions, 4 hours apart, after 20 weeks of gestation, but before the onset of labour. Pre-eclampsia was defined as gestational hypertension or postpartum hypertension, as defined above, developing for the first time after delivery with proteinuria (24-hour urinary protein level of ≥ 300 mg, a spot urine protein : creatinine ratio of ≥ 30 mg/mmol creatinine, or urine dipstick protein level of ≥ 2+/1g/L) or any multisystem complication of pre-eclampsia.[18,19] Mild chronic hypertension was defined as a systolic blood pressure of 140–159 mmHg and/or a diastolic blood pressure of 90–99 mmHg, identified on more than one reading at 15 or 20 weeks of gestation. A pre-pregnancy diagnosis of chronic hypertension was an exclusion criterion for the study. Non-SGA referred to all women who did not have SGA babies, and this group included other pregnancy complications such as preterm birth or pre-eclampsia with a normally grown baby. Perinatal deaths included stillbirths (defined as the birth of an infant at 20 weeks of gestation or later, with no signs of life, including deaths after 20 weeks of gestation as a result of the termination of a pregnancy [n = 4]) and neonatal deaths (defined as the death of a liveborn infant in the first 28 days of life).

Statistical methods

Three control groups were selected for comparisons: for SGA, the referent group was women without SGA infants (non-SGA); for normotensive-SGA, controls were normotensive women without an SGA infant (normotensive non-SGA); and for hypertensive-SGA, the control group comprised hypertensive women with non-SGA infants (hypertensive non-SGA).

Data were available for more than 98% of the participants for all variables included in the SGA database, with the exception of 96.1 and 93.8% complete booking haematocrit and participant birthweight data, respectively.

Missing data were imputed for multivariate analyses using expected maximization,[20] or for variables that were unrelated to other data points, and had <1% missing data, the median (continuous variables) or mode (categorical variables) was used.

Univariate analysis was performed using clinical and ultrasound variables. A Student's t-test or Wilcoxon rank sum test was used for the comparison of continuous variables. Categorical variables were compared using chi-square or Fisher's exact tests. Multivariate analysis was performed using stepwise logistic regression, firstly using clinical variables only, and then using clinical and ultrasound variables, to compare SGA, normotensive-SGA and hypertensive-SGA with their respective controls.

Demographic factors (age, ethnicity and socio-economic index) and risk factors with $P < 0.01$ in univariate analysis were available for inclusion in the multivariate model. Ninety-five, 79 and 48 variables had $P < 0.01$ for SGA, normotensive-SGA and hypertensive-SGA, respectively. Sixty-six, 49 and 34 variables, respectively, were then excluded because the information was covered by other variables, they had cell counts of less than five on chi-square analysis, or the variables were collected for other purposes, such as studies on preterm birth. This resulted in 29 (SGA), 26 (normotensive-SGA) and 12 (hypertensive-SGA) variables being available (details are available in Appendix S1) in the respective logistic regression models. A significance level of 0.05 was required for a variable to stay in a model under stepwise selection.

Results

Healthy nulliparous women with singleton pregnancies (n = 3560) were recruited to the SCOPE study between November 2004 and August 2008 in Auckland, New Zealand, Adelaide, Australia, London and Manchester, UK, and Cork, Ireland, and follow-up was completed in 98.7% of participants (Figure 1). Of the 376 (10.7%) infants who were SGA according to customised centiles, 281 (74.7%) were born to normotensive mothers and 95 (25.3%) were

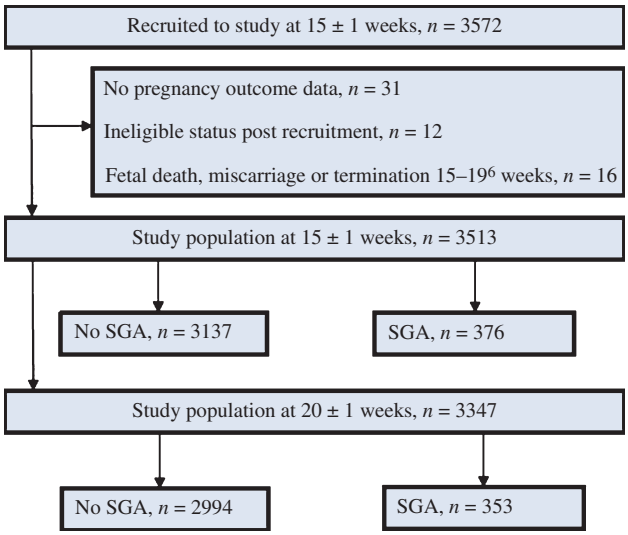

Figure 1. Participants recruited and final study population.

born to hypertensive mothers. Amongst the hypertensive-SGA pregnancies, 44 (46.3%) women had pre-eclampsia, 49 (51.6%) had gestational hypertension and five (5.3%) had mild chronic hypertension alone. Approximately a quarter of SGA babies (100, 26.6%) were diagnosed before birth. Antenatal recognition of SGA was similar amongst normotensive mothers (69, 24.6%) and hypertensive mothers (31, 32.6%); $P = 0.12$.

Maternal characteristics and pregnancy outcomes in relation to SGA status are detailed in Table 1. Mothers in the hypertensive-SGA group had higher body mass index (BMI) values, and their infants were born earlier, with lower birthweight centiles, than normotensive-SGA infants (Table 2). Rates of smoking did not differ between SGA groups. Clinical risk factors, recorded at 15 weeks of gestation, with significant independent associations with SGA, are shown in Table 3. Addition of data from the 20-week scan resulted in fetal measurements and uterine and umbilical artery RI replacing low fruit intake pre-pregnancy. In the final model, 14 variables were associated with an increased risk of SGA, and three were protective.

A subgroup of the risk factors for SGA ($n = 11$) were associated with normotensive-SGA, two of which were protective (Table 4). Amongst the 456 women with hypertensive complications, 95 (20.8%) had SGA babies. The small number of clinical variables independently associated with risk of SGA amongst these hypertensive women are shown in Table 5. A loss of a previous pregnancy before 20 weeks of gestation was associated with an increased risk of hypertensive-SGA, and two-thirds of these previous losses in hypertensive women had occurred with the same partner as in the current pregnancy.

Table 1. Study population characteristics at 15 weeks of gestation and pregnancy outcome

	Non-SGA *n* = 3137	SGA *n* = 376	*P*
Maternal characteristics			
Maternal age (years)	28.1 (5.8)	28.3 (5.9)	0.49
Ethnicity (%)			
White	2731 (87)	319 (85)	0.29
Maori or Pacific Islander*	99 (3)	13 (3)	
Indian	85 (3)	14 (4)	
Asian	139 (4)	14 (4)	
Other**	83 (3)	16 (4)	
Primigravid (%)	2355 (75)	258 (69)	0.007
Single (%)	242 (8)	32 (9)	0.59
No paid employment (%)	504 (16)	76 (20)	0.04
Socio-economic index	41 (17)	40 (17)	0.20
Smoking status at 15 weeks (%)			
Non-smoker	2470 (79)	267 (71)	<0.0001
Ceased smoking before 15 weeks	352 (11)	37 (10)	
Current smoker	315 (10)	72 (19)	
BMI (kg/m^2)	25.4 (5.1)	26.2 (6.0)	0.02
BMI category (%)			
<20.0	240 (8)	31 (8)	0.007
20.0–24.9	1521 (48)	160 (43)	
25.0–29.9	887 (28)	101 (27)	
≥30	489 (16)	84 (22)	
Participant's birthweight (g)	3302 (549)	3155 (560)	0.0001
Systolic blood pressure	108 (11)	110 (11)	0.003
Diastolic blood pressure	65 (8)	66 (9)	0.001
Pregnancy outcome			
Birthweight (g)	3487 (514)	2573 (605)	<0.0001
Gestational age at delivery (weeks)	39.6 (2.0)	38.7 (3.8)	<0.0001
Customised birthweight centile	53.1 (26.1)	4.6 (2.9)	<0.0001
Total preterm births (<37 weeks) (%)	186 (6)	59 (16)	<0.0001
Admitted to neonatal unit (%)	310 (10)	96 (26)	<0.0001
Perinatal deaths (%)	12 (0.4)	5 (1.3)	0.03

Results expressed as *n* (%) or mean (SD).
*Includes 71 Maori and 41 Pacific Islanders.
**Includes 22 Australian Aborigines.

Discussion

This is the first study to report risk factors for SGA infants defined using customised birthweight centiles, and also to describe the risk factors associated with normotensive-SGA and hypertensive-SGA subgroups. The risk profiles for normotensive-SGA and hypertensive-SGA differed, and several of the risk factors identified in this study are modifiable, with potential public health implications. In previous studies of risk factors for infants judged to be SGA by population centiles in developed countries, maternal smoking and small maternal size have dominated.[6] Not surprisingly,

Table 2. Maternal characteristics and pregnancy outcome amongst normotensive- and hypertensive-SGA pregnancies

	Normotensive-SGA *n* = 281	Hypertensive-SGA *n* = 95	*P*
Maternal characteristics			
Maternal age (years)	28.3 (5.8)	28.5 (6.2)	0.69
Ethnicity (%)			
White	235 (84)	84 (89)	0.35
Maori or Pacific Islander*	9 (3)	4 (4)	
Indian	10 (4)	4 (4)	
Asian	12 (4)	2 (2)	
Other**	15 (5)	1 (1)	
Primigravid (%)	197 (70)	61 (64)	0.28
Single (%)	26 (9)	6 (6)	0.38
No paid employment (%)	58 (21)	18 (19)	0.72
Socio-economic index	40 (16)	40 (18)	0.78
Smoking status at 15 weeks (%)			
Non-smoker	201 (71)	66 (69)	0.32
Ceased smoking before 15 weeks	24 (9)	13 (14)	
Current smoker	56 (20)	16 (17)	
BMI (kg/m^2)	25.3 (5.2)	28.8 (7.1)	<0.0001
BMI category (%)			
<20.0	27 (10)	4 (4)	<0.0001
20.0–24.9	136 (48)	24 (25)	
25.0–29.9	69 (25)	32 (34)	
>30	49 (17)	35 (37)	
Participant's birthweight (g)	3163 (579)	3132 (503)	0.65
Systolic blood pressure 15 weeks	108 (10)	115 (12)	<0.0001
Diastolic blood pressure 15 weeks	64 (8)	71 (10)	<0.0001
Pregnancy outcome			
Birthweight (g)	2644 (580)	2364 (632)	<0.0001
Gestational age at delivery (weeks)	39.0 (3.9)	37.6 (3.4)	0.002
Customised birthweight centile	5.0 (2.9)	3.6 (2.8)	<0.0001
Total preterm births (<37 weeks) (%)	27 (10%)	32 (34%)	<0.0001
Admitted to neonatal unit (%)	52 (19%)	44 (46%)	<0.0001
Perinatal deaths (%)	4 (1.4%)	1 (1.1%)	1.0

Results expressed as *n* (%), mean (SD).
*Includes four Maori and nine Pacific Islanders.
**Includes six Australian Aborigines.

risk factors for customised-SGA infants also include cigarette smoking, but maternal height and weight are not risk factors, as these are adjusted for during the calculation of the customised centile.

Risk factors for SGA infants are predominantly influenced by the normotensive-SGA group, as this subgroup comprises three-quaters of all SGA infants. Maternal diet pre-conception influenced the risk of both SGA and normotensive-SGA. The daily consumption of at least three servings of green leafy vegetables in the month prior to pregnancy was associated with an approximate 50% reduction in SGA and normotensive-SGA, whereas women who consumed fruit less than weekly had a two-fold increase in the risk of normotensive-SGA. Others have also reported that a high intake of green leafy vegetables and fruit was associated with higher mean birthweight, or a reduced risk of SGA, as defined by population centiles.[21–23] The specific agents in fruits and vegetables that may be protective are unknown, but potential mediators include micronutrients (such as ascorbate, carotenoids, folate and magnesium), dietary fibre and other phytochemicals. Alternatively, a high vegetable and fruit diet may be a surrogate for a healthier lifestyle or reflect unaccounted confounding factors. In contrast to Mitchell *et al.*,[22] we did not find a significant independent association between not taking folic acid supplements and SGA. This difference may be explained by the high use of folic acid by these SCOPE participants (71.5% at 15 weeks of gestation). Our data therefore suggest that specific foods may confer advantages for fetal growth, but that these beneficial effects may not be seen with nutritional supplements. Given the fast-food culture, possible dietary risk factors for SGA are of importance, as they are potentially amenable to public health interventions.

Cigarette smoking at 15 weeks of gestation was associated with a 30–40% increase in risk for every five cigarettes smoked per day in both SGA and normotensive-SGA groups. We have recently demonstrated that if smoking is ceased by 15 weeks of gestation, the risk of SGA is the same as in non-smokers.[24] Another modifiable risk factor for SGA was the use of recreational drugs in early pregnancy (marijuana, binge alcohol or hard drugs [predominantly methamphetamine]).

Only 1.1% of participants engaged in daily vigorous exercise, but these women had an approximate three-fold increase in SGA and normotensive-SGA. Whereas low to moderate intensity exercise is recommended in pregnancy,[25] previous studies have also reported that high-intensity exercise significantly reduced birthweight,[15,26] perhaps mediated by reduced uterine blood flow.[27] Our data suggest that this effect is not mediated by low maternal BMI.

Consistent with the findings from a previous study,[9] the rhesus-negative maternal blood group was associated with an approximately 50% reduction in SGA and normotensive-SGA. The gene encoding the rhesus factor (*RHD*) lies adjacent to *RHCE*, and within a cluster of genes on chromosome 1, which are associated with transportation mechanisms into cells for several molecules, including zinc,

Table 3. Multivariate comparisons of clinical, behavioural and ultrasound risk factors for SGA by customised birthweight centiles

Risk factors	Non-SGA *N* = 3137	SGA *N* = 376	Clinical data 15 weeks aOR (95% CI)	Clinical data 15+ 20 week Scan***** aOR (95% CI)
Pre-pregnancy				
Participant's birthweight (per 200 g ↓)*	3302 (549)	3155 (560)	1.1 (1.03–1.12)	1.1 (1.03–1.12)
Low fruit intake**	289 (9.2%)	57 (15.2%)	1.5 (1.1–2.1)	–
*High green leafy vegetable intake****	*292 (9.3%)*	*16 (4.3%)*	*0.47 (0.28–0.79)*	*0.55 (0.33–0.93)*
15 weeks of gestation				
Age (per 5 year ↑)	28.1 (5.8)	28.3 (5.9)	1.2 (1.1–1.3)	1.3 (1.1–1.4)
Tertiary education student	97 (3.1%)	22 (5.9%)	2.6 (1.6–4.2)	2.7 (1.6–4.5)
Strong family history of pre–eclampsia	19 (0.6%)	7 (1.9%)	3.1 (1.3–7.5)	3.1 (1.2–8.5)
Smoking (per five cigarettes/day ↑)	315 (10.0%)	72 (19.2%)	1.3 (1.1–1.6)	1.3 (1.2–1.6)
Recreational drug use	48 (1.5%)	17 (4.5%)	2.2 (1.2–4.0)	2.2 (1.1–4.2)
Daily vigorous exercise	31 (1.0%)	10 (2.7%)	2.9 (1.4–6.2)	2.7 (1.1–6.6)
Mean arterial pressure (per 5 unit ↑)	79 (8)	81 (9)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
HDL-cholesterol (per 0.2 mmol/l ↓)	1.81 (0.37)	1.76 (0.40)	1.1 (1.02–1.1.2)	1.1 (1.01–1.2)
Head circumference (per 5 cm ↑)	*55.9 (1.7)*	*55.6 (1.8)*	*0.60 (0.43–0.84)*	*0.62 (0.43–0.88)*
Rhesus-negative blood group	*470 (15.0%)*	*35 (9.3%)*	*0.57 (0.39–0.82)*	*0.54 (0.37–0.80)*
20-week ultrasound**				
Fetal head circumference *Z* score <10th centile	267 (9.0%)	57 (16.2%)		1.8 (1.3–2.5)
Fetal abdominal circumference *Z* score <10th centile	259 (8.7%)	63 (18.0%)		1.9 (1.4–2.7)
Average umbilical resistance index (per 0.1 unit ↑)	0.73 (0.07)	0.75 (0.07)		1.4 (1.2–1.7)
Average uterine RI (per 0.1 unit ↑)	0.56 (0.10)	0.61 (0.11)		1.6 (1.5–1.8)

Results expressed as *n* (%), mean (SD) and median (5th–95th) with non-SGA as the referent group. Italics indicate that the factor is protective.
**n* = 2955 and 352, respectively.
***Less than one piece of fruit per week.
****Three or more servings of green leafy vegetables per day.
*****Reduced cohort after exclusion of participants with missing Doppler data *n* = 3347 (non-SGA *n* = 2994; SGA *n* = 353).

glucose and ammonia.[28] *RHD* is deleted from the genome in people with the rhesus-negative blood group. The *rhesus* gene is also co-located with the gene encoding GLUT1, a major glucose transporter in the placenta.[29] Co-inheritance of specific alleles for these genes may explain the protective effect on fetal growth found in this study.

Also in keeping with previous studies, we found that an elevated uterine artery Doppler resistance index and reduced fetal measurements in mid-pregnancy were both associated with SGA.[30,31] A strong family history of pre-eclampsia was also associated with an increased risk of SGA, suggesting that genetic factors may influence placental function, and is consistent with the literature on pre-eclampsia.[32,33]

A few previous studies have investigated a limited range of risk factors for SGA infants born to hypertensive mothers.[34–36] A small number of risk factors for SGA infants born to hypertensive mothers were identified, including small fetal measurements at the 20-week scan, which were common to all groups of SGA. Amongst hypertensive women, a previous early pregnancy loss (two-thirds of which occurred with the same partner as in the current pregnancy) was associated with an approximate two-fold increase in risk of an SGA infant. The inconsistency between our findings and those reported by Saftlas,[37] i.e. the protective effect of a previous early pregnancy loss to the same partner on pre-eclampsia, is explained by differences in the comparison groups. In our study, we are reporting the risk of SGA occurring amongst women with hypertensive complications, whereas Saftlas was comparing cases of pre-eclampsia with women without pre-eclampsia.[37]

Conception by *in vitro* fertilisation, which occurred in 9.5% of hypertensive-SGA cases and 2.8% of hypertensive non-SGA cases, was associated with an approximate four-fold increase in the risk of hypertensive-SGA. Our data are compatible with studies that have found both increased rates of pre-eclampsia and also SGA infants in pregnancies conceived by *in vitro* fertilisation.[37,38]

In contrast to the findings of Odegard *et al.*,[36] who reported that maternal smoking reduced fetal growth in women with pre-eclampsia, we did not find a significant effect of smoking on the risk of hypertensive-SGA after multivariate analysis. This may relate to the lower prevalence of smoking in our study compared with theirs

Table 4. Multivariate comparisons of clinical, behavioural and ultrasound risk factors for normotensive-SGA by customised birthweight centiles

Risk factors	Normotensive non-SGA *n* = 2776	Normotensive-SGA *n* = 281	Clinical data 15 weeks aOR (95% CI)	Clinical data 15 + 20 weeks aOR (95% CI)*
Pre-pregnancy				
Participant's birthweight (per 200 g ↓)**	3311 (544)	3163 (579)	1.1 (1.04–1.4)	1.1 (1.03–1.14)
Low pre-pregnancy fruit intake***	246 (8.9%)	46 (16.4%)	1.9 (1.3–2.8)	1.7 (1.2–2.6)
*High green leafy vegetable****	*271 (9.8%)*	*12 (4.3%)*	*0.44 (0.24–0.81)*	*0.48 (0.26–0.88)*
15 weeks				
Age (per 5 year ↑)	28.2 (5.7)	28.3 (5.8)	1.2 (1.1–1.3)	1.2 (1.1–1.4)
Tertiary education student	87 (3.1%)	19 (6.8%)	2.7 (1.6–4.7)	2.8 (1.6–5.0)
Smoking (per 5 cigarettes/day↑)	283 (10.2%)	56 (19.9%)	1.4 (1.2–1.7)	1.4 (1.2–1.6)
Daily vigorous exercise	28 (1.0%)	9 (3.3%)	3.3 (1.5–7.2)	3.2 (1.3–7.9)
Rhesus negative blood group	*420 (15.1%)*	*22 (7.8%)*	*0.47 (0.30–0.74)*	*0.44 (0.27–0.71)*
20 week Ultrasound***				
Fetal head circumference z score <10th percentile	243 (9.2%)	42 (16.2%)		1.7 (1.2–2.5)
Fetal abdominal circumference z score <10th percentile	230 (8.7%)	51 (19.8%)		2.2 (1.5–3.2)
Average uterine RI (per 0.1 unit ↑)	0.56 (0.1)	0.61 (0.1)		1.6 (1.4–1.8)

Results expressed as *n* (%) or mean (SD) with participants who were normotensive and did not have an SGA infant as the referentgroup. Italics indicate variable is protective.
*Based on a reduced cohort after exclusion of participants with missing Doppler data, *n* = 2908 (controls *n* = 2648 and SGA *n* = 260).
***n* = 2614 and 262, respectively
***Less than one piece of fruit per week
****Three or more servings of green leafy vegetables per day.

Table 5. Multivariate comparisons of clinical, behavioural and ultrasound risk factors for hypertensive-SGA by customised birthweight centiles

Risk factors	Hypertensive non-SGA *n* = 361	Hypertensive SGA *n* = 95	Clinical data 15 weeks aOR (95% CI)	Clinical data 15 + 20 weeks* aOR (95% CI)
Pre-pregnancy				
Previous pregnancy loss before 20 weeks of gestation	69 (19.1%)	34 (35.8%)	2.3 (1.4–3.8)	2.3 (1.4–3.8)
In vitro fertilisation conception	10 (2.8%)	9 (9.5%)	3.4 (1.3–8.7)	4.1 (1.5–10.9)
20-week ultrasound*				
Fetal femur length *Z* score <10th percentile	25 (7.3%)	15 (16.1%)		2.8 (1.4–5.6)

Results expressed as *n* (%) with participants who were hypertensive non-SGA as the referent group.
*Based on a reduced cohort after the exclusion of participants with missing Doppler data *n* = 439 (controls *n* = 346; SGA *n* = 93).

(11 versus 20%), and hence a reduced power to detect an effect.

The strengths of our study include its prospective design, excellent follow-up of a large cohort (98.7%) and real-time data monitoring procedures that ensured the quality of the data. The SCOPE study is also one of the first large prospective pregnancy cohorts where such comprehensive risk-factor information has been collected. Our database contains variables covering a large range of known and hypothesised risk factors for SGA infants. A limitation imposed by this study design and our rich data is that we could not pre-select a limited number of variables based on prior knowledge for our logistic regression models. Consequently, we used a univariate pre-selection process, and only selected variables with $P < 0.01$ to be potentially available to our logistic regression models. We then further reduced variable numbers by excluding those containing overlapping information, and those that were not collected for the purposes of SGA studies. The final number of variables included in our models were 29, 26 and 12 for SGA, normotensive-SGA and hypertensive-SGA, respectively, which results in a ratio of events to variables of 13, 11 and eight, respectively, which is within the acceptable range for multivariate model building.[39] Our findings should be con-

sidered as preliminary, and the reproducibility will be assessed in the next 3500 healthy nulliparous women recruited to the SCOPE study. Future studies will be necessary to determine whether these potential risk factors and protective factors identified in a healthy nulliparous cohort are generalisable to different populations of pregnant women.

Conclusion

A number of risk factors for infants judged to be SGA by customised centiles have been identified. The risk factor profile for SGA and normotensive-SGA includes lifestyle factors, several of which are modifiable, such as dietary components, recreational drugs and smoking, as well as vigorous exercise. Our findings require validation in future studies.

Disclosure of interests

None.

Contribution to authorship

All listed authors meet the requirements for authorship as outlined by the British Journal of Obstetrics and Gynaecology. Their contribution to authorship is outlined as follows: participation in conception and design, LMcC, RN, GD, RM-M; execution of research, LMcC, RN, RT, GD, LK, PB, CTR; analysis of data, EC, RT, LMcC; interpretation of data, LMcC, RN, GD, LK, LC, CR, RM-M; drafting, revising, critical discussion and final approval of article, LMcC, RN, EC, RT, GD, CR, LK, RM-M, LC, P Baker.

Details of ethics approval

Procedures for the study received ethics approval from the relevant institutional ethic committees responsible for human experimentation. In New Zealand, approval for the SCOPE study was given by Northern Region Ethics Committee on 23 April 2003, study number AKX/02/00/364. In Australia, approval was granted by Central Northern Adelaide Health Service Ethics of Human Research Committee on 2 September 2005, study number REC 1714/5 and application number 2005082. In London and Manchester, approval was granted by the NHS South East Research Ethics Committee and the Central Manchester Research Ethics Committee, reference number 06/MRE01/98 on 19 January 2007, and in Ireland by the UCC, Cork Clinical Research Ethics Committee ECM5(10)05/02/08 on 6 February 2008.

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Trial registry name

Screening nulliparous women to identify the combinations of clinical risk factors and/or biomarkers required to predict pre-eclampsia, small-for-gestational-age babies and spontaneous preterm birth (www.anzctr.org.au; registration number ACTRN12607000551493).

Supporting information

The following supplementary materials are available for this article:

Appendix S1. List of all variables available to go into the three models.

Additional Supporting Information may be found in the online version of this article.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author. ■

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