1   **Relationships of Maternal Body Mass Index and Plasma Biomarkers with Childhood Body Mass Index**

2   **and Adiposity at 6 years; the Children of SCOPE study**

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26 **Abbreviations**

27 Bioelectrical impedance analysis – BIA

28 Bioimpedance spectroscopy - BIS

29 Body Mass Index – BMI

30 Children of SCOPE – CoS

31 Fat free mass - FFM

32 Gestational diabetes mellitus - GDM

33 Interquartile range – IQR

34 Body fat percentage – BFP

35 Placental Growth Factor - PlGF

36 Screening for Pregnancy Endpoints – SCOPE

37 Standard deviation – SD

38 Sum of Skinfold Thicknesses - SST

39 World Health Organisation – WHO

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45 **Abstract**

46 **Background:** Maternal obesity has been implicated in the origins of childhood obesity through a sub-

47 optimal environment in-utero.

48 **Objective:** We examined relationships of maternal early pregnancy body mass index (BMI),

49 overweight/obesity and plasma biomarkers of obesity, inflammation, insulin resistance and placental

50 function with measures of childhood BMI and adiposity.

51 **Methods:** BMI z-score, sum of skinfold thicknesses (SST), body fat percentage (BFP, by bioelectrical

52 impedance), waist, arm and hip circumferences were measured in 1,173 6-year-old children of nulliparous

53 pregnant women in the SCOPE study, New Zealand. Relationships of maternal early pregnancy (15 weeks'

54 gestation) BMI and biomarkers with these childhood anthropometric measures were assessed by linear

55 regression, with appropriate adjustment.

56 **Results:** 28.1% of mothers were overweight and 10.1% obese; compared with normal weight mothers,

57 the BFP of their children were 5.3% higher [0.16 SD (95% CI 0.04 to 0.29) p=0.01] and 7.8% higher [0.27

58 (0.08 to 0.47) p=0.006] with comparable values for BMI z-score, arm, waist and hip circumferences. Early

59 pregnancy maternal BMI and plasma placental growth factor (PlGF) were associated with higher child's

60 SST, BMI z-score, hip circumference and BFP. None of the metabolic or inflammatory maternal biomarkers

61 were associated with childhood obesity.

62 **Conclusion:** In this contemporary large prospective cohort study with extensive maternal/childhood

63 phenotyping and a high prevalence of maternal overweight/obesity, we found independent relationships

64 of maternal early pregnancy BMI with childhood BMI and adiposity, similar associations were observed

65 with PlGF which may imply a role for placenta function in the developmental programming of childhood

66 obesity risk.

Introduction

The World Health Organisation (WHO) have estimated that more than 41 million children under the age of 5 are overweight or obese [1]. The global epidemic of obesity, reflected in women of reproductive age and in pregnancy, has led to concerns that the metabolic consequences of maternal obesity may contribute to the early life determinants of childhood obesity [2–5], with most supporting evidence being derived from mother-child cohorts [6–11]. We have also recently reported that 6-month-old children born to mothers in the intervention arm of a randomised controlled trial of diet and physical activity showed reduced adiposity suggesting that improved diet and reduced gestational weight gain in pregnancy could make a contribution to preventative strategies against childhood obesity [12]. Policy makers, including the World Health Organisation now highlight nutritional status in pregnancy as a potentially modifiable target for prevention of childhood obesity [1].

The hypothesis proposing gestational origins of childhood obesity has most frequently been tested in cohorts with a low prevalence of obesity, recruited prior to the current obesity epidemic, in which the estimation of childhood adiposity has often been limited to body mass index (BMI). The international Screening for Pregnancy Endpoints (SCOPE) study of 5623 primiparous women and their children recruited between 2004 and 2011 was one of the most detailed large prospective maternal cohorts to date, with 43% (n=2421) of mothers affected by overweight or obesity. Whilst primarily focusing on prediction of adverse pregnancy outcomes, SCOPE has offered the potential to address relationships between maternal obesity and childhood obesity with appropriate adjustment for social and environmental determinants [13].

In this study, we have explored associations in the SCOPE cohort between maternal BMI during pregnancy and childhood BMI and measures of anthropometry as assessed by body fat percentage

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(BFP), BMI z-score, weight, height, arm, waist and hip circumferences and sum skinfold thicknesses in 6-year-old children of 1,173 mothers recruited to the study from Auckland, New Zealand (Children of SCOPE (CoS) study). With the goal of predicting late pregnancy complications the SCOPE study also measured 55 maternal biomarkers, including 15 with relevance to obesity, inflammation, insulin resistance and placental function. We have therefore explored whether these biomarkers could play a role in the relationship observed between maternal BMI and obesity and childhood adiposity.

Methods

Setting

Children of SCOPE was a cross-sectional study of 6-year-old children and their mothers who participated in SCOPE. These low risk, nulliparous pregnant women were recruited in Auckland, New Zealand between November 2004 and August 2008 [13]. Women were excluded if they were at high risk of preeclampsia, or of delivery of small for gestational age infants or preterm birth due to underlying medical conditions, had at least three previous miscarriages or terminations of pregnancy, with major fetal anomaly or abnormal karyotype prior to recruitment, or if they had received interventions that may modify pregnancy outcome. Of the 5,623 women originally recruited in the international SCOPE study, 2,032 took part in the Auckland SCOPE study and 1,961 agreed to be contacted for the CoS study (Figure 1). All women with potentially eligible children were contacted. Children with life-threatening health problems, major congenital abnormalities or chromosomal abnormalities were excluded. All women provided written consent for the recruitment of their children. Ethical approval was granted by the Auckland Ethics Committee (AKX/02/00/364).

Maternal Data

For the purposes of this study, we addressed relationships between maternal early-pregnancy BMI (primary exposure) and measures of childhood BMI and anthropometry. Maternal BMI was calculated from height and weight measured at 15 (standard deviation (SD 0.75)) weeks' gestation, by research staff. To assess the role of potential confounders, we included maternal demographic, clinical and lifestyle data obtained at 15 weeks' gestation, pregnancy outcome data and lifestyle data at the child's follow up (age 6). Details of maternal and childhood variables recorded are provided in the Supplementary Table 1. Women were screened for gestational diabetes mellitus (GDM) at 28 weeks' gestation according to New Zealand guidelines [14]. Details of the SCOPE cohort have been previously described [15,16].

Biomarkers

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Blood samples were taken from all women at 15 (SD 0.75) weeks' gestation. For the purpose of prediction of late pregnancy complications, a total of 55 relevant biomarkers were measured. In the CoS study, 15 biomarkers were selected *a priori* based on known associations with obesity and placental function and/or for implications in causal pathways underpinning associations between maternal obesity and childhood obesity. A list of these biomarkers is provided in Supplementary Table 2 and divided into three categories: metabolic (n=7), inflammation (n=4) and growth (n=4).

Childhood Body Fat and Anthropometric Measurements

BFP was estimated by bioelectrical impedance analysis (BIA (ImpediMed SFB7 tetra polar bioimpedance spectroscopy (BIS)); using the weight of the child, the fat mass is derived from fat free mass. Fat free mass (FFM) was calculated by: FFM = 0.65 (height^2/impedance) + 0.686 * age + 0.15 [17]. BFP was calculated as (weight-FFM)/weight*100. BIA derived fat mass has been previously validated against several direct measures of body fat composition [18]. Anthropometric measures included BMI-for-age z-scores [19], height (cm), arm, waist and hip circumferences (cm) and sum skinfold thicknesses (triceps, biceps, subscapular and suprailiac, mm). Height was measured in cm with the child standing erect on the floor board of a stadiometer with their back to the vertical backboard of a stadiometer or wall. Arm circumference was measured at the half way point between the right elbow and the edge of the acromion. The waist was measured at the half way point between the top of the hip (iliac crest) and lowest rib. Hip circumference was measured as the distance around the maximal diameter of buttocks. Skinfold thicknesses were measured using Holtain skinfold callipers. The skinfold thicknesses from the 4 sites were summed to give a single measure (sum of skinfold thicknesses, SST). Height, arm, waist and hip measurements were taken in triplicate and mean values calculated. Childhood obesity was defined as BMI z-score>2SD as recommended by WHO's child growth standards training (2008) [20,21].

Statistical Analysis

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Single imputation was performed using the median (continuous variables) or mode (binary/categorical) variables) for variables unrelated to other data points that had <1% missing data in the original SCOPE study, described in detail elsewhere[15,22]. The number of children with complete outcome data is n=1162 (99.1%). Maternal sociodemographic characteristics between the available study population and the original Auckland SCOPE participants was compared using Chi-square tests, Wilcoxon rank-sum tests and t-tests as appropriate. Descriptive statistics are presented as mean (SD), frequency (percentage) or median (interquartile range) as appropriate.

Linear regression was used to investigate the relationships between maternal BMI and six childhood adiposity outcomes (BFP, BMI z-score, height, arm, waist and hip circumference). Two models (A & B) were utilised; model A, a simple linear regression with no adjustment for confounders and model B, a multiple linear regression including confounders. To aid the selection of confounders in the analysis of the relationship between maternal BMI and childhood BMI and adiposity, linear regression was used to identify maternal clinical factors and biomarkers associated with childhood adiposity outcomes, independent from maternal BMI. Confounders selected for model B, Supplementary Table 1, were chosen *a priori* [23] based on known associations with obesity or implication in the causal pathway between maternal BMI of childhood obesity. These were decided upon with the use of directed acyclic graphs (DAGs, Supplementary Figure 1) [23]. Results were corrected for multiple testing using Benjamini & Hochberg's False Discovery Rate (FDR) [24]. The variables used in the adjusted model were, infant mode of feeding, infant sex and maternal: ethnicity, socioeconomic status, green leafy vegetable intake pre-pregnancy, multivitamin use pre-pregnancy, alcohol intake pre-pregnancy, cigarette smoking in first trimester, time spent watching television in first trimester, depression in first trimester, sleep assessed at 20 weeks' gestation, maternal hypertension, GDM diagnosis, and placental growth factor.

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For model A and B, the β-coefficients for the relationship between maternal BMI and each childhood anthropometric measurement are presented as standardised coefficients (SC). Standardised coefficients represented the SD in adiposity measure per SD change in exposure (maternal BMI) enabling comparison across outcomes and models. Assumptions for normality were checked for all predictors; candidate biomarkers were log transformed (using natural logs). Data were analysed using Stata software, version 15.0 (StataCorp, College Station, Texas).

Results

At follow-up 1,208 (59%) of the 2,032 mothers from the original New Zealand SCOPE participants were studied. Although there was no difference observed in BMI, mothers who participated in the CoS study were more likely to be older, Caucasian, have a higher education and socio-economic status and were less likely to smoke in their first trimester than woman who did not take part; gestational age at delivery was similar in both groups, but participants in the follow up were less likely to have delivered before 37 weeks' gestation (Supplementary Table 3). Of the 1,208 mother-child dyads available for analysis, 35 (3%) were excluded due to missing (n=32) or implausible BFP (n=3) (Figure 1). The study population comprised 1,173 mother-child dyads.

Maternal and child characteristics

Mean (SD) maternal age at baseline (SCOPE study 15 weeks' gestation visit) was 31 (4) years and most (87.6%) women were Caucasian (Table 1). The median BMI was 23.9 kg/m^2 (Interquartile range (IQR) 21.8 to 26.6) and 28.1% (n=329) of women were overweight (BMI $\geq$25kg/m^2) and 10.1% (n=118) were obese (BMI $\geq$30kg/m^2). Median gestational age at delivery was 40.0 weeks' (38.9 to 40.9). Mean age of the children was 6.0 (0.2) years. Mean child's BFP was 22.8% (6.3) and BMI z-score was 0.27 (0.91). Mean arm, waist and hip circumferences were 18.6 (1.7), 55.4 (4.0) and 61.6 (4.9) cm, respectively, and the sum of skinfold thicknesses was 30.5 (9.4) mm. 15.7% (185/1173) were overweight and 3.6% (42/1173) of the children were classified as obese according to the WHO definition using BMI [20] (Table 1).

Maternal early-pregnancy BMI and childhood BMI Anthropometric Measures

Following adjustment for significant maternal confounders (Supplementary Table 1), maternal BMI (measured continuously) was associated with all measures of child adiposity and BMI; BFP (β=0.11 (95% confidence interval 0.05 to 0.17), p<0.001), BMI z-score (β=0.23 (0.18 to 0.28), p<0.001), arm

(β=0.20 (0.14 to 0.25), p<0.001), waist (β=0.17 (0.12 to 0.23), p<0.001), hip circumference (β=0.16 (0.10 to 0.22), p<0.001) and sum of skinfold thicknesses (β=0.15 (0.09 to 0.21), p<0.001) (Table 2, model B). There was no significant difference for height for the models A and B, p=0.4 and p=0.6, respectively, furthermore, no interactions were observed between child sex at 6 years of age.

Early-pregnancy obesity was associated with a 0.63 SD (95% CI 0.46 to 0.80) increase (p<0.001) in child's BMI z-score, in comparison to mothers with normal BMI, after adjustment for confounders (Figure 2). Similarly, maternal obesity was associated with 7.8% higher child's BFP (β=0.27 (0.08 to 0.47), p=0.006), 4.5% higher mid-arm (β=0.52 (0.33 to 0.72), p<0.001), 3.1% higher waist (β=0.50 (0.30 to 0.69), p<0.001) 3.1% higher hip circumferences (β=0.42 (0.23 to 0.61), p<0.001) and 11.5% increase sum of skinfold thicknesses (β=0.42 (0.23 to 0.61), p<0.001) compared to normal weight mothers (Figures 2 and 3).

Biomarkers

All but one maternal biomarker measured at 15 weeks' gestation showed no association with childhood anthropometric measures. Maternal placental growth factor (PlGF) was positively associated with increased child's hip circumference and SST (p=0.001), Child body fat percentage (p=0.009 and BMI z-score (P=0.006) and waist circumference (p=0.02) (Supplementary Table 4). Although the relationship between PlGF and arm circumference and BMI z-score did not reach statistical significance the point estimates were in the same direction.

Exploratory Analyses

The evaluation of relationships between maternal variables and offspring adiposity, as assessed by simple linear regression and adjusted for multiple testing, provided information on potential

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confounders for the analysis described above, and described some novel associations of interest between maternal PlGF and offspring adiposity (Supplementary Table 4).

Lifestyle and dietary factors during pregnancy

Smoking during the 1st trimester was associated with increased child body fat β=0.19 (p=0.01), BMI z-score β=0.30 (p=0.001), arm β=0.37 (p<0.001), waist β=0.26 (p=0.008), and hip circumferences β=0.41 (p<0.001) and SST β=0.28 (p=0.005). Similarly, children born to women who watched >4 hours of TV per day, in comparison to mothers who watched less than 2 hours of TV a day, had higher hip circumferences β=0.26 (p=0.04) and were categorised as obese β=3.78 (p=0.01). Conversely, increased maternal sleep (measured at 20 weeks' gestation) was associated with lower child's body fat β=-0.06 (p=0.04), BMI β=-0.07 (p=0.01), waist β=-0.06 (p=0.03) and arm circumference β=-0.08 (p=0.009). Alcohol during the 1st trimester and multivitamin use pre-pregnancy was associated with lower body fat in the child (β=-0.03, p=0.03 and β=-0.15, p=0.01) respectively. Folate use during the 1st trimester was not associated with childhood adiposity outcomes.

Obstetric complications

Gestational hypertension or preeclampsia was associated with increased body fat (p=0.007) at age 6 years, and gestational diabetes was associated with increased child's hip circumference (p=0.03), independent of maternal BMI.

Postnatal factors

Girls had higher body fat (p<0.001), arm (p=0.001) and hip (p=0.006) circumferences and SST (p<0.001), and decreased height (p=0.001) compared to boys. Independent of maternal BMI, exclusive breastfeeding at hospital discharge was associated with decreased body fat (p=0.03) at age 6 years.

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Ethnicity and Sociodemographic

Māori and Pacific women had a higher BMI compared to their Caucasian counterparts (median 30kg/m^2 and 26 kg/m^2 respectively vs 24 kg/m^2, p<0.001). Similarly, children born to women identified as Māori and Pacific Islanders had higher BFP (p=0.03), BMI z-score (p<0.001), arm (p=0.007), waist (p<0.001) and hip circumferences (p<0.001) and SST (p=0.03) and were more likely to be overweight or obese (p<0.001) in comparison to mothers identified as Caucasian. Maternal low socioeconomic status was also associated with increased BFP (p=0.03), BMI z-score (p=0.003), arm (p=0.04) and waist circumferences (p=0.03) and risk of obesity at age 6 years (p=0.09), in comparison to 'normal' socioeconomic status (New Zealand Socio-economic Index score between 32 to 55).

Discussion

This study supports the hypothesis that maternal obesity in early pregnancy is associated with offspring BMI and measures of adiposity at six years of age. We confirm a robust relationship between maternal BMI and childhood adiposity through multiple and complementary estimates of childhood fat mass in a large contemporary mother-child cohort of New Zealand low risk nulliparous women, of whom 38% were overweight or obese in early pregnancy.

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The observed effects for all child adiposity outcomes in SCOPE study were not explained by numerous maternal environmental and lifestyle confounders which included maternal sleep duration, depression, socioeconomic status and breastfeeding practice, suggesting intrauterine mechanisms may exert a considerable influence on later adiposity in this cohort with a large portion of obese or overweight women at the time of early pregnancy. In regard to previous cohort studies, 38% (n=447) of the SCOPE cohort women who returned for the 6 year follow-up were overweight or obese compared to 28% in the Generation R study cohort and 16% in the ALSPAC cohort [8,25]. When compared with Generation R studied between 2001 and 2006, the standardised effect size of the relationship between maternal BMI and child's BMI was larger in the NZ children aged 6 years (β=0.23 vs β=0.14) [7] which may reflect the higher incidence of overweight and obesity in the NZ children studied almost a decade later (2011-2014). The present study suggests that children of overweight mothers are likely to have a 0.4kg/m^2 increase in BMI and in those of mothers affected by obesity this rises to an increase of 1.0kg/m^2 compared to children of normal weight mothers. Long term follow-up studies have found that even modest centile variation in early life BMI is associated with greater cardiovascular disease in adulthood [26]. Previous studies have also shown that weight management programmes in adults have successfully shown a reduction of 1 kg/m^2 in BMI. Our study suggests that if this were to be achieved in women with overweight or obesity prior to pregnancy [27], this would reduce the risk of increased infant adiposity. It is therefore plausible that the effect sizes found are meaningful at a population level. Moreover, overweight or obesity during early infancy or childhood is associated with poorer cardiovascular and metabolic outcomes during childhood and a higher risk of obesity in later life [8,28–35] this study adds to an increasing literature from human cohorts and animal models to suggest that many common disorders may have origins in the earliest stages of life. Although this study indicates an independent relationship between maternal BMI and offspring BMI, well recognised childhood exposures will inevitably contribute to obesity in the children, providing a second hit, and compounding the risk of adulthood obesity and related morbidities.

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Whilst dual-energy x-ray absorptiometry is often considered the gold standard of adiposity measurement, we found that childhood WHO BMI-for-age adjusted z-scores demonstrated the highest standardised beta coefficient in the relationship between maternal obesity and childhood obesity, when compared to body fat percentage as measured by polar BIS and also arm, waist and hip circumferences and SST.

Mechanistically a number of in utero 'exposures' have been implicated in the causal pathway linking maternal obesity to childhood obesity; these include inflammatory markers, dyslipidaemia, hyperinsulinaemia and hyperleptinaemia which, it has been suggested, may permanently reset the fetal adipoinsular axis or pathways of energy balance resulting in adiposity and altered energy homeostasis during childhood [36–38]. In this study we found no association with any measure of infant adiposity and biomarkers of the inflammatory response measured at 15 weeks of pregnancy, including - C reactive protein, intercellular adhesion molecule 1, interleukin 1 receptor antagonist and macrophage migration inhibitory factor. Neither was there any association with maternal lipids (total cholesterol, HDL-cholesterol or LDL cholesterol and triglycerides) or with the adipokines, leptin and adiponectin, or insulin. The positive association of the angiogenic factor, PlGF with measures of child SST adiposity has to our knowledge not previously been reported. These associations may reflect that PlGF is a marker of healthy placental function, associated with placental angiogenesis and reduced vascular resistance [39]. Theoretically, higher PlGF and reduced placental vascular resistance could enhance nutrient transport and predispose the child to increased adiposity and later obesity. Of relevance, a recent study addressing the relationship between later pregnancy PlGF and infant birth weight found a significant association between PlGF and macrosomia, although this was an investigation of mothers with pre-existing diabetes [40].

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Our findings confirm the association between mothers identified as Māori or Pacific Islanders and increased offspring adiposity as recently shown in The Early Life Factors study which recruited women during 2008 to September 2011 in Wellington, Auckland and Christchurch, New Zealand [41]. A later study, the New Zealand Heath Survey (2015/2016) reported that 60% of Pacific and 44% of Māori children affected by were overweight or obesity in comparison to 30% of children aged between 5 to 9 [42]. We found that the rate of obesity in Pacific and Māori children was approximately 4 and 6 times higher respectively than those identified as 'Caucasian'. These findings highlight that the relationship between ethnicity and maternal weight during pregnancy and obesity risk continues through childhood and demonstrate an urgent need for prevention strategies targeting high-risk ethnic pregnant women in these populations.

We found an inverse association between maternal alcohol use in the 1st trimester and body fat percentage at age 6 years following adjustment for confounders. Heavy alcohol exposure during early life or pre-pregnancy is associated with reduced birthweight and adverse pregnancy outcomes [43,44] which may have a persistent influence on childhood growth. A recent study of over 7,000 British mother-child dyads (ALSPAC birth cohort) demonstrated a similar association in young children, however this was no longer evident at the age of 10 years [45]. Previous reports have suggested that the relationship between excess maternal alcohol intake and delayed weight in later childhood may be explained by maternal nutritional intake, genetics, socioeconomic status and ethnicity [46].

We also found associations between gestational hypertension and offspring body composition independent of maternal BMI. Higher blood pressure may reflect poor placental function; resulting in increased risk of childhood metabolic outcomes and obesity. Similar results have been reported in a cohort of 618 mother and child dyads [47], the authors found associations between maternal hypertension and offspring risk of overweight or obesity at 4 years of age. Similarly there are previous

reports of an association between maternal GDM and offspring adiposity, although, a recent systematic review concluded that the relationship between GDM and offspring BMI z-score was not evident following adjustment for maternal BMI [48].

Strengths

Research midwives conducted interviews prospectively with pregnant women using a detailed standard operating procedure, and a database that incorporated automated data queries. There was a high follow up rate and minimum missing data in the extensive dataset of pregnant women in the original Auckland SCOPE study; a key strength of this study. The Children of SCOPE study of mother-child dyads was purposely designed to assess childhood obesity; strength lies in the rigorous assessment of adiposity and richness of data for potential confounders in mothers recorded in a narrow window in early pregnancy (15±0.75 weeks' gestation), and at follow up of children at 6 years born to a heterogeneous cohort of low risk women.

Limitations

Follow up data was available for 1,208 (59%) mothers from the original Auckland SCOPE study, which could result in biased estimates if associations between maternal BMI and childhood adiposity differ between those included and not included. The participants in the Auckland SCOPE study were not representative of women giving birth in Auckland. There were more Caucasians, well-educated women and non-smokers than the general pregnant population and under representation of Māoris. Residual confounding due to unmeasured maternal lifestyle related variables, common genetic variants related to obesity in mother and child. Our analyses found a strong relationship between maternal and childhood obesity, although a limitation is that we were not able to examine the child's obesity polygenic risk score (PRS) as an explanation for the finding, but other studies suggest that genetic influences, reflected in PRS, are unlikely to have anything more than a modest influence on the association [49]. The measures of body composition utilised in this study have limitations. BMI which

was used to define obesity in the mothers is an indirect measure fat mass. For the children Bioelectrical Impendence Analysis was not validated against DEXA, a gold standard for measuring adiposity. Furthermore, the observational study design may overestimate the effect of intrauterine exposures and limit causal inferences. Previous studies have also reported an association of maternal BMI with offspring adiposity, which is mediated through gestational weight gain[9,50,51]. A limitation of this study is that we did not routinely measure gestational weight gain and were therefore unable to assess the impact on childhood BMI. This is mitigated somewhat by the results of a recent individual participant meta-analysis of 162,129 mothers and children from 37 pregnancy and birth cohorts which reported small effects of GWG on childhood overweight/obesity comparison to a much greater influence of maternal BMI *per se* [52].

Conclusions

This investigation from a large contemporary, detailed prospective mother-child cohort study with multiple measures of childhood fat mass provides robust evidence for an independent relationship between maternal BMI in early pregnancy and childhood adiposity at 6 years of age. Whilst we have recently shown that a maternal behavioural intervention in pregnant women with obesity has the potential to reduce infant adiposity and to produce a sustained improvement in maternal diet at 6 months postpartum (UK Pregnancies Better Eating and Activity randomised controlled Trial)[12], the size effect was modest and further trials with more effective maternal interventions are required to elucidate causality.

Conflict of Interest

KMG reports reimbursement from Nestle Nutrition Institute, has a patent Phenotype prediction issued, a patent Predictive use of CpG methylation issued, a patent Maternal Nutrition Composition pending, a patent Vitamin B6 in maternal administration for the prevention of overweight or obesity

Authors Contributions

SB and JMDT analysed and interpreted the data. EAM directed the Children of Scope Study, EAM, KMG, LP, WC, RN, WC, LMEMcC and AS conceptualised the study, CW, RN and YH were involved in data collection, investigation and analysis, KVD and PTS completed additional analyses for the data, KVD, LP, KMG and EAM had overall responsibility for the manuscript. All authors have read and approved the final manuscript.

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Table and Figure legends

Figures 1. Flow diagram of the study population

Figure 2. Box and whisker plots of maternal body mass index categories at 15 weeks' gestation by child's body fat percentage and child's BMI z-score.

Figure 3. Box and whisker plots of maternal body mass index categories at 15 weeks' gestation by child's anthropometry at age 6 years. Maternal BMI by child's arm circumference (cm). Maternal BMI by child's waist circumference (cm). Maternal BMI child's hip circumference (cm). Maternal BMI by child's sum of triceps, biceps, subscapular and suprailiac skinfold thicknesses (mm).

Table 1: Maternal, infant and childhood characteristics, lifestyle and pregnancy outcomes in the Children of SCOPE study (n=1173).

Table 2: Association between early-pregnancy maternal body mass index (BMI) and childhood anthropometric measures at age 6, multivariate analysis

Supplementary Figure 1: Directed acyclic graph of interactions of maternal early pregnancy body mass index and childhood body fat percentage.

Supplementary Table 1: Variables used in the investigation of the relationship between early-pregnancy maternal body mass index and measure of childhood anthropometry at age 6 years

Supplementary Table 2: List of biomarkers measured at 15 (SD 0.75) weeks' gestation and the assay method.

Supplementary Table 3. Characteristics of the participants in the Auckland Children of SCOPE study and original Auckland participants who did not participate in follow up.

Supplementary Table 4: Association between early-pregnancy Placental Growth Factor (PLGF) and childhood adiposity at age 6 years old, analysis adjusted for maternal body mass index at 15 (SD± 0.75) weeks' gestation.

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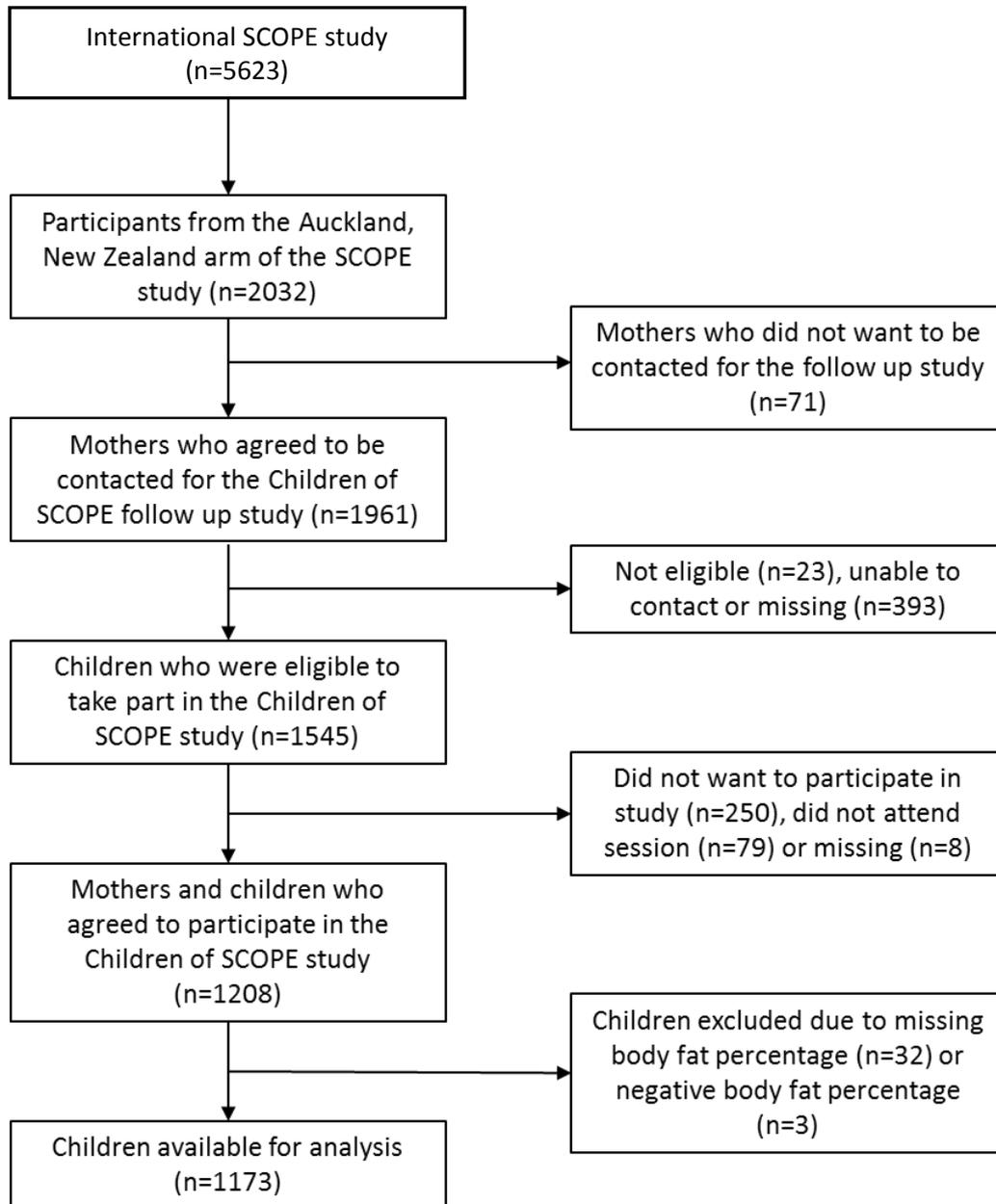
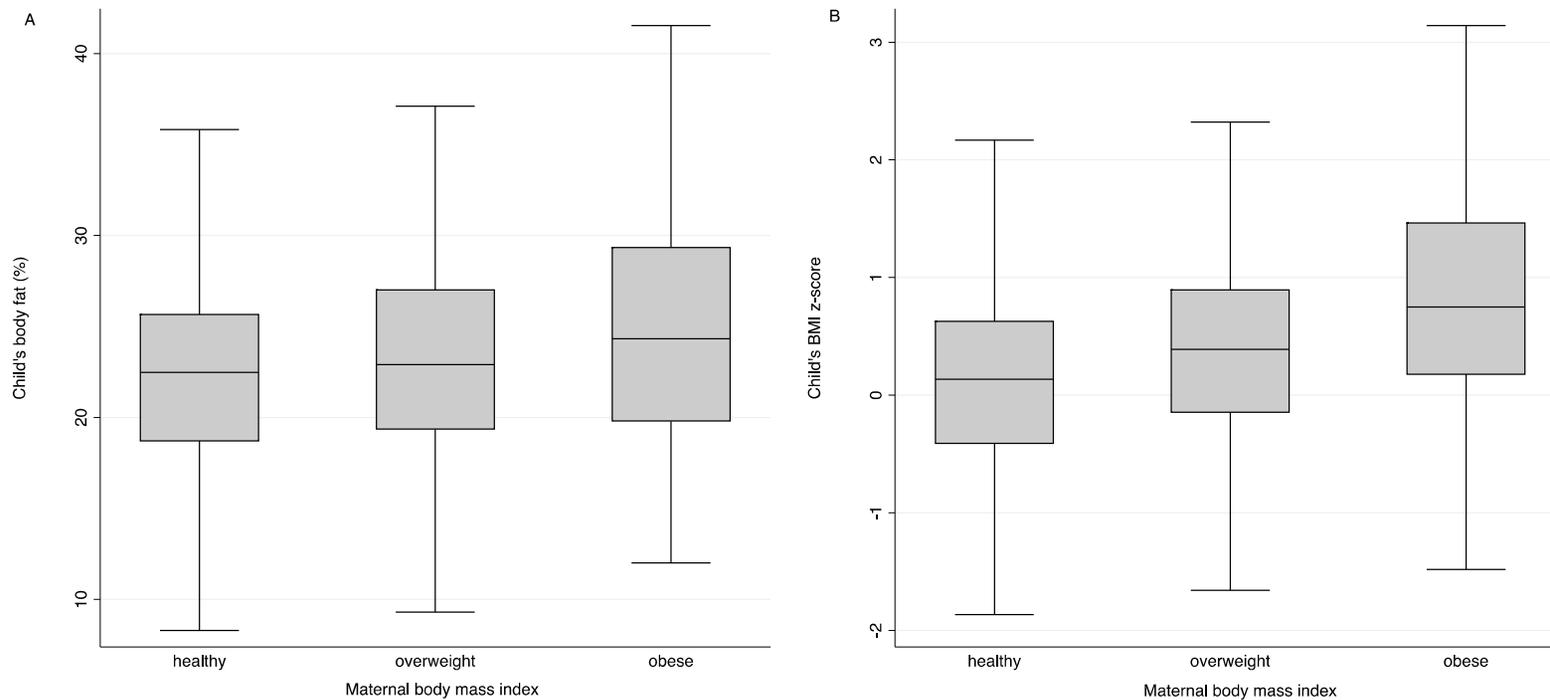**Figures 1: Flow Diagram of Study population**

Figure 2. Box and whisker plots of maternal body mass index categories at 15 weeks' gestation by child's body fat percentage and Child's BMI z-score. Box plots excludes women who were underweight (n=9) and outside values. Sample size n=1164 (healthy BMI (18.5 to 24.9 kg/m^2) n=717, overweight (25 to 29.9 kg/m^2) n=329 and obese (≥30 kg/m^2) n=118). In an adjusted model, maternal early-pregnancy overweight (p=0.01 and p<0.001) and obesity (p=0.006 and p<0.001) is associated with childhood body fat percentage and BMI z-score, respectively, at age 6 years in comparison to 'normal' BMI mothers.
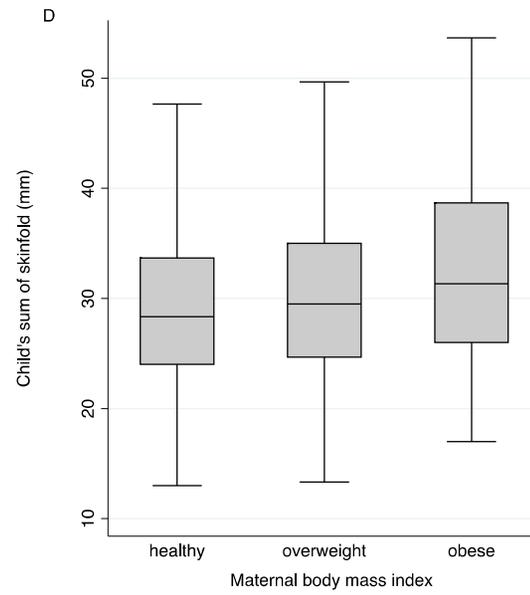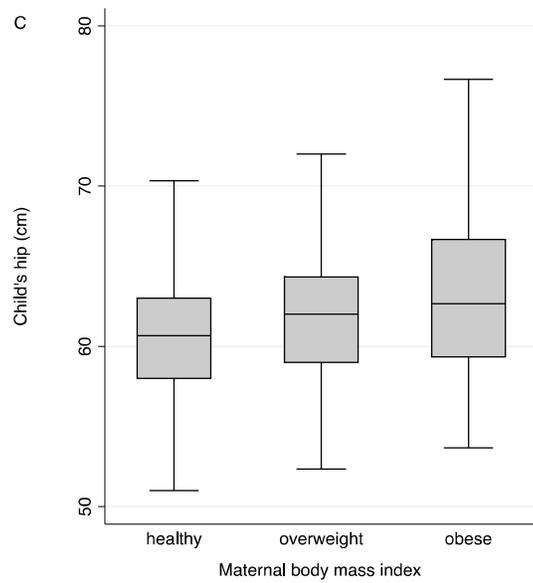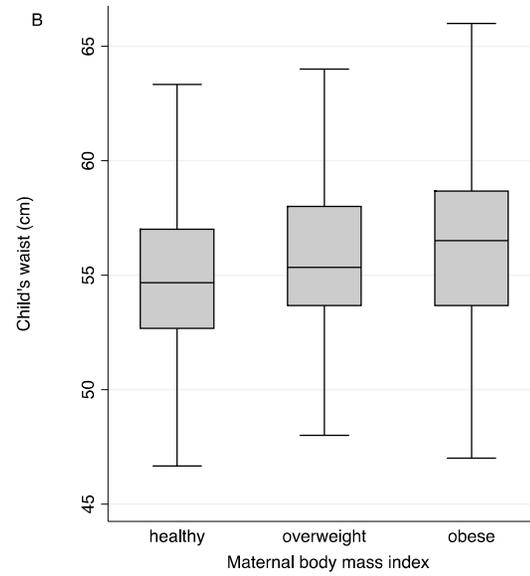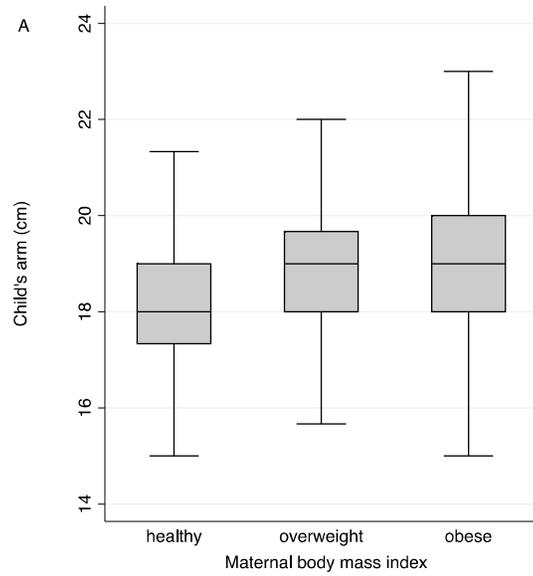
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Figure 3. Box and whisker plots of maternal body mass index categories at 15 weeks' gestation by child's anthropometry at age 6 years. child's arm circumference (cm), child's waist circumference (cm), child's hip circumference (cm), child's sum of skinfold thicknesses (mm). Sample size n=1,164. Healthy BMI (18.5 to 24.9 kg/m2) n=717, overweight (25 to 29.9 kg/m2) n=329 and obese (≥30 kg/m2) n=118. After adjustment for confounders for children at 6 years of age arm, waist and hip circumferences were associated with maternal early-pregnancy overweight (p<0.001) and obesity (p<0.001). Child's sum of skinfold was also associated with maternal early-pregnancy overweight (p<0.06) and obesity (p<0.001) in comparison to 'normal' BMI mothers,

Table 1: Maternal, infant and childhood characteristics, lifestyle and pregnancy outcomes in the Children of SCOPE study (n=1173)

Maternal characteristics at baseline (15 weeks of pregnancy)	Mean (SD), median (IQR) or frequency (%)		Mean (SD), median (IQR) or frequency (%)
Age (years)	31.0 (4.3)	Depression [d] (EPDS) (n=1170)	6.6 (4.3)
BMI*	23.9 (21.8-26.6)	Stress [e] (PSS) (n=1166)	14.3 (5.9)
BMI (categorical)		Anxiety [e] (STAI) (n=1170)	32.0 (10.3)
< 18.5	9 (0.8%)	High consumption of vegetables [f]	167 (14.2%)
18.5 to 24.9	717 (61.1%)	Hours TV watched / day [e, g] (n=1170)	1
25.0 to 29.9	329 (28.1%)	*<2*	497 (42.5%)
> 30+	118 (10.1%)	*2 to 4*	601 (51.4%)
Maternal ethnicity		*>4*	72 (6.2%)
Caucasian	1027 (87.6%)	**Pregnancy outcomes**	
Asian	45 (3.8%)	Premature birth [h]	70 (5.9%)
Indian	40 (3.4%)	Gestational age (weeks)*	40.0 (38.9-40.9)
Māori	34 (2.9%)	Birthweight (grams)*	3470 (3140-3790)
Other	16 (1.4%)	Breastfeeding exclusively at discharge postpartum (n=1172)	881 (75.2%)
Pacific	11 (0.9%)	**Characteristics at follow up**	
Maternal SES (NZSEI)		Maternal BMI* (n=1172)	24.1 (21.8-27.8)
high	324 (27.6%)	Maternal BMI (categorical)	
medium	694 (59.2%)	*< 18.5*	23 (2.0%)
low	155 (13.2%)	*18.5 to 24.9*	640 (54.6%)
Education (years)		*25.0 to 29.9*	336 (28.7%)
<12	65 (5.5%)	*> 30+*	173 (14.8%)
12 to 13	1089 (92.8%)	Child's age	6.0 (0.2)
>13	19 (1.6%)	Child's sex (female)	587 (50.0%)
Marital status		Child's weight (kg)*	21.7 (20.0-23.7)
Married	842 (71.8%)	Child's height (cm)[i]	117.9 (4.9)
De facto [a]	296 (25.2%)	Child's BMI (z-score)	0.27 (0.91)
Single	27 (2.3%)	Child overweight (BMI z-score >1SD <2SD)[i]	185 (15.7%)

Same sex partner	6 (0.5%)	Child obese (BMI z-score >2SD)[l]	42 (3.6%)
Separated or divorced	2 (0.2%)	Child's body fat (%)	22.8 (6.3)
Smoking in at 15 weeks'	110 (9.4%)	Child's arm circumference (cm)[i]	18.6 (1.7)
Alcohol [b] (n=1160)	631 (54.4%)	Child's waist (cm) [i]	55.4 (4.0)
Folate use [e]	870 (74.1%)	Child's hip (cm) [i]	61.6 (4.9)
Multivitamin use [c] (n=1163)	391 (33.6%)	Child's triceps (mm) [i] (n=1163)	10.7 (3.2)
Hypertension	61 (5.2%)	Child's biceps (mm)[i] (n=1163)	7.2 (2.5)
GDM (n=1078)	19 (1.8%)	Child's subscapular (mm)[i](n=1162)	6.2 (2.1)
Sleep/ hours at night on weekdays [d] (n=1167)	8.1 (1.14)	Child's suprailiac (mm)[i] (n=1163)	6.5 (2.9)
		Child's sum of skinfolds [k] (mm)	30.5 (9.4)

Abbreviations: SES - socio-economic status, NZSEI - New Zealand Socio-Economic Index (10 to 31 low, 32 to 55 medium, 56 to 90 high), BMI - body mass index, GDM – Gestational Diabetes Mellitus, EPDS - Edinburgh Postnatal Depression Scale (continuous, 0 to 30), PSS - Perceived Stress Scale (continuous, 0 to 40), STAI – adapted State-Trait Anxiety Inventory (continuous, 20 to 80); [a] stable relationship, not married; [b] alcohol exposure in the 1st trimester (yes/no); [c] any use pre-pregnancy; [d] hours at night, weekdays; [e] at 15 weeks of pregnancy; [f] High consumption of green leafy vegetables 3+ times per day 1 month prior to conception; [g] per day in the last month; [h] <37 weeks; [i] mean of triplicate measurements; [k] sum of triceps, biceps, subscapular and suprailiac *median, quartiles, [l] World Health Organisation (2007)

Table 2: Association between early-pregnancy maternal body mass index (BMI) and childhood anthropometric measures at age 6, multivariate analysis

Measure of childhood adiposity at age 6 years	Model A (unadjusted)			Model B (adjusted)		
	n	Standardised coefficient (β) (95% CI)	P value	n	Standardised coefficient (β) (95% CI)	P value
Percentage body fat	1173	0.15 (0.10 to 0.21)	<0.001	1143	0.11 (0.05 to 0.17)	<0.001
BMI z-score [a]	1173	0.25 (0.20 to 0.30)	<0.001	1167	0.23 (0.18 to 0.28)	<0.001
Height (cm)	1173	0.03 (-0.03 to 0.08)	0.4	1170	0.02 (-0.04 to 0.07)	0.6
Arm (cm)	1173	0.22 (0.17 to 0.28)	<0.001	1164	0.20 (0.14 to 0.25)	<0.001
Waist (cm)	1173	0.20 (0.14 to 0.26)	<0.001	1167	0.17 (0.12 to 0.23)	<0.001
Hip (cm)	1173	0.20 (0.14 to 0.25)	<0.001	1072	0.16 (0.10 to 0.22)	<0.001
Sum of skinfolds (mm) [b]	1162	0.17 (0.11 to 0.22)	<0.001	1159	0.15 (0.09 to 0.21)	<0.001
Obese (BMI z-score >2SD) [c]	1173	1.11 (1.05 to 1.18)	<0.001	1104	1.08 (1.03 to 1.15)	0.005

Standardised coefficient (β), representing the standard deviation (SD) change and 95% confidence interval in adiposity measure per SD change in exposure enabling comparison across outcomes and models; Model A (simple regression) - univariate association between maternal BMI (at 15 weeks' gestation) and childhood adiposity at age 6 years, Model B (multiple regression) - maternal BMI in association with childhood adiposity, each outcome adjusted for infant mode of feeding, infant sex and maternal: ethnicity, socioeconomic status, green leafy vegetable intake pre-pregnancy, multivitamin use pre-pregnancy, alcohol intake pre-pregnancy, cigarette smoking in first trimester, time spent watching television in first trimester, depression in first trimester, sleep assessed at 20 weeks' gestation, maternal hypertension, GDM diagnosis, and placental growth factor.; [a] World Health Organisation (2007) BMI for age z-score; [b] sum of triceps, biceps, subscapular and suprailiac skinfold thicknesses (mm); [c] odds ratio