Programming of adiposity in childhood and adolescence: associations with birth weight and cord blood adipokines

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Cord blood measures and long-term adiposity

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Context: Exposure to maternal adiposity during pregnancy is associated with higher offspring birthweight and greater adiposity through childhood and adult life. As birthweight reflects the summation of lean and fat mass, the extent to which fat mass at birth tracks into later life is unknown.

Objective: Determine whether fat mass at birth is associated with child and adolescent adiposity.

Design, Setting and Participants: UK birth cohort with markers of neonatal fat mass; cord blood leptin, adiponectin, and birthweight and adiposity outcomes at age 9 (N=2775) and 17years (N=2138).

Main Outcomes: Offspring BMI, waist circumference, DXA-determined fat mass and obesity at age 9 and 17years.

Results: Higher cord blood leptin was associated with higher z-scores of fat mass (difference in mean per 10pg/ml: 0.03SD,95%CI 0.00-0.06), waist circumference (0.04SD,95%CI 0.00-0.07), and BMI (0.04SD,95%CI 0.00-0.08), at age 9. However, by age 17 the adjusted results were attenuated to the null. Cord blood adiponectin was not associated with measures of adiposity at age 9. At age 17, cord blood adiponectin was positively associated with fat mass (0.02SD per 10µg/ml,95%CI 0.02-0.03) and waist circumference (0.04SD per 10µg/ml,95%CI 0.03-0.05). Birthweight was positively associated with waist circumference (0.03SD per 100g,95%CI 0.02-0.04) and BMI (0.02SD per 100g,95%CI 0.00-0.03), but not fat mass or odds of obesity. Cord blood leptin and adiponectin were not associated with obesity at either age.

Conclusions: Increased cord blood leptin and adiponectin, known surrogates of fetal fat mass, were weakly associated with increased fat mass in late childhood and adolescence respectively.

PRECIS: We found that cord blood leptin and adiponectin, known surrogates of fetal fat mass, were weakly positively associated with some measures of fat mass in late childhood and adolescence.

Introduction

Exposure to maternal adiposity during pregnancy is associated with higher offspring birth weight and greater adiposity through childhood and adult life (1). Developmental overnutrition has been proposed as a mechanism, by which excessive transplacental passage of nutrients facilitates the development of larger babies with greater fat mass. Evidence from

within sibling studies, comparisons of maternal and paternal exposures and the use of genetic variants as proxies for the maternal exposures support maternal adiposity and developmental overnutrition causing greater adiposity in offspring at birth (2-4). However, whether this causal effect extends to long-term offspring adiposity is unclear. A longer-term effect may occur as a result of tracking of birth fatness across the life course. However, because birth weight is unable to distinguish relative contributions of lean versus fat mass (5,6), few studies to date have been able to determine the extent to which greater fat mass at birth tracks into later life.

Umbilical cord blood leptin is widely recognized as an accurate biomarker for neonatal fat mass (7). Maternal exposures, including maternal adiposity which may cause developmental overnutrition, have been associated with increased cord leptin and neonatal adiposity at birth (8,9). In animal models, fetal leptin has also been proposed to contribute the long-term programming of hypothalamic feeding circuits, thereby providing a means by which leptin can influence long-term adiposity independent of tracking of adiposity from birth(10). Use of cord blood leptin in determining whether neonatal fat mass tracks across childhood has however been limited (11-14). This primarily reflects the scarcity of large prospective birth cohorts with cord blood samples and detailed measures of offspring adiposity as well as potential confounders. Studies that have made some assessment of this to date have had relatively small sample sizes (N=56-588) (11-14), and we are not aware of any study having followed children beyond age 7 years. These studies have reported non-consistent results with higher cord leptin associated with both a lower (11) and higher (12) BMI at age 3 years, and a higher BMI at age 7 years (14).

Neonatal levels of adiponectin, which has insulin sensitizing effects in adults, are approximately 4-7 times higher than maternal levels. Furthermore, while maternal circulating concentrations of adiponectin are inversely associated with BMI, higher levels of cord blood adiponectin are associated with higher birth weight (11,15). That higher cord blood adiponectin concentrations might reflect increased fat mass in neonates is suggested by mouse studies where over-expression of fetal adiponectin was positively related to the size of fat depots in early life, while adiponectin knockout fetuses display lower body weight and lower fat content(16). Given this effect of adiponectin on body composition, specifically, its fat deposition enhancing effect in mice, and the known relationships of leptin in humans to fat mass, we hypothesized that both cord blood leptin and adiponectin would be positively associated with offspring adiposity in pre-pubertal children and adolescents.

The aim of this study was to determine whether cord blood leptin and adiponectin were positively associated with later obesity, BMI, waist circumference and fat mass and whether this is independent of maternal BMI. For comparison, we also examined associations of birthweight with these outcomes.

Research Design and Methods

Study Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective birth cohort study investigating the health and development of children (17,18). The study website contains details of all the data that is available through a fully searchable data dictionary; http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the National Health Service local ethics committees. A total of 14,541 women were initially enrolled, with 5011 mother-offspring pairs having a suitable cord blood sample. A detailed outline of the exclusion criteria for the analysis reported here and numbers with missing data is shown in Figure 1. We included participants if they had 1) attended and completed assessments at either the 9 or the 11-year clinic assessment, or 2) attended the 15 or 17-year clinic assessment. The eligible

cohort for the current analysis was 2775 mother-offspring pairs at age 9-11 years and 2138 mother-offspring pairs at age 15-17 years.

Cord blood Assays

Cord blood samples were collected at the time of delivery, initially stored at 4°C for 0 to 8 days before plasma was separated and then stored at -20°C before being transferred to long-term storage at -80°C. Cord blood leptin and adiponectin were measured using commercially available ELISA kits (Quantikine human leptin immunoassay (Cat No PDLP00), Quantikine Human Total Adiponectin/Acrp30 (Cat No PDRP300) both R&D Systems). Analysis of the cord blood was completed within a maximum of three freeze-thaw cycles and remained at -80°C in between thaws. The inter-assay coefficients of variability were 9.5% for leptin and 3.2% for adiponectin.

Obstetric/Perinatal Data

Six trained research midwives retrospectively extracted data from obstetric medical records and error rates were consistently <1%. These data included weight at every antenatal clinic visit (used to determine gestational weight gain), complications during pregnancy (hypertensive or diabetic disorders) and mode of delivery. Gestational age, offspring's sex and birthweight were obtained from hospital records at the time of birth. Maternal age, pre-pregnancy height, and weight, smoking status (defined as never smoked, smoked before but not during pregnancy and smoked during pregnancy), parity, occupational social class and highest educational attainment were obtained from questionnaires completed by the mothers in early and advanced stages of pregnancy. Occupation was used to allocate social class groups using the 1991 British Office of Population and Census Statistics classification.

Offspring Childhood and Adolescent Adiposity Measurements

Identical protocols were used at all follow-up clinics. At each clinic assessment participants' age in months was recorded and their weight and height measured in light clothing and without shoes. Weight was measured to the nearest 0.1kg using Tanita scales. Height was measured to the nearest 0.1cm using a Harpenden stadiometer. DXA scans were used to measure total fat mass. Waist circumference was measured to the nearest 1mm at the midpoint between the lower ribs and the pelvic bone with a flexible tape and with the child breathing normally. Offspring obesity was classified using BMI and criteria defined by the International Obesity Task Force (19).

Statistical Analysis

The relation between exposures (birthweight and cord blood adipokines) and outcomes (BMI, waist circumference, and fat mass at ages 9-11 years and 15-17 years) was examined by Spearman correlation. Linear (offspring BMI, waist circumference, and fat mass) and logistic (offspring obesity) regression models were used to examine the associations between birthweight and cord blood measures and offspring BMI, waist circumference, fat mass and obesity at age 9 and 17 years. Offspring waist circumference and fat mass were log transformed to produce approximately normal distributions of regression model residuals. Within cohort logged fat mass and waist circumference z-scores (participant value minus mean for the sex and age category ÷ standard deviation for the sex and age category) were created using one year age categories. BMI z-scores were created using the UK 1990 British growth reference (20). Birthweight was adjusted for sex, gestational age and number of offspring (singletons or twins) using nonlinear regression fitting a Gompertz curve.

Three incremental analyses were performed to adjust for potential confounders (Supplemental Figure 1). The basic model (model 1) adjusted for offspring sex and age at outcome measurement alone (and offspring height when fat mass is the outcome). In model 2 we additionally adjusted for maternal confounders (age, smoking, parity, occupational social class, education, and pre-pregnancy BMI). In the fully adjusted model (model 3) we

additionally adjusted for pregnancy characteristics (gestational age at birth, mode of delivery, gestational weight gain, hypertensive and diabetic disorders of pregnancy). In these analyses since we have scaled the exposures (birthweight, cord blood leptin, and adiponectin) and outcomes (BMI, waist, and fat mass) on their standard deviations the resultant differences in means from the multivariable linear regression models are equivalent to partial (adjusted) correlation coefficients and can be interpreted in this way.

There were small amounts of missing data on some co-variables included in the multivariable models (Figure 1). Twenty imputation data sets were generated by chained equations (21), with all cord exposures, birthweight, the covariates specified for model 3 and the measurements from the 11-year clinic and 15-year clinic informing imputation of missing values in the 9-year clinic and 17-year clinic respectively. For convenience hereafter referred to as 9 and 17-year. The distributions of observed and imputed variables were similar (Supplemental Table 1). In the main paper, we present results from the imputed datasets and for present comparison results from those with complete confounders (N = 1041 to 1776) in Supplementary material (Supplemental Tables 5-8)

All statistical analyses were performed using Stata (version 13.0) software (Stata Inc., College Station, TX.).

Results

Table 1 summarizes the maternal and offspring characteristics for those participants with cord blood measures, who completed at least one clinic assessment, with Supplemental Table 1 demonstrating the similarity of the observed and imputed data. Supplemental Table 2 shows the Spearman's correlation between exposures (birthweight and cord blood adipokines) and outcomes (markers of anthropometry at age 9 and 17). Birthweight was positively correlated with cord blood leptin (n=4751, r=0.33) and, to a lesser degree, with cord blood adiponectin (n=4707, r=0.14). Cord leptin and adiponectin were positively correlated (n=4962, r=0.11). Birthweight and leptin also positively correlated with fat mass, BMI and waist circumference at age 9 and 17. There was a weak inverse association between cord adiponectin and waist circumference and BMI at age 9. Among those participants with assessments at both clinics (at age 9 and 17), measurements at each clinic were highly correlated (0.74 for BMI, 0.74 for fat mass and 0.66 for waist circumference).

Table 2 shows the multivariable associations between cord blood leptin, adiponectin and birthweight and z-scores of offspring fat mass, waist circumference, BMI and obesity at age 9 years. Cord blood leptin was positively associated with fat mass, waist circumference, and BMI at age 9 (model 1). The effect size was largely attenuated with adjustment for maternal and pregnancy characteristics (Table 2), with the individual univariate association of maternal and pregnancy characteristics on cord leptin, cord adiponectin and birthweight shown in Supplemental Table 3. A similar but weaker pattern was observed for measures at age 17 where cord leptin was associated with z-scores of fat mass, waist circumference, and BMI and with the risk of obesity (Table 3). These associations were similarly attenuated to the null after adjustment for potential confounders.

Cord blood adiponectin was not associated with any measures of adiposity at age 9 (Table 2). At age 17, cord blood adiponectin was positively associated with fat mass and waist circumference, with the effect size strengthened after adjustment for maternal and pregnancy characteristics (Table 3).

Birthweight was positively associated with fat mass, waist circumference and BMI at age 9 years and 17 years and showed a weak relationship with obesity in both age groups (Tables 2 and 3). After adjustment for maternal and pregnancy characteristics increasing birthweight remained associated with greater waist circumference and BMI, with the association with fat mass and obesity attenuated to the null.

Results did not differ substantially when absolute measures of adiposity at age 9 (Supplemental Table 4) or age 17 were considered (Supplemental Table 5). Results were similar for non-imputed analyses but with wider confidence intervals (Supplemental Tables 6-9).

Discussion

In this prospective birth cohort study, cord leptin, a marker of neonatal fat mass, exhibited relatively weak relationships with later measures of adiposity. These were largely attenuated by adjustment for maternal factors, particularly in later childhood. By contrast, adiponectin exhibited no relationship with measures of fat mass at age 9 and showed a weak relationship with fat mass and waist circumference at ages 15. Neither cord leptin nor adiponectin was associated with the risk of being classed as obese in late childhood or adolescence. Taken together this would suggest that neonatal fat mass per se has a limited contribution in determining fat mass in adolescence.

To date birthweight, as a proxy for intrauterine growth, and its' relation to adult BMI has been extensively studied. Similar to our findings, studies principally demonstrate a positive association between birthweight and childhood and adult fat mass, BMI and waist circumference (22). To try to examine whether birthweight is simply acting as a surrogate for neonatal fat mass, we previously utilized ponderal index (birth weight/length^3), a measure of fatness and demonstrated positive associations with lean body mass, total body fat and the fat-to-lean mass ratio at age 9-years (23). Although this suggests that neonatal fat mass is related to later adiposity, ponderal index is a relatively poor measure of neonatal total body fat (24).

To extend and improve on this work, the current study utilized cord blood leptin, a strong correlate of neonatal fat mass as assessed by skinfolds or total body electrical conductivity (25) and adiponectin, which in mouse studies is suggested to be a further positive correlate of fat mass (16). That cord blood leptin was positively associated with several adiposity measures and specifically fat mass z-score at age 9-years, suggests that there is either accretion of adipose tissue during intrauterine life that is maintained throughout childhood, the propensity to develop fat mass may be maintained, or there is a direct effect on the programming of hypothalamic feeding circuits. However, given our observed effect size, the contribution of neonatal fat to later fat mass is likely to be small. For example, a 10pg/ml increase in cord leptin would be associated with a BMI increase from 22 to 22.1kg/m^2 at age 9-years.

In accordance with some (26-28) but not all (29,30) previous studies we observed that adiponectin was weakly positively correlated with birthweight and cord leptin. We found some evidence for weak associations of cord blood adiponectin with adiposity at the older age (15-17) but none that this was mediated by increased (and persistent) fat mass through childhood. Why adiponectin is not related to adiposity outcomes in earlier childhood, as leptin is, is not clear. Perhaps these associations emerge after puberty which has a major impact on body composition and adipocyte number(31). It is also possible that given the multiple tests performed; some associations are due to chance, and we would caution against assuming these associations are real without further replication.

As previously shown in this cohort (32), we observed consistent positive associations of birth weight with later BMI and waist in both early childhood and adolescence, though null associations (coefficients equal to zero) were found for fat mass at both ages.

Our study has several strengths including its size, duration of follow-up, and the availability of data on a range of maternal, pregnancy and social factors pregnancy characteristics to facilitate a robust analysis. This is also one of the very few studies with DXA measurements of body composition at different time points, thereby overcoming the

potential increase in overall mass attributed to the expected increase in bone density that results from increased adiposity. We do however acknowledge some limitations. The number of children who were overweight or obese was smaller than many contemporary populations. That birthweight and cord measures were not associated with the risk of being obese may reflect this. Another limitation of the study is the loss to follow-up. Our results may be biased if associations were substantially different among excluded participants due to conditioning on the variables in the model. We acknowledge that engaged participants may exhibit different characteristics at birth beyond gestational age and birthweight which are representative of the whole cohort, and also for the two outcomes. Replication of our analyses in additional birth cohorts with different metabolic risk profiles would strengthen our findings. Cord blood sample degradation may have contributed to variability, but leptin and adiponectin do appear to be stable with long-term storage (33-38). This is in stark contrast to c-peptide the preferred index of fetal glucose exposure, which we were unable to measure accurately due to degradation with long-term storage, a phenomenon previously reported by others (39).

In conclusion, we found that cord blood leptin and adiponectin, known surrogates of fetal fat mass, were weakly positively associated with some measures of fat mass in late childhood and adolescence. That these associations were robust to a wide range of confounders that may reflect intrauterine, maternal and shared environmental exposures suggests that neonatal fat mass may track into later life. However, we acknowledge replication of our findings in cohorts with a different risk profile is critical, and that the magnitude of the observed associations is small, potentially limiting the impact that neonatal life adiposity has on later outcomes.

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Author Contributions

JS performed the laboratory cord blood analysis, contributed to statistical analysis, participated in data interpretation and drafted the manuscript. AS contributed to the statistical analysis and data interpretation. AF, NS, RL, SR, GDS and DAL contributed to obtaining funding and data interpretation. SMN conceived the study, obtained funding, contributed to the statistical analysis, data interpretation and drafted the manuscript. All authors contributed to the preparation of the manuscript and approved the final version.

Conflict of Interest: none

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Figure 1: ALSPAC participant flow chart.

Table 1: Maternal and Offspring Characteristics

Maternal Characteristics	Attended at least one clinic assessment (n=2955)	
	N obs (%)	Median (IQR)
Age	2914	29 (26, 32)
Smoking		
Never	2103 (73.8)	
Before, not during pregnancy	212 (7.4)	
During pregnancy	533 (18.7)	
BMI	2587	22.2 (20.5, 24.4)
Parity		
0	1274 (45.5)	
1	1011 (36.1)	
2	383 (13.7)	
3	101 (3.6)	
4+	30 (1.1)	
Education		
Left school at 16	1713 (61.3)	
A level	689 (24.8)	
Degree	391 (14.0)	
Social Class		
I (least disadvantaged)	140 (5.9)	
II	807 (33.7)	
IIIa	1038 (43.5)	
IIIb	162 (6.8)	
IV	203 (8.5)	
V (most disadvantaged)	40 (1.7)	
Pregnancy Characteristics		
Gestational age at birth (weeks)	2914	40 (39, 41)
Model of delivery		
Spontaneous	2253 (77.9)	

Breech	36 (1.3)	
Caesarean	249 (8.6)	
Forceps	167 (5.8)	
Vacuum	154 (5.3)	
Other	32 (1.1)	
Gestational weight gain (kg)	2668	12.5 (9.5, 15.2)
Hypertension and pre-eclampsia		
No hypertensive disorders	2449 (84.5)	
Hypertension, no pre-eclampsia	420 (13.9)	
Hypertension and pre-eclampsia	49 (1.7)	
Diabetes		
No glycosuria or diabetes	2651 (95.8)	
Existing diabetes	10 (0.4)	
Gestational diabetes	16 (0.6)	
Glycosuria	91 (3.3)	
Offspring Characteristics		
Sex		
Male	1414 (47.9)	
Female	1541 (52.2)	
Birthweight (kg)	2891	3.5 (3.1, 3.8)
Cord leptin (pg/ml)	2952	6.4 (3.6, 12.1)
Cord adiponectin (µg/ml)	2927	75.7 (53.6, 98.4)
Height (cm)	Age 9: 2561	140 (136, 144)
	Age 11: 2363	151 (146, 156)
	Age 15: 1816	169 (163, 175)
	Age 17: 1648	170(164, 178)
Fat mass (kg)	Age 9: 2460	7.3 (4.9, 11.2)
	Age 11: 2327	10.0 (6.8, 15.7)
	Age 15: 1716	13.7 (8.6, 20.6)
	Age 17: 1594	16.7 (11.0, 23.5)
Waist circumference (cm)	Age 9: 2574	61.1 (57.4, 66.6)
	Age 11: 2362	66.0 (61.8, 73.5)
	Age 15: 1475	75.4 (71.0, 81.5)
BMI (kg/m^2)	Age 9: 2560	17.0 (15.7, 19.1)
	Age 11: 2359	18.4(16.6, 21.0)
	Age 15: 1811	20.7 (19.0, 23.1)
	Age 17: 1647	22.0 (20.2, 24.7)
Obese	Age 9: 102 (4.0)	
	Age 11:116 (4.9)	
	Age 15: 78 (4.3)	
	Age 17:105 (6.4)	
Age at clinic attendance (years)	Age 9: 2583	9.8 (9.6, 10.0)
	Age 11: 2378	11.8 (11.6, 11.8)
	Age 15: 1838	15.4 (15.3, 15.6)
	Age 17: 1695	17.8 (17.6, 17.9)

Median (Interquartile range)
Figures are numbers (%) unless stated otherwise

Table 2: Associations of birthweight and cord blood analyte with fat mass, waist circumference and BMI z-scores, and obesity outcome at age 9 years. N= 2775

	Outcome	Fat mass z-score *			Waist circumference z-score			BMI z-score			Obesity		
Exposure		Coefficient	95% CI	P	Coefficient	95% CI	P	Coefficient	95% CI	P	OR	95% CI	P
Leptin (per 10pg/ml)	Model 1	0.07	0.04, 0.10	<0.001	0.08	0.05, 0.12	<0.001	0.11	0.07, 0.15	<0.001	1.15	1.00, 1.31	0.046
	Model 2	0.04	0.00, 0.07	0.023	0.05	0.01, 0.08	0.008	0.06	0.02, 0.10	0.003	1.00	0.85, 1.17	0.993
	Model 3	0.03	0.00, 0.06	0.086	0.04	0.00, 0.07	0.045	0.04	0.00, 0.08	0.029	0.95	0.81, 1.12	0.548
Adiponectin (per 10µg/ml)	Model 1	0.00	-0.01, 0.01	0.828	-0.01	-0.02, 0.00	0.072	0.00	-0.02, 0.01	0.602	0.99	0.94, 1.05	0.845
	Model 2	0.00	-0.01, 0.01	0.916	-0.01	-0.02, 0.00	0.118	0.00	-0.01, 0.01	0.858	1.00	0.94, 1.05	0.874
	Model 3	0.00	-0.01, 0.01	0.875	-0.01	-0.02, 0.00	0.100	0.00	-0.01, 0.01	0.767	0.99	0.94, 1.05	0.834
Birthweight‡ (per 100g)	Model 1	0.01	0.00, 0.02	0.006	0.03	0.03, 0.04	<0.001	0.04	0.03, 0.05	<0.001	1.06	1.02, 1.10	0.006
	Model 2	0.00	0.00, 0.01	0.192	0.03	0.02, 0.04	<0.001	0.04	0.03, 0.04	<0.001	1.03	0.99, 1.07	0.193
	Model 3	0.00	-0.01, 0.01	0.741	0.02	0.02, 0.03	<0.001	0.03	0.02, 0.04	<0.001	1.01	0.96, 1.05	0.852

Model 1: Adjusted for offspring sex and age at measurement.
Model 2: Adjusted for offspring sex, age at measurement and maternal confounders (age, smoking, parity, occupational social class, education and pre-pregnancy BMI).
Model 3: Adjusted for offspring sex, age at measurement and maternal confounders plus pregnancy confounders (gestational age at birth, mode of delivery, gestational weight gain, hypertensive disorders and diabetic disorders of pregnancy).
* Fat mass adjusted for height
‡ Birthweight adjusted for sex, gestational age and singleton/twin pregnancy

Table 3: Associations of birthweight and cord blood analyte with fat mass, waist circumference (at age 15 years), BMI z-scores and obesity outcomes at age 17 years. N= 2138

	Outcome	Fat mass z-score *			Waist circumference z-score			BMI z-score			Obesity		
Exposure		Coefficient	95% CI	P	Coefficient	95% CI	P	Coefficient	95% CI	P	OR	95% CI	P
Leptin (per 10pg/ml)	Model 1	0.07	0.03, 0.11	<0.001	0.06	0.02, 0.10	0.003	0.09	0.04, 0.14	<0.001	1.13	0.99, 1.28	0.060
	Model 2	0.02	-0.02, 0.06	0.263	0.01	-0.03, 0.05	0.545	0.03	-0.02, 0.07	0.272	0.96	0.83. 1.12	0.629
	Model 3	0.02	-0.02, 0.05	0.444	0.01	-0.03, 0.05	0.598	0.02	-0.03, 0.06	0.481	0.95	0.81, 1.11	0.497
Adiponectin (per 10µg/ml)	Model 1	0.01	0.00, 0.03	0.034	0.01	0.00, 0.03	0.033	0.01	-0.01, 0.02	0.245	1.03	0.98, 1.08	0.238
	Model 2	0.02	0.00, 0.03	0.006	0.02	0.00, 0.03	0.008	0.01	0.00, 0.03	0.076	1.04	0.99, 1.10	0.660
	Model 3	0.02	0.00, 0.03	0.007	0.02	0.00, 0.03	0.008	0.01	0.00, 0.03	0.080	1.05	0.99, 1.10	0.613

Birthweight‡ (per 100g)	Model 1	0.02	0.02, 0.03	<0.001	0.04	0.03, 0.05	<0.001	0.04	0.03, 0.05	<0.001	1.05	1.02, 1.09	0.004
	Model 2	0.01	0.00, 0.02	0.010	0.03	0.02, 0.04	<0.001	0.02	0.01, 0.03	<0.001	1.02	0.98, 1.06	0.241
	Model 3	0.01	0.00, 0.02	0.098	0.03	0.02, 0.04	<0.001	0.02	0.01, 0.03	<0.001	1.01	0.97, 1.05	0.516

Model 1: Adjusted for offspring sex and age at measurement.
Model 2: Adjusted for offspring sex, age at measurement and maternal confounders (age, smoking, parity, occupational social class, education and pre-pregnancy BMI).
Model 3: Adjusted for offspring sex, age at measurement and maternal confounders plus pregnancy confounders (gestational age at birth, mode of delivery, gestational weight gain, hypertensive disorders and diabetic disorders of pregnancy).
* Fat mass adjusted for height
‡ Birthweight adjusted for sex, gestational age and singleton/twin pregnancy