

The impact of maternal body mass index on the phenotype of pre-eclampsia: a prospective cohort study

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Objective We hypothesised that among nulliparous women with pre-eclampsia, overweight or obese women would have a different phenotype of pre-eclampsia compared with normal weight women with pre-eclampsia. Specifically, they are more likely to develop term pre-eclampsia and less likely to have indicators of impaired placental perfusion, e.g. abnormal uterine artery Doppler or a small-for-gestational-age (SGA) infant.

Design Prospective, multicentre, cohort SCOPE study ($n = 3170$).

Setting New Zealand and Australia.

Population Nulliparous women who developed pre-eclampsia.

Methods Participants were interviewed at 14–16 weeks of gestation, uterine artery Doppler studies were performed at 19–21 weeks and pregnancy outcome was tracked prospectively.

Main outcome measures Rates of abnormal uterine artery Doppler indices, term/preterm birth and SGA infants were compared between normal, overweight and obese women with pre-eclampsia. Multivariable analysis was performed to examine

the association between body mass index (BMI) and term pre-eclampsia.

Results Of 178 women with pre-eclampsia, one underweight woman was excluded and 66 (37%) were normal weight, 52 (29%) were overweight and 59 (34%) were obese. Pre-eclampsia developed preterm in 26% of women and at term in 74% of women. There were no differences in the rates of term/preterm pre-eclampsia, abnormal uterine artery Doppler indices or SGA infants between BMI groups ($P > 0.10$). No independent association between BMI and term pre-eclampsia was found ($P = 0.56$).

Conclusions Among women with pre-eclampsia, those who are overweight or obese in early pregnancy are not more likely to have term pre-eclampsia compared with women with a normal BMI. Overweight and obese women require vigilant surveillance for the development of preterm as well as term pre-eclampsia.

Keywords Body mass index, obesity, overweight, pregnancy outcomes, preterm pre-eclampsia, small for gestational age, term pre-eclampsia.

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Introduction

Pre-eclampsia, which affects up to 7% of nulliparous women, is a major cause of maternal and perinatal morbidity and mortality globally.¹ It is widely recognised that there are sub-phenotypes of pre-eclampsia.^{2,3} Pre-eclampsia arising preterm is typified by the presence of defective trophoblast remodelling of the uterine spiral arteries and secondary fetal growth restriction.^{2–4} In contrast, term

pre-eclampsia is usually associated with normal uteroplacental blood flow (as indicated by normal uterine artery Doppler waveforms) and normal fetal growth, and is thought to result largely from an exaggerated maternal response to pregnancy.^{3,5}

Maternal obesity predisposes a woman to developing pre-eclampsia and a dose-dependent relationship between increasing body mass index (BMI) and the risk of developing pre-eclampsia is well established.^{6,7} Many studies have

investigated obstetric complications in obese women, but the few data reporting clinical features of pre-eclampsia associated with being overweight or obese are conflicting.^{7–11} Consequently the clinical phenotype of pre-eclampsia in obese women is poorly characterised. A recent retrospective cohort study of 850 000 women reported that compared with control women of normal BMI, obesity was more strongly associated with pre-eclampsia occurring at 34 weeks of gestation or beyond than pre-eclampsia before 34 weeks of gestation.⁷

In our international prospective SCOPE (Screening for Pregnancy Endpoints) study, 45% of the nulliparous participants were overweight or obese by ethnicity-specific BMI criteria.¹² We hypothesised that among women with pre-eclampsia, the phenotype of pre-eclampsia would differ by BMI. In particular, pre-eclampsia in women who were overweight or obese by ethnicity-specific BMI criteria would be more likely to occur at term and less likely to be associated with abnormal uterine artery Doppler resistance indices (RI) or infants who were small for gestational age (SGA) by customised birthweight centiles compared with pre-eclampsia in women who had a normal BMI.

Methods

Healthy nulliparous women with singleton pregnancies were recruited to the SCOPE study between November 2004 and October 2008 in Auckland, New Zealand and Adelaide, Australia. SCOPE is a prospective, multicentre cohort study with the main aim of developing screening tests to predict pre-eclampsia, fetal growth restriction and spontaneous preterm birth.^{13,14} Ethical approval was obtained in each centre from the local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008) and all women gave written informed consent. Exclusion criteria included being at high risk of pre-eclampsia, SGA or spontaneous preterm birth because of underlying medical conditions such as chronic hypertension requiring anti-hypertensive therapy, diabetes, gynaecological history, or if they received interventions that may modify pregnancy outcome, e.g. low-dose aspirin.¹³

Detailed study methods have been previously published.¹³ In brief, women were interviewed and examined at 14–16 weeks of gestation by a research midwife and details of their sociodemographic, medical, gynaecological and family history, history of medical and obstetric disorders and health in current pregnancy were obtained. Dietary and lifestyle questionnaires were completed. Maternal physical measurements obtained by a research midwife included blood pressure (two consecutive manual blood pressure measurements with mercury or aneroid sphygmomanometer, with a large cuff if the arm circumference was ≥ 33 cm and Korotkoff V for diastolic blood pressure),

height (in cm) and weight (in kg).¹³ The estimated date of delivery was calculated from a certain last menstrual period (LMP) date and was only adjusted if either (1) an ultrasound scan performed at less than 16 weeks of gestation found a difference of ≥ 7 days between the scan gestation and that calculated by the LMP or (2) on the scan at 19–21 weeks a difference of ≥ 10 days was found between the scan gestation and that calculated from the LMP. If an LMP date was uncertain, then scan dates were used to calculate the estimated date of delivery.

An ultrasound scan performed at 19–21 weeks of gestation included fetal growth measurements, fetal anatomy and uterine artery Doppler RI. Ultrasound examinations were performed in clinical practice by sonographers with Diplomas in Medical Ultrasound from the Australasian Society of Ultrasound in Medicine, in accordance with a standard operating procedures manual.¹⁵ Mean uterine artery RI was calculated from the left and right uterine RI and an abnormal uterine artery Doppler result was defined as a mean RI greater than the 90th centile for gestation for the SCOPE population (RI > 0.695).¹⁵

Women were followed prospectively, with pregnancy, birth and neonatal outcome data collected by research midwives from hospital records and interview usually within 72 hours of birth. These data included end of pregnancy outcomes (e.g. pre-eclampsia, SGA or spontaneous preterm birth), labour and delivery data and maternal and neonatal postpartum complications.¹³ All data were entered into an internet accessed, auditable database (Medscinet^{AB}, Stockholm, Sweden) and were monitored for accuracy and completeness.

Women were classified into normal, overweight and obese groups according to ethnicity-specific BMI criteria.¹⁶ This classification accounts for differing body fat and muscle masses between ethnicities, resulting in lower BMI criteria for overweight and obesity in Asian/Indian women (normal 18.5–22.9 kg/m², overweight 23–27.4 kg/m² and obese ≥ 27.5 kg/m²) and higher BMI criteria for overweight and obesity in Pacific and Maori women (normal 18.5–25.9 kg/m², overweight 26–31.9 kg/m² and obese ≥ 32 kg/m²). For European women and women of all other ethnicities, standard World Health Organization (WHO)¹⁷ criteria were used (normal 18.5–24.9 kg/m², overweight 25–29.9 kg/m² and obese ≥ 30 kg/m²). To check the influence of ethnicity-specific BMI classification on our results, we also performed analyses with all women classified using standard WHO BMI categories.

Pre-eclampsia was defined as systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg on at least two occasions 4 hours apart after 20 weeks of gestation but before the onset of labour, or postpartum, with either proteinuria (24-hour urinary protein ≥ 300 mg or spot urine protein:creatinine ratio ≥ 30 mg/mmol creatinine

or urine dipstick protein $\geq 2+$) or any multi-system complication of pre-eclampsia.^{13,14} Multi-system complications included any of: acute renal insufficiency, defined as a new increase in serum creatinine concentration $\geq 100 \mu\text{mol/l}$ antepartum or $>130 \mu\text{mol/l}$ postpartum; effects on liver, defined as raised aspartate transaminase or alanine transaminase concentration, or both, $>45 \text{ IU/l}$ 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 $<100 \times 10^9/\text{l}$), disseminated intravascular coagulation, or haemolysis.¹³ Preterm and term pre-eclampsia was defined as pre-eclampsia resulting in delivery before 37 weeks of gestation or at 37 weeks or beyond, respectively.

SGA and large for gestational age (LGA) were defined as an infant birthweight less than the 10th and greater than the 90th customised centile respectively, adjusted for maternal height, booking weight, parity, and ethnicity as well as delivery gestation and infant sex.¹⁸

Statistical methods

Among women with pre-eclampsia, characteristics related to pre-eclampsia phenotype (rates of abnormal uterine Doppler indices, multi-system complications, SGA infant, LGA infant and term/preterm pre-eclampsia) were compared between the three BMI categories using the chi-square test (Table 1). Maternal and infant characteristics were compared between term and preterm pre-eclampsia, using the chi-square test for categorical variables and the Student's *t* test for continuous variables (Table 2). Kaplan–Meier survival analysis of gestation to onset of pre-eclampsia was performed with log-rank test of equality to compare groups. A *P* value of <0.05 was considered significant.

Multivariable logistic regression was performed to determine if BMI was associated with term pre-eclampsia, adjusting for maternal age, primigravidity, ethnicity, mean arterial blood pressure at 14–16 weeks of gestation and SGA infant. An interaction term between BMI and SGA was included in the model. Uterine Doppler indices were considered on the causal pathway and not included in the model.

All statistical tests were performed using SAS® version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Of 3234 women recruited to the SCOPE study in Auckland and Adelaide, 38 (1.2%) women were excluded after recruitment because of miscarriage, termination of pregnancy or ineligible status discovered after recruitment. Follow up was complete in 3170 (99.2%) of eligible participants (Figure 1) of whom 178 (5.6%) developed pre-eclampsia. The overall rate of pre-eclampsia increased with increasing BMI (1.8% in underweight women, $n = 1$ of 55, not shown in figure; 4.0% in normal weight women, $n = 66$ of 1669; 5.7%, in overweight women, $n = 52$ of 899; and 10.7% in obese women, $n = 59$ of 547; Figure 2). After exclusion of the woman who was underweight, the final population with pre-eclampsia in this study was 177.

Among women with pre-eclampsia, pregnancy characteristics relating to pre-eclampsia phenotype according to BMI groups, are shown in Table 1. There were no differences in the rates of term/preterm pre-eclampsia, abnormal uterine artery Doppler indices, pre-eclampsia with multi-system complications, SGA or LGA between overweight or obese women with pre-eclampsia and women with pre-eclampsia with a normal BMI in early pregnancy (all *P* values >0.10).

Table 1. Among women with pre-eclampsia, rates of term and preterm pre-eclampsia, abnormal uterine Doppler indices, multi-system complications, SGA and LGA infants according to body mass index categories

	Pre-eclampsia		
	Normal weight ($n = 66$)	Overweight ($n = 52$)	Obese ($n = 59$)
Term pre-eclampsia (delivered ≥ 37 weeks)	48 (73)	39 (75)	44 (75)
Preterm pre-eclampsia (delivered <37 weeks)	18 (27)	13 (25)	15 (25)
Uterine artery Doppler indices*			
Abnormal uterine artery RI	14 (22)	9 (18)	11 (19)
Bilateral notch	12 (19)	11 (22)	10 (17)
Multi-system complications	34 (52)	19 (37)	24 (41)
SGA (<10th customised centile)	16 (24)	11 (21)	16 (27)
LGA (>90th customised centile)	4 (6)	6 (12)	8 (14)

Results are expressed as *n* (%). All comparisons between normal weight, overweight and obese were non-significant ($P > 0.10$).

*Performed at 19–21 weeks; missing data in Normal $n = 3$, missing data in Overweight $n = 2$.

Table 2. Characteristics of term (≥ 37 weeks of gestation) and preterm pre-eclampsia

	Pre-eclampsia		P value
	Term (n = 131)	Preterm (n = 46)	
Maternal characteristics at 14–16 weeks			
Body mass index*			
Normal (%)	48 (37)	18 (39)	0.95
Overweight (%)	39 (30)	13 (28)	
Obese (%)	44 (33)	15 (33)	
Maternal age (years)	26 (5.5)	28 (6.0)	0.05
White ethnicity (%)	111 (85)	40 (87)	0.71
Primigravida (%)	103 (79)	31 (67)	0.13
Family history of pre-eclampsia (%)	24 (18)	10 (22)	0.61
Systolic blood pressure (mmHg)	113 (10.5)	117 (12.7)	0.06
Diastolic blood pressure (mmHg)	68 (7.7)	72 (9.8)	0.02
Uterine artery Doppler indices at 19–21 weeks**			
Mean uterine artery RI	0.58 (0.10)	0.66 (0.12)	<0.01
Abnormal uterine artery RI (%)	13 (10)	21 (47)	<0.01
Bilateral notch (%)	16 (12)	17 (37)	<0.01
Maternal characteristics at end of pregnancy			
Gestation at diagnosis of pre-eclampsia (weeks)***	38.2 (2.1)	33.1 (2.7)	
Maximum systolic blood pressure (mmHg)	160 (15)	176 (23)	<0.01
Maximum diastolic blood pressure (mmHg)	101 (9)	113 (9)	<0.01
Proteinuria (%)	112 (86)	42 (91)	0.31
Multi-system complications (%)	49 (37)	28 (61)	<0.01
Pregnancy outcomes			
Gestation at delivery (weeks)	39.1 (1.3)	34.4 (2.2)	
Birthweight (g)	3370 (501)	2062 (644)	<0.01
SGA (<10th customised centile) (%)	17 (13)	26 (57)	<0.01

Results expressed as mean (SD) or *n* (%) as appropriate. *P* values are comparisons between groups using chi-square or Student's *t* test as appropriate.

*Body mass index according to ethnicity-specific categories.

**Missing data in Term *n* = 4, Preterm *n* = 1.

***Missing data in Term *n* = 4.

Maternal and infant characteristics of women with term and preterm pre-eclampsia are shown in Table 2. Compared with the preterm pre-eclampsia group, women with term pre-eclampsia were younger, had lower blood pressure in early pregnancy, and were less likely to have multi-system complications, abnormal uterine artery Doppler indices or an SGA infant. After adjusting for maternal age, primigravida, ethnicity, mean arterial blood pressure at 14–16 weeks of gestation and SGA, the BMI group was not associated with term pre-eclampsia ($P = 0.56$). There was no interaction between BMI and SGA ($P = 0.25$).

Kaplan–Meier survival analyses of gestational age at onset of pre-eclampsia by BMI category showed similar profiles with no difference between groups ($P = 0.12$) (Figure 3).

Analyses were also performed using standard WHO BMI categories for all women, and no changes in statistical significance were observed.

As this is a secondary analysis of data from the SCOPE study, we performed a sample size calculation to determine if there was adequate power to detect a clinically important difference between groups. Among nulliparous women with pre-eclampsia, if the true proportion of term pre-eclampsia was 70% in women of normal weight^{1,19} and 90% in women who were overweight or obese, then at an α value of 0.05 we had power of approximately 80% to detect this difference with the number of women observed.

Discussion

Although it is well established that obese women are at increased risk of pre-eclampsia,^{1,6–9} we report that overweight and obese women are at increased risk of both preterm and term pre-eclampsia. This is the first prospective study to provide detailed information about the clinical phenotype of pre-eclampsia in women who were

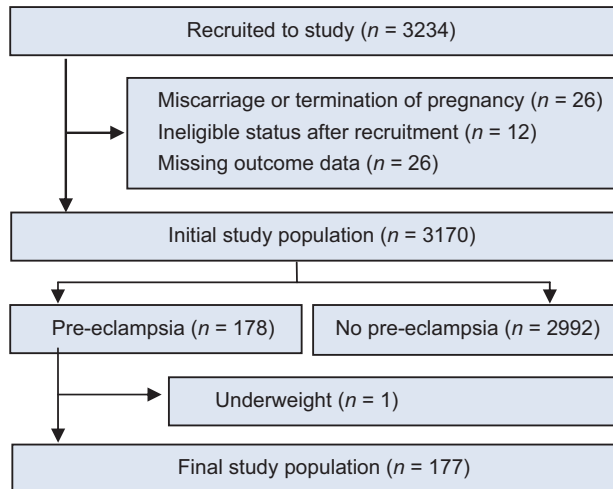


Figure 1. Flow of study participants.

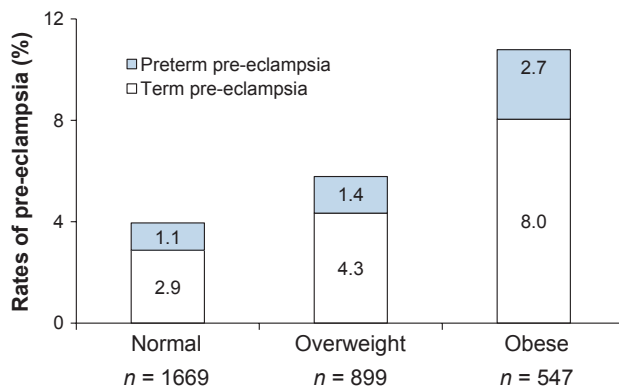


Figure 2. The rate of term (≥ 37 weeks of gestation) and preterm pre-eclampsia by body mass index classification among the cohort ($n = 3170$).

overweight and obese in early pregnancy. Contrary to our hypothesis, the phenotype of pre-eclampsia in nulliparous women did not differ according to maternal BMI categories. Overweight and obese women with pre-eclampsia were not more likely to have term pre-eclampsia than women of normal weight with pre-eclampsia and had similar rates of abnormal uterine artery Doppler indices and SGA infants.

With rising rates of obesity in the general population, the incidence of pre-eclampsia has increased.²⁰ Obesity and pre-eclampsia have a number of biochemical and physiological changes in common, including increased oxidative stress, inflammation, hyperlipidaemia, endothelial dysfunction and vasoconstriction.^{21,22} This has given credence to the concept of an exaggerated maternal response occurring in obese women that typically manifests as late-onset or term pre-eclampsia. However, we demonstrate that the rates of both preterm and term pre-eclampsia increase proportionally with higher maternal BMI. This suggests that the predisposition to pre-eclampsia conferred with

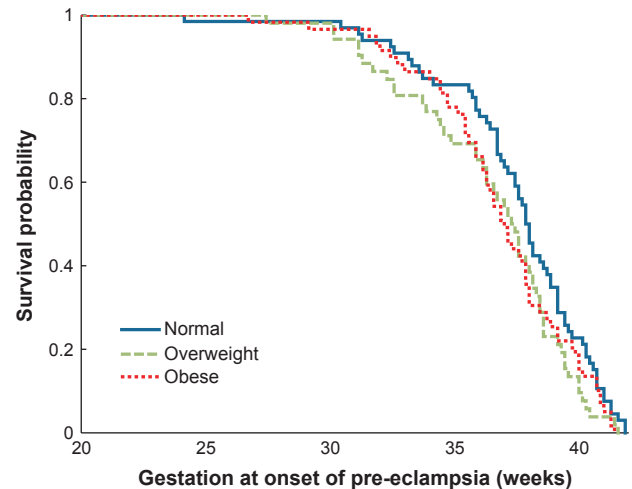


Figure 3. Kaplan–Meier survival of gestation at onset of pre-eclampsia according to ethnic-specific body mass index category.

obesity contributes both to the impaired placentation associated with preterm pre-eclampsia and the exaggerated maternal response seen in term pre-eclampsia.

Consistent with our findings, a case–control study from Norway reported an increase in both early and late pre-eclampsia in women weighing more than 70 kg compared with those whose weight was < 70 kg at pregnancy booking.⁸ A large retrospective study found increasing rates of pre-eclampsia with increased BMI, but found a stronger odds ratio association between obesity and late-onset (≥ 34 weeks of gestation) pre-eclampsia compared with early-onset (< 34 weeks of gestation) pre-eclampsia.⁷ Despite this association, the absolute percentages of women with early-onset and late-onset pre-eclampsia in the normal BMI group and each of the obesity categories were very similar.⁷ Of interest, Mbah et al.⁷ also reported that mothers with early-onset pre-eclampsia had a higher self-reported pre-pregnancy BMI (27.5) than the mean BMI (24.6) in women with late-onset pre-eclampsia. The use of self-reported maternal pre-pregnancy weight was acknowledged as a limitation in this study because overweight and obese pregnant women are more likely to under-report weight and over-report height.^{7,23}

A strength of our study is the longitudinal tracking throughout pregnancy, which enabled us to accurately measure early pregnancy height, weight and blood pressure and, at 19–21 weeks of gestation, to perform uterine artery Doppler studies as a surrogate for uteroplacental perfusion. The BMI was calculated using weight and height measured by a research midwife at 14–16 weeks of gestation rather than rely on recall of pre-pregnancy weight because of the bias of underestimation of weight in pregnancy.²³ There are no data on whether first-trimester weight gain differs between women who develop term compared with preterm

pre-eclampsia, but it is unlikely to have substantially changed the BMI classification of participants. Additionally, our cohort included women of different ethnicities, so we used ethnicity-specific BMI criteria to adjust for differences in the ratio of body fat to lean body mass and provide more accurate classification of obesity than the standard WHO criteria. Of note, results were unchanged when all women were classified using standard WHO criteria.

A potential limitation of this study is that smaller differences between groups may not be detected secondary to our study size. It is unlikely that the minimal missing data on uterine artery Doppler RI ($n = 5$) would have influenced our findings.

Conclusion

Contrary to our hypothesis, among nulliparous women with pre-eclampsia we did not find a higher occurrence of term pre-eclampsia in overweight and obese women when compared with women with pre-eclampsia and a normal BMI. Further, overweight and obese women were not less likely to have abnormal uterine artery Doppler studies or SGA infants than women with a normal BMI. These findings aid our understanding of the phenotypes of pre-eclampsia occurring in overweight and obese mothers and suggest that the increased rate of pre-eclampsia with an elevated BMI is not solely the result of an exaggerated maternal response to pregnancy late in gestation. Overweight and obese women therefore require vigilant surveillance for the development of preterm as well as term pre-eclampsia.

Disclosure of interests

RN has consultancy relationships with Pronota and Alere and declares patent PCT number WO/2009/108073.

Contribution to authorship

NA, RN, LM and GD designed the study. EF and RT acquired data. NA, RN, LM and AS planned the analyses and interpreted the data. EC performed the data analyses. NA drafted the manuscript and all authors edited the manuscript and approved the final version.

Details of ethics approval

Local ethics approval was gained for New Zealand (AKX/02/00/364) and Australia (REC 1712/5/2008).

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