No additional effect to infant birthweight if both parents are obese to that of one: retrospective analysis of 1479 singleton term births following assisted reproductive treatment

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Abstract

Objective: To determine the combined effects of maternal and paternal preconception overweight and obesity on infant birthweight. Design: Retrospective data analysis, fresh cycles (2009-2017), Repromed, South Australia. Setting: Assisted Reproductive Technology. Population: Couples undergoing either in vitro fertilisation or intracytoplasmic sperm injection with their own gametes and transfer of a single blastocyst (N=1479). Methods: Maternal and paternal BMI were recorded prior to cycle initiation. Infant birthweight was recorded at delivery. The impact of paternal and maternal overweight and obesity and their interaction on infant birthweight was assessed using quantile regressions constructed at 5th, 10th, 50th, 90th and 95th birthweight percentiles based on Australian standards. Main Outcome Measures: First, singleton, term birth ([?] 37 weeks' gestation) birthweight. Results: There was weak evidence for an interaction between parental BMI for median birth weight (β=-0.98; 95%CI=[-1.90, -0.05], p=0.04) with infants having increasing birth weight with increasing parental BMI, when one parent has normal weight. When either parent is overweight or obese, although birth weights are higher (maternal β=15.9; 95%CI=[1.63, 30.1], p=0.03; paternal β=7.33; 95%CI=[0.297, 14.4] p=0.04), they are not associated with increasing BMI of the other parent. Conclusions: Both maternal and paternal overweight and obesity at conception independently increase median infant birthweight. These findings necessitate the need for a family centered approach for preconception counselling on healthy BMI prior to pregnancy. Further studies are warranted in other ART or general population cohorts to support or refute our findings. Funding: NOM is the recipient of an NHMRC Early Career Fellowship.

INTRODUCTION

Obesity is a significant public health concern. There is a rising trend for increased body mass index (BMI) across all age groups with obesity rates tripling over the past 40 years [1]. The World Health Organization (WHO) reported that 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese with obesity being a major risk factor for non-communicable diseases including type 2 diabetes and cardiovascular diseases [2]. A global systematic analysis found that women of reproductive age demonstrate a particularly steep increase in obesity prevalence [3], with 38.9 million pregnant women estimated to be overweight and 14.6 million estimated to be obese, in 2014 [4]. In Australia, nearly half of women who gave birth were overweight or obese in 2017 [5]. A similar trend in overweight and obesity prevalence has also been seen in men of reproductive age[3].

There is consistent evidence that maternal preconception BMI affects infant birthweight, such that maternal overweight or obesity increases the likelihood for an infant being born large for gestational age (LGA) (OR=1.45; 95%CI=[1.29, 1.63] and OR=1.88; 95%CI=[1.67, 2.11], respectively) or macrosomic (OR=1.70; 95%CI=[1.55, 1.87] and OR=2.92; 95%CI=[2.67, 3.20], respectively) [6]. In comparison the risk of delivering a small for gestational age (SGA) baby are increased in underweight mothers (OR = 1.67; 95% CI =

[1.49-1.87]); but decreased with overweight (OR=0.71; 95%CI=[0.66, 0.76]) or obese mothers (OR=0.88; 95%CI=[0.78, 0.99]) [6]. Increased maternal BMI also influences child overweight and obesity risks up to 14 years of age[7] and increases future risk for obesity and cardio-metabolic diseases later life for both mother and child[8]. Problematically, the potential impact of paternal BMI is rarely considered in these studies, despite a small body of evidence suggesting that paternal preconception overweight and obesity may also contribute to infant birthweight including the delivery of an SGA or LGA infant [9, 10]. Thus the involvement of paternal overweight and obesity on infant birthweight demonstrates a role for the father's preconception health in programing fetal outcomes[11].

It is evident that maternal preconception BMI affects infant birthweight, however the influence of paternal preconception BMI is less studied. Further it is unclear whether there is an additional effect on infant birthweight if both parents are overweight or obese. We hypothesise that the combination of both maternal and paternal preconception overweight/obesity has a larger contribution to infant birthweight than their independent parental effects. The objective of this study is to assess the independent and combined effects of maternal and paternal preconception overweight and obesity on infant birthweight utilising an assisted reproductive technologies (ART) cohort where preconception parental BMI is routinely collected.

METHODS

Study population and data collection

Retrospective data analysis of fresh cycles from 2009-2017 at Repromed (Dulwich, South Australia and Darwin, Northern Territory clinics). Cycles including either *in vitro* fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) with autologous sperm and eggs and the transfer of a single blastocyst embryo were assessed (Figure S1). First singleton term birth ([?] 37 weeks' gestation) with a birth weight recorded were included in the analysis. Pre-term (<37 weeks' gestation), twin births and second pregnancies from the same patient couple were excluded from the analysis (Figure S1). Parental data was collected from case notes including demographic data (socioeconomic index for areas (SEIFA), ART information (insemination method and infertility diagnosis) and maternal and paternal age. SEIFA was calculated by patient's postcode [12]. A high score indicates greater social advantage, while a low score indicates relatively greater disadvantage; the average SEIFA score is 1000 and the middle two-thirds of SEIFA scores will generally fall between ˜900 and 1100 [12].

Birth outcomes including infant birthweight (g), gestational age (weeks), sex (male/female), twin deliveries, and delivery method (vaginal/caesarean), were supplied by the treating obstetrician as per the ART treatment act that indicates mandatory reporting to the Australian and New Zealand Assisted Reproduction Database (ANZARD). Small for gestational age (SGA) infants were classified as [?]10$^{\text{th}}$ percentile, while large for gestational age (LGA) infants were classified as [?]90$^{\text{th}}$ percentile, based on Australian specific birthweight standards reported in Dobbins*et al.* [13].

Human ethics

Repromed's Scientific Advisory Board (SAC) approved the retrospective study (14/11/2019); the study was exempt from HREC review at the University of Adelaide. Formal consent for this type of study is not required.

Assessment of parental BMI

As part of clinical practice at Repromed, BMI is routinely recorded before cycle initiation. Both maternal and paternal height is measured with a stadiometer (cm) and weight (kg) measured with electronic scales, assessed by a clinical nurse prior to cycle commencement. Body mass index was calculated using the formula weight/height^{2}and categorized based on the WHO; underweight (<18.5 kg/m^2); normal weight (18.5–24.9 kg/m^2); overweight (25.0–29.9 kg/m^2); obesity (>30.0 kg/m^2), with obesity class I, 30.0–34.9 kg/m^2, obesity class II, 35.0–39.9 kg/m^2, and obesity class III, >40 kg/m^2.

IVF protocol

Women primarily underwent a GnRH antagonist protocol of treatment with vaginal progesterone gel (Crinone) / estradiol valterate luteal support or human-derived hCG luteal support (pregnyl) as previously described[14]. At the time of study (2009-2017) there were minimal changes to laboratory protocols including culture media, consumables or equipment used. Eggs were fertilised by either standard IVF or ICSI in fertilization medium (G-IVF-PLUS, Vitrolife, Gothenberg, Sweden). Embryos were cultured using the sequential culture media system supplied by Vitrolife at 6% CO_2, 5% $O_2$and 89% N_2 where cleavage-stage embryos were grown until day 3 in G1 PLUS and then moved into G2 PLUS which supports blastocyst development until embryo transfer on day 4 or day 5. The best morphological graded embryo was transferred back into the patient using EmbryoGlue transfer medium (Vitrolife). Patients were in the care of their treating IVF physician until confirmation of a viable pregnancy following ultrasound at 6-8 weeks' gestation, where they were then referred onto primary obstetrics care.

Statistical Methods

For continuous demographic, treatment and outcome factors, means (standard deviations (SDs)) and medians (ranges) are reported, and for discrete factors, frequencies (percentages) are reported. The impact of paternal and maternal BMI on infant birthweight was assessed using quantile regressions, adjusting for baby sex (male or female), gestational age, delivery method (vaginal or caesarean), transfer method (IVF or ICSI), maternal age, paternal age and parental SEIFA score. Non-linear associations using restricted cubic splines (knots at 5^{th}, 10^{th} 50^{th}, 90^{th} and 95^{th} percentiles) were included for gestational age and maternal BMI. An interaction between the maternal and paternal BMI factors (both linear) was also included. These quantile regressions were constructed for the 5^{th}, 10^{th}, 50^{th}, 90^{th} and 95^{th} weight percentiles based on Australian specific birthweight standards [13](Figure S2). Multiple imputation using chained equations (100 datasets were imputed each with 100 iterations) was employed to account for the substantial missing paternal BMI data. Analyses were performed in R (version 3.6.3) using the *mice* and *rms* packages. P-values of 0.05 were considered statistically significant.

RESULTS

Patient demographics

A total of 1479 couples were included in the analysis (Figure 1). The median age of mothers was 32.9 years (range=[19.9, 45.2]), which was lower than the median age of fathers (35.2 years; range=[20.5, 65.4]) (Table 1). The median BMI of mothers (24.4 kg/m^2; range=[16.2, 55.9]), was in the normal weight category, although BMI spanned both underweight (<18.5 kg/m^2) through obese class III (>40 kg/m^2) categories. The median BMI of fathers (27.4 kg/m^2; range=[17.3, 54.2]), was in the overweight category, and similar to mothers, spanned from underweight to obese class III (Table 1). The mean (SD) SEIFA score was 994 (72), indicating a slightly lower score than the Australian benchmark of 1000, indicating social disadvantage. Male factor infertility was the biggest contributing infertility diagnosis (55%) to the cohort (Table 1). ICSI insemination was used in over 80% of cases with delivery method (vaginal vs caesarean) and infant sex (female vs male) split approximately 50% (Table 1).

Other risk factors and infant birthweight

Table 2 and Table 3 presents the three quantile regression models for SGA and LGA infants, and Figure S3 presents model estimates for continuous covariates. Infants born to older mothers were more likely to be SGA (10^{th} percentile: β=-15.2, 95%CI=[-23.0, -7.34], p=0.001), but not LGA (p=0.59) and had a reduced median birthweight (50^{th} percentile: β=-7.5, 95%CI=[-14.9, -0.05], p=0.05). While older fathers had a reduced risk of fathering an SGA infant (10^{th} percentile: β=9.5, 95%CI=[4.15, 14.8], p=0.0005). Higher SEIFA scores were associated with increased median infant birthweight (β=44.3, 95%CI=[16.7, 71.8], p=0.002) and a reduced risk of an SGA infant (β=32.0, 95%CI=[7.92, 56.1], p=0.009.

Male infants had higher birthweight compared with females by a similar amount in all regression analysis (all p[?]0.03). Birthweight increased non-linearly with gestational age with smaller increases in weight for gestational ages >40 weeks. This tapering in the increase in birth weight was more extreme for SGA

(10^{th}percentile: p=0.003 and 5^{th} percentile: p=0.004) than for LGA (90^{th} percentile: p=0.16 and 95^{th} percentile: p=0.03). Infants delivered by caesarean section were more likely to be heavier (90^{th}percentile: β=133, 95%CI=[62.3, 203], p<0.0002), however their risk for SGA was not different to babies delivered vaginally (p=0.82). There was no detectable influence of insemination method on infant birthweight.

Parental preconception BMI and infant birthweight

Figure 1 presents model estimates for parental BMI associations with infant birthweight. There was weak evidence for an interaction between parental BMIs for median birth weight (β=-0.98; 95%CI=[-1.90, -0.05], p=0.04) with infants having increasing birth weight with increasing parental BMI, when one parent has normal weight (Figures 1A and 1C). When either parent was overweight or obese, although median infant birthweight are higher (maternal β=15.9; 95%CI=[1.63, 30.1], p=0.03 and paternal β=7.33; 95%CI=[0.297, 14.4] p=0.04), they were not associated with increasing BMI of the other parent (Figure 1B and Figure 1D).

Maternal overweight and obesity was associated with increased risk of extreme LGA (95^{th} percentile: β=-25.1; 95%CI=[5.07, 45.1], p=0.01), while there was no effect of increasing paternal BMI (90^{th} percentile: p=0.50; 95^{th}percentile: p=0.43). In both the median, 90^{th} and 95^{th} percentile models, there was no evidence of a non-linear association between maternal BMI and birthweight (median: p=0.61; 90^{th} percentile: p=0.32; 95^{th} percentile: p=0.70). However, in the 5^{th} and 10^{th} percentile regression there was a strong non-linear association between maternal BMI and infant birthweight (p=0.002 and p=0.03). Such that infant birthweight increased with maternal BMI, approximately 27.5kg/m^2or lower, but for maternal BMIs in the obese range (>30kg/m^2), the 5^{th}percentile of infant birthweight plateaued, indicating a greater divergence from the median baby weights and greater risks of SGA. There was no effect of paternal BMI and risk of SGA infants (5^{th} percentile: p=0.60; 10^{th}percentile: p=0.52).

DISCUSSION

Main Finding

In a retrospective cohort study of 1479 singleton births following ART, we demonstrate no additional impact on infant birthweight when both parents were overweight or obese compared to just one parent alone. That is, while infants born to overweight and obese mothers or fathers were heavier, the joint effect is not additive.

Strengths and Limitations

To our knowledge, this is the first study assessing the combined contribution of maternal and paternal preconception overweight and obesity on infant birthweight. The strengths of our study include the use of a database in which preconception health, IVF cycle outcomes and pregnancy rates were registered prospectively, thereby minimising selection bias; BMI was calculated from clinically recorded measurements of maternal and paternal preconception weights and heights; the analysis only included first singleton term births; and the large population size from a singular ART unit limited variability in clinical protocols. Limitations of our study include the retrospective study design, which limits the degree of causal inference; reduced ability to control for some key parental factors that can influence infant birthweight, including parental smoking [15, 16] and maternal gestational weight gain [17] and further, the fact that the utilization of an ART cohort is confounded by subfertility and*in vitro* embryo culture. However, infertility diagnosis has been previously shown to not influence infant birthweight in term pregnancies[18, 19], thus the subfertility diagnosis is unlikely to be contributing to the reported outcomes.

Interpretation

Contrary to our hypothesis, we found no additional effect of having two overweight or obese parents on infant birthweight outside what was seen if one parent was overweight or obese. Evidence from our rodent model of obesity also suggests that the effect on infant birthweight may unlikely be additive, but an accumulation of both the negative maternal and paternal phenotypes [20]. This seems to be evident in our human cohort where infant birthweight increased from 3.13kg 95%CI=[3.03, 3.23] to 3.44kg 95%CI=[3.31, 3.56] in normal weight mothers compared with obese mothers when fathers were of a normal weight. When fathers were

obese, this increase was much smaller (3.33kg 95%CI=[3.20, 3.45] to 3.41kg [3.32, 3.51]). This is likely because infants born to fathers who are obese already start out heavier (˜200 g) and therefore, only require a small additional increase in size to match the effect of obese mothers. Whilst we saw no additive effect of combined parental BMI on infant birthweight, the effects maybe may be present as the infants grow. For instance, in another rodent model, insulin resistance and liver steatosis were greatest in offspring when both parents were fed a high fat diet prior to and during gestation, compared to just one parent[21]. In humans, Rath *et al.,*[22], found that parental obesity was the strongest predictor of offspring adult BMI. These data suggest that the combined effect of having two obese parents on infant programming may manifest later in life.

There is a large body of literature demonstrating the impact of maternal BMI on infant birthweight including LGA [23], and there is some suggestion for paternal BMI also having an impact on infant birthweight [9]. Unfortunately, much of the literature on paternal BMI included self-reported paternal height and weight from the mother, or, collection during pregnancy, at birth, or when the child was a toddler, rather than preconception [24, 25]. Furthermore, studies that have assessed preconception paternal BMI have not always adequately controlled for maternal and other parental cofactors, and therefore, the results are currently conflicting. For example Chen *et al.,* [26] found that paternal overweight and obesity only influence male infant birthweight, with a 1 unit increase in paternal BMI associated with a 19.5 g increase in infant birthweight, while Noor *et al* .,[27] found that fathers with a BMI greater than 25kg/m^2 increased infant birthweight in both sexes (z score, 0.38 [0.91] vs 0.11 [0.96]. In contrast, three other studies found no effect of paternal BMI on infant birthweight [28-30]. Interestingly, when assessing the extreme ends of infant birthweight (SGA or LGA), McCown*et al.,* [31] found that obese men were 1.5 times more likely to father SGA infants, while Yang *et al.,*[32] found that overweight and obese men were 1.3 times and 1.9 times respectively more likely, to father an LGA infant. Similarly, in an ART cohort following frozen embryo transfer Ma *et al.,* [19] found that men who were overweight or obese had an increased odds of having a LGA infant (OR=1.43; 95%CI=[1.27, 1.63] and OR=1.36; 95%CI=[1.04, 1.79] respectively). In our study, we found no evidence for an association between paternal overweight and obesity and SGA or LGA infants (<10$^{\text{th}}$ and >90$^{\text{th}}$ percentiles), although the median birthweight of infants were higher with increased paternal BMI (7.3 g for every 1 unit increase in paternal BMI). The lack of consensus in the reported effects of paternal overweight and obesity on infant birthweight highlights the necessity for further adequately controlled cohort studies. Nevertheless, animal models of male obesity support findings for increased infant birthweight [33-35].

The mechanism for transmission of altered infant birthweight from increasing paternal BMI is likely due to a combination of genetic and epigenetic factors delivered by sperm to the egg at fertilisation[36, 37]. A number of genes are known to play a part in the heritability of weight [38, 39], however these genetic loci do not fully account for the transmission. A number of studies in animal models and humans directly show a link between paternal obesity at conception, sperm epigenetic changes (non-coding RNAs and DNA and histone methylation) and altered fetal phenotypes[27, 40-44], indicating that the paternal effect goes beyond that of a shared living environment, with preconception factors able to influence the health of subsequent offspring.

Our data shows that infants born from mothers or fathers of increasing BMI start their growth trajectory heavier than those infants born to normal weight mothers or fathers. This is of concern as birthweight has been reported to play an important role in the establishment of adolescent and early adulthood BMI [22, 45]. For instance, evidence from the Early Childhood Longitudinal Study in the USA, found that LGA infants made up 1/3 (36%) of all children who were obese by age 14 years [45] and data from the RAINE cohort in Western Australia, Australia, found that both maternal and paternal preconception BMI were strong predictors of childhood, adolescent and adulthood obesity [22]. If obesity aggregates within families, then a focus on preconception planning for family units is recommended. In Australia, there are no primary male preconception health-care initiatives [46]. While Healthy Male (Andrology Australia) does provide education on the reproductive health of men, focusing on fertility, sexuality and fathering, and the Australian men's health policy addresses various issues related to sexual problems, neither of these primarily focus on pre-conception health [46]. Further, missing data for paternal preconception BMI in our study was nearly double

that of missing maternal BMI (33% vs 18%). While some of this may be due to the lack of males in preconception care appointments, it highlights the dogma that mother's preconception health is a key focus rather than fathers. Therefore, it is recommended that preconception health messages focus on 'healthy couples', emphasising the need to improve lifestyle for the family unit prior to pregnancy.

Conclusion

In conclusion, utilising close to 1500 singleton term births from an ART cohort, our results demonstrate that maternal or paternal overweight and obesity increases infant birthweight independent to the BMI of the other partner, with no additive effects seen if both parents were overweight or obese. Further studies are warranted in both ART and general population cohorts to support or refute our findings. Our results highlight the notion for family unit preconception health initiatives.

DISCLOSURE OF INTERESTS

NOM and DZ are paid employees of Monash IVF Group Ltd. The remaining authors have no disclosures.

CONTRIBUTIONS TO AUTHORSHIP

NOM conception, acquisition, interpretation of data, drafting, revising and final approval of the manuscript. AV conception, analysis, interpretation of data, revising and final approval of the manuscript. DZ conception, revising and final approval of the manuscript. JAG conception, interpretation of data, drafting, revising and final approval of the manuscript.

FUNDING

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ETHICS APPROVAL

Repromed's Scientific Advisory Board (SAC) approved the retrospective study (14/11/2019); the study was exempt from HREC review at the University of Adelaide. Formal consent for this type of study is not required.

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FIGURE LEGENDS

Figure 1: Joint association of parental BMI on infant birthweight.

The effect of the interaction is illustrated by varying maternal (**A** & **B**) and paternal BMI (**C** & **D**) with the other parental BMI set at 20 and 35 kg/m^{2}respectively. Grey circles are observed birth weights. Solid red lines are the median model estimates, dashed lines are 10thand 90th percentiles and dotted lines are the 5th and 95th percentile models. 95% confidence intervals (blue bars) are presented for parental BMIs of 20 kg/m^2, 27.5 kg/m^2 and 35 kg/m^2. These estimates are for IVF insemination, vaginal births and female babies and have other continuous covariates set at their median values.

Figure S1: Cohort inclusion flow-diagram.

Figure S2: Comparison of baby weights with population estimates reported in Dobbins *et al.* 2007.

A Female birthweight and **B** male birthweight. Solid black lines represent population median estimates, dashed lines are 10th and 90th percentiles and dotted lines are the 1st and 99thpercentile.

Figure S3: Associations of risk factors on infant birthweight.

A Gestational age, **B** SEFIA score, **C** maternal age and **D** paternal age. Grey circles are observed birth weights. Solid red lines are the median model estimates, dashed lines are 10th and 90th percentiles and dotted lines are the 5th and 95thpercentile models. These estimates are for IVF insemination, vaginal births and female babies and have continuous covariates set at their median values.

Table 1 : **Summary of parental demographics, treatment choices and birth outcomes.**

			N = 1479
Parental Characteristics	**Parental Characteristics**	**Parental Characteristics**	
	Maternal age (years)	Maternal age (years)	
		Median (range)	32.9 (19.9, 45.2)
		Mean (SD)	32.83 (4.17)
	Paternal age (years)	Paternal age (years)	
		Median (range)	35.2 (21.3, 62.8)
		Mean (SD)	36.15 (6.27)
	Maternal BMI (kg/m^2)	Maternal BMI (kg/m^2)	
		Median (range)	24.4 (16.2, 55.9)

			N = 1479
		Mean (SD)	25.9 (5.96)
		Missing	6 (<1%)
	Paternal BMI (kg/m^2)	Paternal BMI (kg/m^2)	
		Median (range)	27.4 (17.3, 54.2)
		Mean (SD)	28.11 (4.65)
		Missing	278 (19%)
	SEFIA	SEFIA	
		Median (range)	1000 (673, 1151)
		Mean (SD)	995 (69)
		Missing	22 (1%)
Infertility Diagnosis	**Infertility Diagnosis**	**Infertility Diagnosis**	
	Tubal factor	Tubal factor	112 (8%)
	Endometrial factor	Endometrial factor	101 (7%)
	Male factor	Male factor	818 (55%)
	Other	Other	536 (36%)
	Unexplained	Unexplained	282 (19%)
Birth Factors	**Birth Factors**	**Birth Factors**	
	Insemination method	Insemination method	
		IVF	232 (16%)
		ICSI	1247 (84%)
	Delivery method	Delivery method	
		Vaginal	871 (59%)
		Caesarean	607 (41%)
		Missing	1 (<1%)
	Gestational length (weeks)	Gestational length (weeks)	
		Median (range)	39.14 (37, 42.14)
		Mean (SD)	39.13 (1.08)
	Infant Sex	Infant Sex	
		Female	745 (50%)
		Male	734 (50%)
	Infant birthweight (g)	Infant birthweight (g)	
		Median (range)	3345 (1587, 4998)
		Mean (SD)	3367.66 (453.1)

BMI = body mass index; SEIFA = socioeconomic index for areas; SD = standard deviation; IVF = In vitro fertilisation; ICSI = intracytoplasmic sperm injection;

Table 2: Quantile regression fits for infants small for gestation age (SGA).

	5th Percentile	5th Percentile	10th Percentile	10th Percentile	M
	Est [95% CI]	p-value	Est [95% CI]	p-value	Es
Birth Factors					
Sex (male v female)	112 [46.5, 178]	**0.0008**	63.3 [7.28, 119]	**0.03**	10
Gestational age	275 [193, 358]	**<0.0001**	212 [129, 294]	**<0.0001**	20
Gestational age (non-linear)		**0.004**		**0.003**	
Insemination method (ICSI v IVF)	-3.36 [-90.4, 83.7]	0.94	-30 [-103, 42.6]	0.42	-8
Delivery (caesarean vs vaginal)	-13 [-82.5, 56.5]	0.71	7.09 [-54.5, 68.7]	0.82	80
Parental Factors					
Maternal age	-12.3 [-21.4, -3.17]	**0.008**	-15.2 [-23, -7.34]	**0.0001**	-7

	5th Percentile	5th Percentile	10th Percentile	10th Percentile	M
Paternal age	6.97 [2.05, 11.9]	**0.006**	9.5 [4.15, 14.8]	**0.0005**	2.
SEIFA	32.9 [-4.36, 70.1]	**0.08**	32 [7.92, 56.1]	**0.009**	44
Maternal BMI	37.4 [18.3, 56.6]	**0.0001**	29.9 [11.9, 47.8]	**0.001**	15
Maternal BMI (non-linear)		**0.002**		**0.03**	
Paternal BMI	3.07 [-8.26, 14.4]	0.60	2.43 [-4.91, 9.78]	0.52	7.
Interaction: Maternal BMI x Paternal BMI	0.0621 [-1.25, 1.38]	0.93	-0.241 [-1.3, 0.82]	0.66	-0

BMI = Body mass index; ICSI = intracytoplasmic sperm injection; IVF = In vitro fertilisation; SEIFA = socioeconomic index for areas.

Table 3: Quantile regression fits for infants large for gestation age (LGA).

	Median	Median	90th Percentile	90th Percentile	95t
	Est [95% CI]	p-value	Est [95% CI]	p-value	Est
Birth Factors					
Sex (male v female)	106 [55.9, 157]	**<0.0001**	142 [77.5, 207]	**<0.0001**	130
Gestational age	209 [160, 258]	**<0.0001**	175 [112, 237]	**<0.0001**	215
Gestational age (non-linear)		**0.002**	-	0.16	
Insemination method (ICSI v IVF)	-8.87 [-73.1, 55.4]	0.79	-33.2 [-116, 49.2]	0.43	-98
Delivery (caesarean vs vaginal)	80.4 [26, 135]	**0.004**	133 [62.3, 203]	**0.0002**	157
Parental Factors					
Maternal age	-7.47 [-14.9, -0.0572]	**0.05**	2.57 [-6.8, 11.9]	0.59	3.5
Paternal age	2.86 [-1.97, 7.69]	0.25	0.0827 [-6.4, 6.57]	0.98	0.3
SEIFA	44.3 [16.7, 71.8]	**0.002**	20.4 [-14, 54.9]	0.25	28.
Maternal BMI	15.9 [1.63, 30.1]	**0.03**	9.48 [-7.99, 26.9]	0.29	25.
Maternal BMI (non-linear)		0.61		0.32	
Paternal BMI	7.33 [0.297, 14.4]	**0.04**	3.28 [-6.15, 12.7]	0.50	4.5
Interaction: Maternal BMI x Paternal BMI	-0.977 [-1.9, -0.0537]	**0.04**	-0.577 [-1.87, 0.719]	0.38	-0.

BMI = Body mass index; ICSI = intracytoplasmic sperm injection; IVF = In vitro fertilisation; SEIFA = socioeconomic index for areas.