Paternal Contribution to Small for Gestational Age Babies: A Multicenter Prospective Study

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Our aims were to investigate whether men who fathered small for gestational age (SGA) infants themselves had lower birthweight, were more likely to be obese, have central adiposity and elevated blood pressure in adult life compared with men who fathered non-SGA infants. A total of 2,002 couples participating in the Screening for Pregnancy Endpoints (SCOPE) study were enrolled in early pregnancy and pregnancy outcome data collected prospectively. SGA was defined as birthweight <10th customized centile, obesity as BMI ≥30 kg/m², central adiposity as waist circumference >102 cm. Logistic regression was used to compare rates of obesity, and central adiposity between men who fathered SGA infants compared with those with non-SGA infants and the final model was adjusted for maternal and paternal confounders. The men who fathered an SGA infant (209 (10.4%)) themselves had lower mean birthweight (3,291 (530) g vs. 3,472 (584) g, $P < 0.0001$), were more likely to be obese (50 (24.8%) vs. 321 (18.3%), adjusted odds ratio (OR) 1.50, 95% confidence interval 1.05–2.16, adjusted for maternal and paternal factors) and to have central adiposity (52 (25.1%) vs. 341 (19.2%), adjusted OR 1.53, 95% confidence interval 1.06–2.20) compared with men who fathered a non-SGA infant. Elevated paternal blood pressure was not associated with SGA. In conclusion, we report a novel relationship between paternal obesity/central adiposity and birth of an SGA infant, which appears to be independent of maternal factors associated with fetal growth restriction.

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INTRODUCTION

Being born small for gestational age (SGA) significantly increases the risk of morbidity and mortality in the perinatal period (1,2). In adult life, SGA birth has been associated with increased rates of obesity, central adiposity and hypertension as well as type 2 diabetes and other cardiovascular diseases (3–6). Although many authors have investigated maternal risk factors for SGA, few have investigated the potential contribution of the father.

Earlier studies reported that maternal obesity was associated with a reduced risk of SGA (7,8), but recent data from obese cohorts have found that maternal obesity is associated with an increased risk of SGA (9,10). The few studies investigating the relationship between paternal factors and either birthweight or SGA in the offspring have recently been reviewed (11). The majority of these reported that paternal weight or BMI was either not independently associated with offspring weight (12–14) or there was a positive relationship between paternal BMI and offspring birthweight (15). Previous studies included cohorts recruited before the obesity epidemic (15) and some were underpowered (13). It is also possible that a relationship between paternal obesity and low birthweight in the offspring could have been masked by a coexisting association between paternal obesity and large babies (16). None of these previous studies investigated the relationship between paternal BMI and risk of SGA offspring.

Both maternal and paternal birthweight have been positively correlated with infant birthweight (15,17). Furthermore a recent study reported both men and women who were SGA at birth were more likely than those with normal birthweight to parent an SGA infant (18).

In the current study, we have investigated the relationship between paternal variables and birth of an SGA infant in the prospective Screening for Pregnancy Endpoints (SCOPE) study, which has contemporary records of both maternal and paternal data. In view of the reported association of SGA birth with later obesity and hypertension and also between SGA birth in the father and offspring SGA we hypothesised that fathers of SGA infants would have (i) lower birthweight and (ii) higher rates of obesity, central adiposity, and high blood pressure than fathers of non-SGA infants.

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METHODS AND PROCEDURES

The SCOPE study is an international, multicenter, prospective screening study which aims to develop early pregnancy screening tests for preeclampsia, SGA babies, and spontaneous preterm birth. Healthy nulliparous women with singleton pregnancies were recruited between November 2004 and July 2007 in Auckland, New Zealand and Adelaide, Australia. Women considered at high risk of preeclampsia, SGA or spontaneous preterm birth because of underlying medical conditions, previous gynaecological history or who received interventions that may modify these outcomes were excluded. Those who agreed to participate were interviewed and examined by a research midwife at 15 ± 1 and 20 ± 1 weeks' gestation. At the time of the interview, data were entered into an internet accessed auditable database developed by MedSciNet AB, Sweden. Pregnancy outcome data and infant measurements were collected following the birth, usually within 72 h. Ethical approval was gained from local ethics committees (New Zealand AKX/02/00/364 and Australia REC 1712/5/2008) and all women and partners provided written informed consent.

If a participant was certain of the identity of the infant's father and she consented, the father was invited to participate in the SCOPE study. Male participants provided written informed consent and were interviewed at either the 15 ± 1 or 20 ± 1 weeks' SCOPE visit. Paternal data collected included age, ethnicity, job situation, socioeconomic index (19), birthweight and history of diabetes, hypertension, and ischemic heart disease. The men were asked to confirm their birthweight from their newborn health records where possible. If birthweight could not be obtained from the health record or was not known by the father this data-point was not completed. Paternal height, weight, abdominal circumference, and blood pressure were measured by the research midwife.

The estimated date of delivery was calculated from a certain last menstrual period date. The estimated date of delivery was only adjusted if either (i) a scan performed at <16 weeks' gestation found a difference of ≥7 days between the scan gestation and that calculated by the last menstrual period or (ii) on 20-week scan a difference of ≥10 days was found between the scan gestation and that calculated from the last menstrual period. If the last menstrual period date was uncertain, then scan dates were used to calculate the estimated date of delivery. The estimated date of delivery was adjusted by scan findings in 387/2,002 (21.3%) of participants.

Outcome measures

SGA was defined as birthweight <10th customized birthweight centile (20). Obesity was defined as BMI ≥30 kg/m^2 and central adiposity as waist circumference >102 cm (21,22). Paternal high blood pressure was defined as either systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg.

Univariate statistical analyses were performed using SAS system 9.1 for comparisons between SGA and non-SGA infants. For continuous variables a two-sample Student's *t*-test, or Wilcoxon rank sum test, was used as appropriate. For categorical variables comparisons were performed using the χ^2 test. R version 2.8.0 (http://cran.r-project.org) was used to fit logistic regression models to each of the end points (SGA vs. non-SGA), with the regression coefficients used to provide estimates of ORs. Unadjusted ORs were calculated and if significant, adjusted ORs were then calculated in two stages; first by adding paternal and then maternal confounding factors. For the paternal BMI and central adiposity analyses, the following paternal variables were added to the logistic regression model: age, ethnicity, socioeconomic index, employment, blood pressure, and medical history. The final step for both analyses was adjustment using both the paternal and maternal covariates. These maternal variables were: age, ethnicity, BMI, blood pressure, smoking status, gravidity, and maternal birthweight.

To investigate whether men who were small at birth and now obese were at increased risk of SGA offspring, the ratio of paternal birthweight to paternal BMI and paternal birthweight to paternal waist circumference were calculated and classified according to quartiles. The rate of SGA was compared across paternal birthweight/BMI ratio quartiles and paternal birthweight/waist circumference ratio quartiles using the Cochran–Armitage test for trend. A logistic regression model was then developed to investigate whether maternal BMI had a significant effect on the relationship between the above ratios and risk of SGA.

Data were available for >97% of participants for all variables included in the models except paternal and maternal birthweight (90% and 94% respectively). Missing data were imputed for multivariable analyses using the expectation maximization algorithm (23) for continuous variables, while the mode was used for categorical/binary variables (24).

RESULTS

Of 2,535 women recruited, 23 (0.9%) were lost to follow-up and five were excluded as the biological father of the infant was unknown (**Figure 1**). Among the remaining 2,507 women, 2,002 (80%) fathers participated. The women whose partners participated were more likely to be white (87.7% vs. 82.8%, $P < 0.0001$), married or in a stable relationship (95.2% vs. 83.2%, $P < 0.0001$) and employed (86.1% vs. 81.8% $P = 0.02$) compared with those whose partners did not participate. There were no differences in maternal BMI, socioeconomic indexes, smoking rates, or blood pressure between those whose partners participated and those who did not. Furthermore the rate of SGA infants did not differ between groups, 10.4% (209 of 2,002) in women whose partners participated and 10.7% (54 of 505) in women whose partners did not participate, $P = 0.87$.

Of the 2,002 men, 371 (18.5%) had a BMI ≥30 kg/m^2. **Table 1** shows the paternal and maternal demographics and the paternal clinical characteristics among those with SGA infants compared with those with non-SGA infants. Men who fathered SGA infants were themselves on average 180 g lighter at birth ($P < 0.0001$) and were 1.4 cm shorter ($P = 0.008$) than men who fathered non-SGA infants. Men who fathered an SGA infant were also more likely to be obese and to have central adiposity compared with men who fathered a non-SGA infant and this effect persisted after adjusting for both paternal and maternal factors (**Table 2**). Although there was a significant but weak linear relationship between paternal and maternal BMI, the correlation coefficient was very small ($r = 0.24$, $P < 0.001$). Men who fathered SGA infants were not

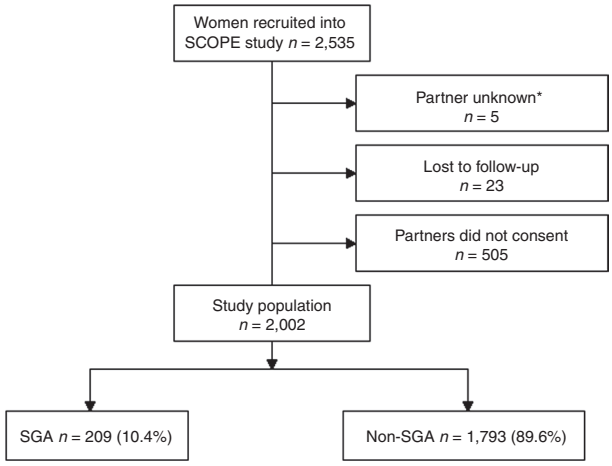

Figure 1 Flow chart of participants.

Table 1 Paternal and maternal characteristics according to SGA status of infant

	SGA (n = 209)	Non-SGA (n = 1,793)	P value
Paternal characteristics			
Age (years)	31.1 (6.3)	31.0 (6.2)	0.80
Ethnicity			0.51
White	174 (84.2%)	1,549 (86.5%)	
Polynesian	12 (5.8%)	99 (5.5%)	
Asian	4 (1.9%)	45 (2.5%)	
Indian	7 (3.3%)	48 (2.7%)	
Other	10 (4.8%)	50 (2.8%)	
Socioeconomic index	42 (16)	43 (16)	0.37
Employed	191 (91.4%)	1,682 (93.8%)	0.18
Birthweight (g)	3,291 (530)	3,472 (584)	<0.0001
Medical history[a]	7 (3.3%)	66 (3.7%)	0.81
Height (cm)	177.9 (6.9)	179.3 (6.9)	0.006
Weight (kg)	86.0 (15.8)	86.4 (15.2)	0.70
BMI ≥30 kg/m^2	50 (24.8%)	321 (18.3%)	0.03
Waist circumference >102 cm	52 (25.1%)	341 (19.2%)	0.04
Systolic blood pressure (mm Hg)	122 (13)	122 (13)	0.57
Diastolic blood pressure (mm Hg)	76 (10)	77 (10)	0.16
Elevated blood pressure[b]	28 (13.7%)	273 (15.5%)	0.16
Maternal characteristics			
Age (years)	28.8 (5.9)	28.4 (5.5)	0.31
Ethnicity			0.35
White	179 (85.7%)	1,576 (87.9%)	
Polynesian	5 (2.4%)	51 (2.8%)	
Asian	9 (4.3%)	83 (4.6%)	
Indian	8 (3.8%)	49 (2.8%)	
Other	8 (3.8%)	34 (1.9%)	
Socioeconomic index	42 (17)	42 (16)	0.61
Employed	171 (81.8%)	1,552 (86.6%)	0.06
BMI ≥30 kg/m^2	42 (20.1%)	272 (15.2%)	0.06

Results are expressed as mean (s.d.) or n (%).
SGA, small for gestational age.
[a]Includes previously diagnosed hypertension, type 2 diabetes, or ischemic heart disease. (Seven men in the SGA group had a history of previous hypertension. In the non-SGA group, 60 had a history of previous hypertension, two had a history of ischemic heart disease and two had type 2 diabetes, one had both ischemic heart disease and hypertension and a further had type 2 diabetes plus hypertension.) [b]Defined as either a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

more likely to have elevated blood pressure compared with men who fathered a non-SGA infant.

To investigate our hypothesis suggesting a link between low paternal birthweight, subsequent obesity and an increased risk of an SGA infant, we explored the relationship between paternal

Table 2 Paternal characteristics and risk of fathering a SGA infant

	Unadjusted OR (95% CI)	OR adjusted for paternal[a] factors (95% CI)	OR adjusted for maternal[b] and paternal[a] factors (95% CI)
BMI ≥30 kg/m^2	1.45 (1.04–2.04)	1.52 (1.07–2.15)	1.50 (1.05–2.16)
Waist circumference >102 cm	1.41 (1.01–1.97)	1.58 (1.11–2.24)	1.53 (1.06–2.20)

Results are expressed as N (%).
CI, confidence interval; OR, odds ratio; SGA, small for gestational age.
[a]Paternal age, ethnicity, socioeconomic index, employment, blood pressure, history of hypertension, type 2 diabetes, and ischemic heart disease. [b]In addition to paternal factors adjusted for maternal age, ethnicity, BMI, mean arterial pressure, smoking status, gravidity, and maternal birthweight.

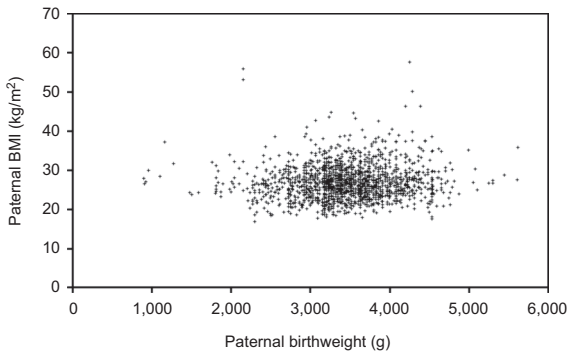

Figure 2 Correlation between paternal birthweight and paternal BMI.

birthweight and paternal BMI. A very weak linear relationship was found (r = 0.07, P = 0.003, Figure 2). A similar weak linear relationship was found between paternal waist circumference and paternal birthweight (r = 0.09, P = 0.0001). Paternal age did not influence paternal BMI and waist circumference as evidenced by no difference in mean paternal BMI or waist circumference across paternal age tertiles (data not shown).

We then investigated the relationship between the ratio of paternal birthweight to paternal BMI and the rate of SGA offspring. SGA offspring were more common among men with a birthweight/BMI ratio in the lowest quartile (14%, 63 of 438) compared to the rate of SGA offspring in the other quartiles (birthweight/BMI ratio 2nd quartile 10%, 3rd quartile 9%, highest quartile 7%, P = 0.0002 using the Cochran–Armitage trend test). A similar relationship was also found for quartiles of paternal birthweight/waist circumference ratios and risk of SGA offspring P < 0.0001 using the Cochran–Armitage trend test (Table 3). To investigate whether maternal BMI was confounding the relationship between the above ratios and risk of SGA offspring we then fitted logistic regression models. Maternal BMI did not have a significant effect in either model. We fitted a further logistic regression model to investigate whether there was a linear relationship between birthweight/BMI ratio and rate of SGA. A weak positive relationship was demonstrated (OR 0.90 (0.82–1.0), P = 0.01 for every 50 unit change in the ratio), consistent with the lower the birthweight/BMI ratio the higher the risk of SGA.

Table 3 SGA offspring in relation to paternal birthweight/BMI and paternal birthweight/waist circumference ratios

	SGA	Non-SGA	*P* value
Paternal birthweight/BMI ratio[a]	*n* = 178	*n* = 1,583	
Quartile 1 (*n* = 438)	63 (14.4%)	375 (85.6%)	0.0002
Quartile 2 (*n* = 446)	45 (10.1%)	401 (89.9%)	
Quartile 3 (*n* = 446)	41 (9.2%)	405 (90.8%)	
Quartile 4 (*n* = 431)	29 (6.7%)	402 (93.3%)	
Paternal birthweight/ waist circumference ratio[b]	*n* = 177	*n* = 1,580	
Quartile 1 (*n* = 405)	55 (13.6%)	350 (86.4%)	<0.0001
Quartile 2 (*n* = 493)	61 (12.4%)	432 (87.6%)	
Quartile 3 (*n* = 445)	39 (8.8%)	406 (91.2%)	
Quartile 4 (*n* = 414)	22 (5.3%)	392 (94.7%)	

P value based on Cochran–Armitage trend test.
SGA, small for gestational age.
[a]Median (interquartile range) 130 (112–151). [b]Median (interquartile range) 37 (32–42).

DISCUSSION

Although a number of studies have explored the relationship between paternal characteristics, including height and weight, and infant birthweight, none have specifically investigated the influence of paternal obesity and central adiposity on the risk of SGA in the offspring. After adjustment for both paternal and maternal confounders, paternal obesity, and central adiposity were both associated with a 60% increase in risk of fathering a SGA infant in our study. Consistent with previous reports, we found that men who fathered SGA infants were themselves ~180 g lighter at birth than men who fathered non-SGA infants (15,17) suggesting that birth size appears to be, in part, heritable through the paternal germ line.

Contrary to our hypothesis, we did not confirm a strong inverse association or a J curve between paternal birth weight and paternal BMI or central obesity in our cohort. Others have also reported lack of a clinically significant relationship between birthweight and later BMI, recently reviewed by Wells *et al.* (25). The relationship between birthweight and later obesity has varied in different populations, by gender, by age at follow-up and according to which variables were included in multivariate analyses (25). To further explore whether the independent association between paternal obesity and offspring SGA may be a manifestation of excessive catch-up growth in those men with low birthweights, we used a low ratio of paternal birthweight to BMI and paternal birthweight to waist circumference as surrogate measures for catch-up growth in the subgroup of men with low birthweight who were now obese and or had central adiposity. Men with a birthweight to BMI ratio or birthweight to waist circumference ratio in the lowest quartiles had a higher rate of SGA offspring and this relationship was independent of maternal BMI. These data provide some support for the concept of low birthweight being associated with later obesity and increased risk of SGA offspring. Further research is required to better understand the linkages between paternal birthweight or SGA status, obesity and central obesity as an adult and SGA offspring.

We did not find a relationship between paternal elevated blood pressure and SGA in the infant despite the known association between obesity and hypertension. Because the men in this study had a mean age of 28 years, it may be that even if they had a predisposition to hypertension they were too young for it to be manifested.

The strengths of this study include its prospective design, very low loss to follow-up, and the study population comprising a large modern cohort with rates of paternal obesity of nearly 20%. A limitation is that we were not able to investigate paternal SGA status at birth as we did not collect paternal data relating to gestation at delivery. Therefore the observed association between reduced paternal birthweight and SGA offspring could be partly explained by an increased rate of preterm birth in the fathers. In addition, more accurate measures of adiposity in father and child (e.g., as determined by measurements of skin fold thickness or dual-energy X-ray absorptiometry scan) would have provided additional insight into the relationships between father and child fat mass and should be considered in future studies.

Obesity arises from a combination of genetic and environmental factors. Paternal effects on SGA could potentially be explained by either a common environment shared by the couple, a genetic component or a combination of both. Recent data from a large cohort of obese nulliparous women has reported an increased risk of SGA offspring (10). Shared dietary habits between the mother and the father, resulting in maternal as well as paternal obesity, is one potential explanation for the effect of paternal obesity on SGA infants. As the association between paternal obesity and birth of SGA offspring was still present after adjustment for maternal BMI and the relationship between maternal and paternal BMI was weak, it is unlikely our findings are explained by maternal obesity. However as we did not collect data about maternal and paternal dietary patterns, a contribution of shared dietary habits between mother and father to the observed relationship cannot be excluded entirely. A potential limitation of our study is therefore that at least part of the relationship we have demonstrated between paternal obesity and SGA offspring may be explained by residual maternal confounding.

It is possible that genetic mechanisms may contribute to the association between paternal BMI and SGA offspring. The *IGF2* gene, encoding insulin-like growth factor–II, and the *INS* gene, encoding insulin, are possible candidates since polymorphisms in both are associated with low circulating insulin-like growth factor–II, which is associated with adult obesity, as well as SGA babies (26–29). Furthermore, insulin-like growth factor–II is imprinted and expressed from the paternal copy of the gene and regulates both placental and fetal growth (30).

In conclusion, we have demonstrated a novel relationship between paternal obesity/central adiposity and delivery of an SGA infant, which appears to be independent of maternal factors known to be associated with fetal growth restriction. Further prospective studies are required to confirm this

association and to provide insight into the underlying pathophysiology. It appears unlikely that the relationship between SGA infants and obesity in the fathers simply reflects an association with the fathers' own low birthweight which was then followed by rapid growth and later obesity, but this should be investigated further in future studies. In conclusion, studies which aim to predict the risk of delivery of an SGA infant in the future should explore the potential added value of incorporating paternal BMI with maternal data in prediction models.

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DISCLOSURE

The authors declared no conflict of interest.

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