

ORIGINAL ARTICLE

Increasing maternal prepregnancy body mass index is associated with reduced insulin sensitivity and increased blood pressure in their children

José G. B. Derraik*, Ahila Ayyavoo*†, Paul L. Hofman*†, Janene B. Biggs* and Wayne S. Cutfield*†

*Liggins Institute, University of Auckland, Auckland, New Zealand and †Gravida: National Centre for Growth and Development, Auckland, New Zealand

Summary

Objective We aimed to assess the effects of maternal prepregnancy body mass index (BMI) on insulin sensitivity, metabolism and blood pressure in the offspring.

Methods We studied 70 prepubertal children aged 8.9 ± 1.9 years (range 4–11 years), born 38–40 weeks of gestation and appropriate-for-gestational-age birthweight. Maternal prepregnancy body mass index (MPP BMI) was calculated from self-reported weight. Children's insulin sensitivity was measured using intravenous glucose tolerance tests and Bergman's minimal model. Other clinical assessments included auxology, fasting lipid and hormonal profiles, DXA-derived body composition and 24-h ambulatory blood pressure monitoring. Data were analysed using random effect mixed models, adjusting for important confounders and a random factor to account for sibling clusters.

Results Increasing MPP BMI was correlated with increasing BMI standard deviation scores (SDS) ($r = 0.30$; $P = 0.012$) and lower insulin sensitivity in their children ($r = -0.34$; $P = 0.004$). In multivariate regression models, increasing MPP BMI was associated with lower insulin sensitivity ($\beta = -0.040$; $P = 0.005$), with every 1 kg/m² increase in MPP BMI associated with a 4.0% decrease in offspring insulin sensitivity. Greater MPP BMI was associated with higher systolic blood pressure in the daytime ($\beta = 0.794$; $P = 0.010$) and night-time ($\beta = 0.800$; $P = 0.017$), as well as higher 24-h mean arterial pressure ($\beta = 0.508$; $P = 0.025$) in the offspring.

Conclusion Greater maternal prepregnancy BMI is associated with lower insulin sensitivity and higher blood pressure in their children, effects that were independent of offspring adiposity. Thus, higher maternal BMI prior to pregnancy (even among women of normal BMI) may contribute to increased risk of type 2 diabetes and other metabolic diseases in the subsequent generation.

(Received 25 September 2014; returned for revision 17 October 2014; finally revised 24 October 2014; accepted 6 November 2014)

Introduction

The prevalence of obesity among pregnant women is increasing worldwide, in both developed and developing countries.¹ Maternal prepregnancy obesity is associated with poorer pregnancy outcomes, including higher rates of caesarean section and longer hospital stay.² Maternal overweight or obesity during pregnancy are risk factors for higher birthweight and macrosomia,^{3,4} and with increasing maternal body mass index (BMI), there is an associated increase in the risk of foetal and infant mortality.^{5,6}

Numerous animal studies have shown that maternal obesity during pregnancy is associated with adverse offspring outcomes (particularly obesity), but these effects are often mediated by other factors such as postnatal diet.⁷ Nonetheless, a number of human studies have shown that maternal obesity is associated with adverse effects in the offspring, including obesity, and increased fat mass.⁷ One study in particular, showed that the offspring of obese mothers were more insulin resistant in young adulthood than those born to normal-weight mothers.⁸

Among 1727 Dutch children, increasing maternal prepregnancy BMI (MPP BMI) was associated with increased BMI and percentage body fat in the offspring at 5–6 years of age.⁹ However, it seems that no studies have examined the association of MPP BMI with glucose metabolism (as measured by a gold-standard technique) in the offspring in childhood. Further, studies have focused on the offspring of obese mothers, so that it is not clear whether increased adiposity within the normal-weight range also adversely affects the offspring. Thus, we aimed to assess the potential effects of MPP BMI on insulin sensitivity, metabolism and blood pressure in the offspring prior to puberty.

Methods

Ethics approval

Ethics approval for this study was provided by the Northern Y Regional Ethics Committee (Ministry of Health, New Zealand).

Correspondence: José G. B. Derraik, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand. Tel.: +64 9 923 3794; E-mail: j.derraik@auckland.ac.nz

Written informed consent was obtained from parents or guardians, as well as verbal or written consent from each child as was appropriate to their age.

Participants

This study involved the retrospective analyses of a cohort of children recently studied to identify the effects of birth order on insulin sensitivity.¹⁰ Recruited children were healthy, naturally conceived, born at term (38–40 weeks of gestation) from singleton pregnancies and with birthweights appropriate-for-gestational-age. Participants with signs of puberty (Tanner stage 2 breast development in girls and testicular volume >3 ml in boys or evidence of adrenarche) were excluded. Other exclusion criteria were genetic syndromes, receiving medication that could affect insulin sensitivity, as well as having a first-degree relative or grandparent with diabetes, the metabolic syndrome or any of its features other than central adiposity. Children were also excluded if born to mothers with gestational diabetes, pre-eclampsia, gestational or pre-existing hypertension, chronic illnesses or maternal drug use during pregnancy (including tobacco and alcohol).

Clinical assessments

All children were assessed at the Maurice & Agnes Paykel Clinical Research Unit (Liggins Institute) during a single visit following an overnight fast. Neonatal parameters were recorded, and birthweights were transformed into standard deviation scores (SDS).¹¹

Current maternal weights and heights were measured. Maternal prepregnancy weight was obtained from medical files, having been recorded based on maternal recall during the first antenatal clinic. One study on 6632 Australian women showed a very high correlation ($r = 0.95$) between self-reported prepregnancy weight and weight measured at the first antenatal clinic.² Therefore, self-reported maternal weight as adopted in this study should be considered a reliable measurement. Maternal prepregnancy and current BMI were consequently calculated.

Children's heights were measured using a Harpenden stadiometer. Weight and body composition were obtained using whole-body dual-energy X-ray absorptiometry (DXA, Lunar Prodigy 2000, General Electric, Madison, WI, USA). Height SDS, weight SDS and body mass index (BMI) SDS were derived as per appropriate standards.^{11–13}

Insulin sensitivity was assessed using a 90-min modified frequently sampled intravenous glucose test (FSIGT), modified with insulin and analysed using Bergman's minimal model software.¹⁴ Three baseline samples were drawn at -20, -10 and 0 min. A 25% dextrose infusion (at 0.3 g/kg) started at 0 min and lasted for one minute. Blood samples were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 19 min. Insulin (0.015 units/kg) was then intravenously administered as a bolus at 20 min, and further samples were drawn at 22, 23, 24, 25, 27, 30, 35, 40, 45, 50, 60, 70, 80 and 90 min.

Baseline blood samples were also drawn to measure serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), insulin-like growth factor I (IGF-I), leptin, adiponectin, glucose and insulin concentrations. Assays were performed as described in Ayyavoo *et al.*¹⁰

24-h ambulatory blood pressure was assessed following the clinical visit, when participants were fitted with a Spacelabs 90217 monitor (Spacelabs Medical Inc., Redmond, WA, USA) on the nondominant arm. Measurements were performed every 20 min from 07:00 to 22:00 and every 30 min from 22:00 to 07:00.

Statistical analyses

Simple linear associations between MPP BMI and outcomes were assessed using Pearson's correlation coefficients. Subsequently, random effect mixed models were used to examine possible associations between MPP BMI and outcomes of interest. Models included maternal identification number as a random factor to account for the clustering of siblings. Important confounding factors were adjusted for in the analyses, including sex, age, birthweight SDS, birth order and maternal age at childbirth, as well as height (instead of age) for blood pressure parameters. Multivariate analyses were performed using SAS v.9.3 (SAS Institute Inc. Cary, NC, USA). All outcomes were tested for normality, and parameters associated with glucose homeostasis were log-transformed. For these parameters, β was exponentiated to obtain the percentage change in outcome response for every one unit increase in MPP BMI. All statistical tests were two-tailed and maintained at a 5% significance level. Descriptive data are presented as means \pm standard deviations.

Results

We studied 70 children (27 girls and 43 boys) who were the offspring of 54 mothers (Table 1). Twelve children were born of overweight mothers (17%) and four of obese mothers (6%). Prepregnancy weight and BMI were highly correlated with present maternal weight ($r = 0.75$; $P < 0.0001$) and BMI ($r = 0.71$; $P < 0.0001$). Only five of the 54 mothers were lighter than prior to pregnancy, so that at the time of the study they were on average ~ 7.0 kg heavier ($P < 0.0001$) and of BMI 2.6 kg/m² greater ($P < 0.0001$; Table 1).

Increasing MPP BMI was correlated with increasing BMI SDS in the offspring ($r = 0.30$; $P = 0.012$) and tended to be correlated with greater abdominal adiposity as measured by the android fat to gynoid fat ratio ($r = 0.23$; $P = 0.051$). Greater MPP BMI was correlated with lower insulin sensitivity in their children ($r = -0.34$; $P = 0.004$) and tended to be correlated with increased acute insulin response ($r = 0.23$; $P = 0.057$). Increasing MPP BMI was also correlated with higher leptin ($r = 0.29$; $P = 0.016$) concentrations in the offspring.

Multivariate models showed that increasing MPP BMI was associated with lower insulin sensitivity ($\beta = -0.040$; $P = 0.005$) in their children (Table 2; Table S1), indicating that every 1 kg/m² increase in maternal BMI was associated with a 4.0%

Table 1. Demographic characteristics of mothers and children who participated in this study. Where appropriate, data are means \pm SD, with ranges in brackets

Mothers	
<i>n</i>	54
Age at childbirth (years)	33.0 \pm 4.9 (17.9–42.0)
Prepregnancy weight (kg)	63.1 \pm 9.3 (46.0–87.0)
Prepregnancy BMI (kg/m ²)	23.2 \pm 3.5 (16.8–34.1)
Current weight (kg)	70.0 \pm 12.8 (51.5–115.6)
Current BMI (kg/m ²)	25.9 \pm 4.3 (19.8–36.0)
Children	
<i>n</i>	70
Age (years)	8.9 \pm 1.9 (4.0–11.9)
Sex ratio (boys/girls)	43/27
Ethnicity (New Zealand European)	83%
Birthweight SDS	0.20 \pm 0.81 (–1.47–1.77)
Height SDS	0.44 \pm 0.81 (–1.35–2.23)
BMI SDS	0.25 \pm 0.96 (–1.96–3.74)

decrease in offspring insulin sensitivity. Notably, this association was observed independently of children's adiposity, that is when total body fat percentage was added to the model as a mediator (Table S2). Heavier mothers also tended to have children with greater BMI SDS ($\beta = 0.071$; $P = 0.042$). As observed in simple linear correlations, increasing MPP BMI was associated with higher leptin ($\beta = 0.389$; $P = 0.003$) concentrations in their children (Table 2). There were no observed associations between MPP BMI and other hormones and lipids measured (Table 2).

Maternal prepregnancy BMI affected the offspring blood pressure, particularly systolic. Greater MPP BMI was associated with higher systolic blood pressure in their children in the daytime ($\beta = 0.794$; $P = 0.010$) and night-time ($\beta = 0.800$; $P = 0.017$) (Table 2; Table S1). The offspring of mothers with greater prepregnancy BMI also had higher 24-h mean arterial pressure ($\beta = 0.508$; $P = 0.025$) and tended to have elevated daytime diastolic blood pressure ($\beta = 0.438$; $P = 0.056$) (Table 2; Table S1).

Exploratory analyses were carried out examining potential sex differences in the main outcome responses (Table 3). The association between increased MPP BMI and lower insulin sensitivity was only statistically significant among boys (Table 3). In contrast, the association of MPP BMI with increasing blood pressure was particularly marked among girls (Table 3).

Note that although MPP BMI was not associated with birthweight SDS when the cohort was assessed as a whole ($P = 0.25$), there was a significant interaction indicating a sex-specific effect ($P = 0.020$). When assessed separately, increasing MPP BMI appeared to have no effect on the birthweight of boys ($P = 0.64$), but it was associated with greater birthweight SDS among girls ($\beta = 0.107$; $P = 0.007$).

Discussion

This study shows that increased MPP BMI was associated with lower insulin sensitivity and higher blood pressure in

their children, effects that were independent of offspring fat mass and important confounders. MPP BMI was also positively associated with offspring BMI SDS. There appears to be progressive effects of increased MPP BMI on these offspring parameters. Importantly, 77% of the children we studied were born to mothers of normal BMI, and we also excluded mothers who developed gestational diabetes. Thus, our findings show that higher maternal BMI prior to pregnancy (even among women of normal BMI) may contribute to increased risk of type 2 diabetes and other metabolic diseases in the subsequent generation.

Our findings corroborate previous observations on the association of maternal obesity and glucose metabolism in the offspring. Babies born of obese mothers were found to be more insulin resistant than offspring of lean mothers.¹⁵ In childhood, maternal obesity was associated with increased metabolic syndrome risk.¹⁶ In young adulthood, the offspring of obese mothers were more insulin resistant than those of normal-weight mothers.⁸

A number of studies have focused on the impact of weight gain during pregnancy on offspring obesity.⁷ While an association between maternal weight gain and offspring obesity has been shown to occur,^{17–19} our data suggest that the impact of maternal adiposity on offspring health begins prior to pregnancy.

There is strong evidence that maternal obesity is associated with the developmental programming of adverse effects in the offspring.^{7,20} However, the underpinning mechanisms are poorly understood and may include alterations in foetal nutrient supply combined with genetic and epigenetic mechanisms.²⁰ Our findings suggest that these mechanisms are associated with a gradual change in BMI and not only observed in mothers who are overweight or obese at the time of pregnancy.

Subgroup analysis indicated that adverse effects of increasing MPP BMI were observed in both sexes, but this exploratory analysis suggested differential effects among boys and girls. Unfortunately, the study was not sufficiently powered to adequately assess sex differences in outcome responses, as we examined a relatively small cohort of 70 children born to 54 mothers. Another limitation of our study was the fact that it was not based on actual prospective data measured prior to pregnancy, but relied on maternal weight recall. However, as previously discussed, self-reported prepregnancy weight and weight measured at the first antenatal clinic are highly correlated.² Lastly, we also do not have measurements of weight gain during pregnancy. Nonetheless, our study is unique for associating MPP BMI with insulin sensitivity in children as measured by a gold-standard technique.

In conclusion, our study shows that maternal prepregnancy BMI is an important factor associated with offspring adiposity, glucose metabolism and cardiovascular status during childhood. Notably, the association was also observed across the normal BMI range. Thus, effective strategies are required to optimize a woman's diet and weight during the reproductive years and prior to pregnancy to improve childhood health.

Table 2. Estimated changes in outcome responses per unit increase in maternal prepregnancy body mass index (β), with associated 95% confidence intervals. Note that parameters of glucose homeostasis have been log-transformed for analyses. Multivariate models included adjustments for age, sex, birth order, birthweight standard deviation scores and maternal age at childbirth, as well as height (instead of age) for blood pressure parameters

	Unadjusted			Adjusted		
	β	95% CI	P-value	β	95% CI	P-value
Anthropometry						
BMI SDS (kg/m ²)	0.067	0.000–0.135	0.050	0.071	0.003–0.140	0.042
Total body fat (%)	0.529	0.002–1.055	0.049	0.248	–0.278–0.774	0.35
Android fat to gynoid fat ratio	0.012	0.000–0.024	0.046	0.007	–0.005–0.019	0.27
Glucose homeostasis						
Insulin sensitivity [$\times 10^{-4}$ /min (mU/l)]	–0.044	–0.069 to –0.018	0.001	–0.040	–0.067 to –0.013	0.005
Acute insulin response (mU/l)*	0.048	0.001–0.097	0.048	0.030	–0.020–0.081	0.23
Fasting insulin (mU/l)	–0.002	–0.039–0.035	0.92	–0.006	–0.047–0.034	0.75
24-h ambulatory blood pressure						
Daytime systolic (mmHg)	0.428	–0.139–0.995	0.14	0.794	0.199–1.389	0.010
Daytime diastolic (mmHg)	0.267	–0.168–0.703	0.223	0.438	–0.012–0.888	0.056
Night-time systolic (mmHg)	0.552	–0.048–1.152	0.07	0.800	0.151–1.450	0.017
Night-time diastolic (mmHg)	0.109	–0.334–0.551	0.62	0.196	–0.271–0.663	0.40
Mean arterial pressure (mmHg)	0.333	–0.091–0.758	0.12	0.508	0.068–0.947	0.025
Lipid profile						
Total cholesterol (mmol/l)	–0.014	–0.068–0.040	0.61	–0.007	–0.065–0.050	0.80
LDL-C (mmol/l)	–0.027	–0.071–0.017	0.22	–0.026	–0.072–0.020	0.26
HDL-C (mmol/l)	0.001	–0.020–0.022	0.92	0.000	–0.023–0.023	0.98
Hormones						
IGF-I (ng/ml)	3.007	–1.837–7.851	0.22	2.826	–1.673–7.325	0.21
Leptin (ng/ml)	0.555	0.224–0.887	0.001	0.389	0.137–0.640	0.003
Adiponectin (μ g/ml)	–38.1	–311–235	0.78	–92.7	–371–185	0.51

Statistically significant values at $P < 0.05$ are shown in bold.

*indicates an interaction between MPP BMI and sex at $P < 0.05$.

Table 3. Results from subgroup analyses by sex. Data are estimated changes in outcome responses per unit increase in maternal prepregnancy body mass index (β), with associated 95% confidence intervals. Note that parameters of glucose homeostasis have been log-transformed for analyses. Data are from multivariate models including adjustments for age, birth order, birthweight standard deviation scores and maternal age at childbirth, as well as height (instead of age) for blood pressure parameters

	Boys ($n = 43$)			Girls ($n = 27$)		
	β	95% CI	P-value	β	95% CI	P-value
Anthropometry						
BMI SDS (kg/m ²)	0.035	–0.047–0.117	0.39	0.131	–0.019–0.282	0.08
Total body fat (%)	–0.043	–0.694–0.610	0.90	0.226	–0.835–1.287	0.66
Android fat to gynoid fat ratio	0.005	–0.010–0.021	0.51	0.010	–0.014–0.034	0.41
Glucose homeostasis						
Insulin sensitivity [$\times 10^{-4}$ /min (mU/l)]	–0.029	–0.056 to –0.001	0.040	–0.049	–0.116–0.017	0.14
Acute insulin response (mU/l)	–0.016	–0.080–0.049	0.63	0.089	–0.007–0.185	0.067
Fasting insulin (mU/l)	0.007	–0.049–0.063	0.81	0.003	–0.064–0.070	0.93
24-h ambulatory blood pressure						
Daytime systolic (mmHg)	0.532	–0.362–1.425	0.23	1.458	0.642–2.273	0.002
Daytime diastolic (mmHg)	0.225	–0.462–0.913	0.51	1.101	0.555–1.646	0.0005
Night-time systolic (mmHg)	0.508	–0.302–1.317	0.21	1.281	–0.024–2.585	0.054
Night-time diastolic (mmHg)	–0.178	–0.725–0.369	0.51	0.827	–0.119–1.772	0.08
Mean arterial pressure (mmHg)	0.243	–0.338–0.825	0.40	1.108	0.511–1.704	0.001

Statistically significant values at $P < 0.05$ are shown in bold.

Acknowledgement

We thank the Paykel Trust for long-term support of the Maurice & Agnes Paykel Clinical Research Unit at the Liggins Institute, University of Auckland.

Funding

This study was funded by Gravida: National Centre for Growth and Development and the Australasian Paediatric Endocrine Group (APEG).

Conflict of interest

The authors have no financial or nonfinancial conflict of interests to disclose that may be relevant to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript.

Authors' contribution

A.A., W.S.C., P.L.H. and J.G.B.D. conceived and designed the study. A.A. and J.B. recruited and performed the tests. A.A. and J.G.B.D. collected and compiled the data, which were analysed by J.G.B.D. J.G.B.D. wrote the manuscript with input from other authors. All authors have approved the submission of the final version of this manuscript.

References

- Huda, S.S., Brodie, L.E. & Sattar, N. (2010) Obesity in pregnancy: prevalence and metabolic consequences. *Seminars in Fetal and Neonatal Medicine*, **15**, 70–76.
- Mamun, A., Callaway, L., O'Callaghan, M., et al. (2011) Associations of maternal pre-pregnancy obesity and excess pregnancy weight gains with adverse pregnancy outcomes and length of hospital stay. *BMC Pregnancy and Childbirth*, **11**, 62.
- Alberico, S., Montico, M., Barresi, V., et al. (2014) The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. *BMC Pregnancy and Childbirth*, **14**, 23.
- Jensen, D.M., Damm, P., Sorensen, B., et al. (2003) Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. *American Journal of Obstetrics and Gynecology*, **189**, 239–244.
- Aune, D., Saugstad, O.D., Henriksen, T., et al. (2014) Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. *JAMA*, **311**, 1536–1546.
- Meehan, S., Beck, C.R., Mair-Jenkins, J., et al. (2014) Maternal obesity and infant mortality: a meta-analysis. *Pediatrics*, **133**, 863–871.
- Drake, A.J. & Reynolds, R.M. (2010) Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. *Reproduction*, **140**, 387–398.
- Mingrone, G., Manco, M., Mora, M.E., et al. (2008) Influence of maternal obesity on insulin sensitivity and secretion in offspring. *Diabetes Care*, **31**, 1872–1876.
- Gademan, M.G., Vermeulen, M., Oostvogels, A.J., et al. (2014) Maternal prepregnancy BMI and lipid profile during early pregnancy are independently associated with offspring's body composition at age 5–6 years: the ABCD Study. *PLoS ONE*, **9**, e94594.
- Ayyavoo, A., Savage, T., Derraik, J.G.B., et al. (2013) First-born children have reduced insulin sensitivity and higher daytime blood pressure compared to later-born children. *Journal of Clinical Endocrinology and Metabolism*, **98**, 1248–1253.
- Niklasson, A., Ericson, A., Fryer, J., et al. (1991) An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). *Acta Paediatrica*, **80**, 756–762.
- Tanner, J.M. & Whitehouse, R.H. (1976) Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Archives of Disease in Childhood*, **51**, 170–179.
- Cole, T.J., Freeman, J.V. & Preece, M.A. (1995) Body mass index reference curves for the UK, 1990. *Archives of Disease in Childhood*, **73**, 25–29.
- Cutfield, W.S., Bergman, R.N., Menon, R.K., et al. (1990) The modified minimal model: application to measurement of insulin sensitivity in children. *Journal of Clinical Endocrinology and Metabolism*, **70**, 1644–1650.
- Catalano, P.M., Presley, L., Minium, J., et al. (2009) Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care*, **32**, 1076–1080.
- Boney, C.M., Verma, A., Tucker, R., et al. (2005) Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics*, **115**, e290–e296.
- Mamun, A.A., O'Callaghan, M., Callaway, L., et al. (2009) Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. *Circulation*, **119**, 1720–1727.
- Oken, E., Rifas-Shiman, S.L., Field, A.E., et al. (2008) Maternal gestational weight gain and offspring weight in adolescence. *Obstetrics and Gynecology*, **112**, 999–1006.
- Oken, E., Taveras, E.M., Kleinman, K.P., et al. (2007) Gestational weight gain and child adiposity at age 3 years. *American Journal of Obstetrics and Gynecology*, **196**, 322 e321–328.
- Heerwagen, M.J., Miller, M.R., Barbour, L.A., et al. (2010) Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, **299**, R711–R722.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site.