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Infant Adiposity is Independently Associated with a Maternal High Fat Diet but Not Related to Niacin Intake: The Healthy Start Study

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Abstract

Objectives—Over-nutrition during pregnancy resulting from maternal obesity or an unhealthy diet can lead to excess infant adiposity at birth. Specific dietary macro- and micronutrients have been shown to increase fat cell development in both *in-vitro* and *in-vivo* models and may therefore link maternal diet to increased infant adiposity. We hypothesized that high maternal dietary niacin intake during pregnancy, especially in combination with a high-fat diet (HFD) would increase infant adiposity.

Methods—We included 1,040 participants from a pre-birth cohort of mother-infant pairs. Maternal diet was assessed using multiple 24-hour dietary recalls. HFD was defined as ≥ 30% of calories from fat and ≥ 12% of fat calories from saturated fat. Neonatal body composition (% fat mass [%FM], fat mass [FM], fat-free mass [FFM]) was measured by PEAPOD.. We used multivariate regression to assess the joint effect of maternal dietary niacin and maternal HFD on neonatal body composition..

Results—Dietary niacin was not associated with neonatal body composition, and maternal HFD did not modify this finding. However, maternal HFD was independently associated with %FM (β= 0.8 [0.1, 1.4] %, p<0.01] and FM (β=32.4 [6.7, 58.0] grams, p<0.01).

Conclusions for Practice—Our results suggest that a HFD during pregnancy may increase infant adiposity, therefore supporting the need for improved diet counseling of pregnant women at both the clinical and community levels.

Keywords

dietary niacin; high-fat diet; infant adiposity

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INTRODUCTION

Early life obesity is an alarmingly prevalent condition among youth in the United States. Recent reports from the Centers for Disease Control estimate the overall burden of obesity at 17% in youth ages 2–19 years old (9% in 2–5 year-olds, 17% in 6–11 year-olds, and 20% in 12–19 year-olds) (Ogden, Carroll, Fryar, & Flegal, 2015). The development of early life obesity has been attributed to several risk factors that operate as early as pregnancy, including higher maternal pre-pregnancy body-mass index (BMI) and excessive gestational weight gain (Woo Baidal et al., 2016). These risk factors, themselves are potentially modifiable through the maternal diet during pregnancy, which may also have a direct effect on infant size at birth and risk of obesity in early life.

Maternal diet during pregnancy has been shown to impact fetal growth and development (Liu et al., 2015; Nisar, Dibley, Mebrahtu, Paudyal, & Devkota, 2015; Shapiro et al., 2016). Maternal high-fat diet (HFD) in particular has been shown to be causally associated with higher offspring adiposity and size at birth in animal models (Ashino et al., 2012; Franco et al., 2012; S. M. Krasnow, M. L. Nguyen, & D. L. Marks, 2011; S. M. Krasnow, M. L. T. Nguyen, & D. L. Marks, 2011; McCurdy et al.; McCurdy et al., 2009). However, the evidence supporting this relationship in humans is only recently emerging in smaller controlled trials of diabetic women (Hernandez et al., 2016). Furthermore, while fat from the maternal diet during pregnancy may provide the substrate for fetal fat development, specific micronutrients may in fact drive adipogenic mechanisms responsible for increased neonatal adiposity.

Nicotinamide is a form of niacin or vitamin B3 which occurs in animal-based foods, enriched grain products, and vitamin supplements. Interestingly, this micronutrient in the diet has been shown to increase adipose tissue growth (e.g. increasing adipogenic protein markers) in animal models. Adipose tissue growth, or adipogenesis is controlled by several mechanisms that are sensitive to the energy and nutrition status of the organism. Sirtuin 1 (SIRT1) is involved in one such control mechanism as it is an inhibitor of adipogenic enzyme gene expression and activity (Fischer-Posovszky et al., 2010; Han et al., 2010; Picard et al., 2004). Importantly, nicotinamide is a potent, non-competitive inhibitor of SIRT1 (Bitterman, Anderson, Cohen, Latorre-Esteves, & Sinclair, 2002; Denu, 2005) and may influence adipogenesis through a SIRT1 dependent pathway.

Given the potential links between nicotinamide/niacin, SIRT1and adipogenesis we hypothesized that high dietary niacin intake (as a proxy for dietary nicotinamide), especially in conjunction with a maternal HFD diet during pregnancy, would increase infant adiposity at birth. Furthermore, to gain insight into the hypothesized mechanistic pathway, we investigated the associations between maternal dietary niacin and neonatal SIRT1 protein levels in umbilical cord tissue (UCT), and between neonatal SIRT1 protein levels and neonatal adiposity, in a subset of participants.

SUBJECTS AND METHODS

Study Population

In this analysis we used mother-infant pairs who participated in the Healthy Start study, a longitudinal, pre-birth cohort of ethnically diverse mothers that aims to investigate maternal metabolic and behavioral exposures in pregnancy and their impact on offspring obesity and related outcomes. Details of the Healthy Start study recruitment methods and protocol have been published elsewhere (Harrod et al., 2014; Starling et al., 2015). Briefly, the Healthy Start study recruited 1,410 pregnant women ages 16 and older prior to 24 weeks gestation from the obstetrics clinics at the University of Colorado Hospital during 2010–2014. Women were excluded if they had prior diabetes, a history of prior premature birth or fetal death, asthma with active steroid management, serious psychiatric illness, or a current multiple pregnancy. Participants provided written informed consent prior to the first study visit. The Healthy Start study protocol was approved by the Colorado Multiple Institutional Review Board.

Data Collection

Healthy Start mothers were invited to participate in two research visits during pregnancy. The first visit occurred at a median of 17 weeks gestation (range 8 – 24 weeks) and the second visit was at a median of 27 weeks gestation (range 24 – 32 weeks). At each of the two pregnancy visits maternal fasting blood samples were collected and demographic, behavioral, physical activity (energy expenditure) and dietary surveys were administered.

A third visit occurred at delivery in the hospital during which women were asked to complete surveys identical to those from the second pregnancy visit. Neonatal anthropometrics (e.g. birth length, weight, head circumference, and skin-fold thickness) were measured within 72 hours after delivery, and neonatal body composition, fat mass (FM) and fat-free mass (FFM) were estimated from total mass and volume using air displacement plethysmography (PEA POD); percent fat mass (%FM) was derived by dividing the FM by total mass. Body composition was measured twice for each neonate with a third measurement taken if the first FM or FFM values were greater than two percentage points apart. Values used in this report are the average of the two closest measures.

UCT was also collected at time of birth in a convenience sample (N = 200). Upon delivery of the placenta, trained clinical research nurses excised a 1-inch section of the umbilical cord from the area furthest from the cord’s attachment to the placenta. The tissue was cut in half along the length of the excised section and washed with chilled distilled water to remove any remaining blood. The clean tissue was then snap frozen in liquid nitrogen and stored at −80°C until tissue processing.

Maternal pre-pregnant body mass index (BMI) was calculated using maternal height measured at the first research visit and pre-pregnant weight obtained from medical records (83.7%) or self-reported at the first research visit (16.2%). Pre-pregnant BMI was categorized as normal weight (NW, BMI<25 kg/m^2), overweight (OW, 25≤BMI<30 kg/m^2), and obese (Ob, BMI≥30 kg/m^2) for all analyses. Of the participants who self-reported their weight, the majority were classified as having a normal BMI (53%), while 22% and 25%

were OW and Ob, respectively. These proportions did not differ significantly from those whose data were abstracted from the medical record (NW 56.4%, OW 25.3%, Ob 18.3%). Physical activity in pregnancy was measured using the Pregnancy Physical Activity Questionnaire (Chasan-Taber et al., 2004) from which metabolic equivalent task (MET) values were estimated as described in detail elsewhere (Chasan-Taber et al., 2004; Harrod et al., 2014).

Infant sex, birth weight, and gestational age at birth were abstracted from medical records. Race/ethnicity, household income, smoking during pregnancy, and gravidity were obtained from surveys administered to participants. Race/ethnicity was categorized into non-Hispanic white, non-Hispanic black, Hispanic, and other. Household income was categorized into five levels: < $20,000, $20,000 – $40,000, $40,000 – $70,000, income > $70,000, and "don't know". Maternal age at delivery was calculated based on offspring delivery date and maternal date of birth.

Dietary Assessment

The Healthy Start study collected detailed dietary information on women throughout their pregnancies with repeated Automated Self-administered 24-hour dietary recalls, using an online platform developed and hosted by the National Cancer Institute (ASA24-2014. Bethesda, MD: National Cancer Institute) as well as a Food Propensity Questionnaire (FPQ).

Estimation of usual intake of non-episodically consumed macro- and micronutrients was conducted using the "NCI method", a measurement error model that applies a two-part non-linear mixed effects modeling approach (Kipnis et al., 2009; Tooze et al., 2010; Tooze et al., 2006). This approach resulted in a single individual estimate of usual daily nutrient intake of total energy (kcal), niacin, total fat, and saturated fat for each participant.

SIRT1 Protein Analysis in Umbilical Cord Tissue

Snap-frozen UCT was segmented into pieces weighing approximately 30 mg and thawed in a 200 ul solution of tissue lysis buffer (Sigma, #C3228) with 5 ul/ml protease inhibitor (Sigma, #P8340). Thawed samples were homogenized and spun at 16,000xg for 10 minutes. The supernatant was collected and stored at −80°C until protein analysis.

SIRT1 protein content was analyzed using the Simple Western (WES) method (Protein Simple, San Jose, CA). SIRT1 antibody (Santa Cruz Biotechnology, #sc-15404) was optimized in-house for use on WES at a 1:50 dilution with a protein concentration of 0.4 mg/ml. For assurance of quality control a pooled sample was run on each WES plate (%CV =11%). The Area-Under-the-Curve (AUC) value was used for SIRT1 quantification; all AUC values were normalized to the pooled sample. Normalized SIRT1 values were square root-transformed to achieve a normal distribution and used for all analyses.

Statistical Analysis

Means (SD) and frequencies of the maternal and infant characteristics were compared across BMI categories (normal weight, overweight, and obese) of the mother by ANOVA for

continuous variables or Cochran Mantel-Haenszel tests of general association for categorical variables.

Average daily dietary niacin intake was used as a continuous variable in all models and was energy adjusted. Energy-adjusted niacin was derived by estimating the residual value for total energy regressed on niacin. We defined a HFD using the American Heart Association criteria. Specifically, a diet was classified as a HFD if ≥30% of caloric energy was derived from fat (total fat) and ≥12% of total fats consumed were saturated fat.

To test the hypothesis that a maternal HFD modifies the effect of maternal dietary niacin consumption on neonatal body composition we fit a general linear multivariable model, and used a planned, backwards stepwise approach to examine the effects of maternal HFD (yes/no), estimated usual daily dietary niacin intake (mg/day), and their interaction on neonatal %FM. Covariates for inclusion in this model were chosen based on their potential as confounders and included maternal age, race/ethnicity, pre-pregnancy body mass index (BMI), infant sex, gestational age at birth, and usual daily energy intake (kcal/day). We did not observe a significant interaction between maternal HFD and dietary niacin ($p > 0.1$). In a reduced model, without the interaction term, we tested the main effect of HFD, and the main effect of dietary niacin, while controlling for covariates. We applied this same modeling approach for the general multivariate linear model used to examine the association between maternal HFD and dietary niacin on FM and FFM.

We analyzed the relationships among maternal HFD, dietary niacin, UCT SIRT1 protein levels and neonatal body composition using two separate general linear multivariable models. Specifically, the first of these models tested the association between dietary niacin and UCT SIRT1 protein levels while controlling for maternal age, pre-pregnancy BMI, total energy (kcal/day), and gestational age at birth. In our second model we tested the association between SIRT1 protein levels and neonatal %FM and whether a maternal HFD modified this relationship. Here we controlled for the same group of covariates as in our first model. When a statistically significant interaction was not found ($p > 0.1$), we then tested the independent associations of maternal HFD and SIRT1 protein levels with %FM.

RESULTS

At the conclusion of recruitment in September 2015, a total of 1,410 pregnant women had been enrolled in the Healthy Start cohort. Healthy Start participants were eligible for the current analysis if they had at least one dietary recall (N=1,366). Neonates born at less than 37 weeks gestation or those without body composition measures at birth were also excluded (n=273). Women who had been diagnosed with gestational diabetes mellitus (n=53) were further excluded from the eligible cohort to give a final sample size of 1,040 for the full analytic cohort used in the first of our analyses investigating the relationship between maternal dietary niacin and neonatal body composition. In our analysis of maternal diet, UCT SIRT1 protein levels, and neonatal body composition we included 173 of the total 200 mother-infant pairs from whom we were able to collect UCT as these individuals also met the above inclusion criteria. This subsample did not differ significantly from the full analytic cohort when we compared maternal and infant characteristics such as maternal age, race/

ethnicity, household income, maternal pre-pregnancy BMI, birth weight, and neonatal body composition, among others (data not shown).

Table 1 presents mother and infant characteristics by pre-pregnancy BMI status in the full analytic cohort of 1,040 pairs. Mothers whose pre-pregnancy BMI was classified as >35 kg/m^2 (obese) were more likely to be non-Hispanic Black, have a higher gravidity, gain excessive weight over the gestation period, have an annual household income of less than $27,000, and smoke during pregnancy ($p<0.001$ for all, respectively). These women were also more likely to deliver by cesarean section ($p=0.01$). Infants of mothers with obesity prior to pregnancy were significantly heavier overall ($p=0.04$) with higher absolute FM and %FM ($p<0.001$ for both, respectively).

Maternal HFD but not maternal dietary niacin intake was significantly associated with %FM and FM (Table 2). Moreover, there were no significant joint effects of maternal niacin intake and maternal HFD ($p >0.05$ for interaction). Mothers who ate a HFD during pregnancy gave birth to neonates who had, on average 0.8 percentage points greater %FM ($\beta=0.8$, 95% CI: 0.1, 1.4, $p<0.05$) and 32.4 g higher absolute FM ($\beta=32.4$, 95% CI: 6.7, 58.0, $p<0.01$). However, FFM was not associated with a HFD. As expected, obesity prior to pregnancy, older maternal age at delivery, higher gestational age at birth, and female sex of the infant were all significantly associated with higher %FM and FM ($p<0.01$ for all, respectively). These covariates were also significantly associated with FFM and birth weight. Finally, infants of non-Hispanic Black mothers had significantly lower FM, FFM, %FM and birth weight, compared with NHW peers ($p<0.001$ for all, respectively).

In mother infant pairs on whom we measured SIRT1 protein in the UCT, we found no association between maternal dietary niacin intake and umbilical cord SIRT1 protein levels, nor did we find that any covariates in this model related to SIRT1 protein in the UCT (data not shown). Neither SIRT1 ($\beta=0.5$, 95% CI: −1.3, 2.2) nor HFD ($\beta=0.7$, 95% CI: −0.6, 2.0) were associated with %FM in the sub-cohort, but as expected, gestational age at birth and female sex of the infant were significantly and positively associated with %FM ($p <0.01$ for all, respectively).

DISCUSSION

In this large, diverse pregnancy cohort we did not find a significant association between maternal dietary niacin intake and infant body composition, nor were we able to provide supporting evidence that a maternal HFD influenced this relationship. However, maternal HFD was a significant and independent predictor of %FM and FM. Our finding that a maternal HFD during pregnancy was significantly associated with neonatal adiposity but not with either FFM or birth weight, suggests that the effect of maternal dietary fat intake during pregnancy may selectively increase fetal fat accretion rather than total body mass. While we previously reported on the association between maternal obesity and infant adiposity (Starling et al., 2015), our finding of a significant association between maternal HFD and infant adiposity, independent of maternal pre-pregnancy BMI is novel with potentially important public health implications.

Our study did not observe an association between intake of the specific micronutrient, dietary niacin, and neonatal body composition. It is possible that the association between maternal HFD and neonatal adiposity is not driven by the hypothesized niacin-SIRT1 pathway. However, certain limitations of our study may have limited our ability to detect an association between dietary niacin and neonatal adiposity. For example, the non-significant association between dietary niacin and neonatal body composition may be due, at least in part, to our dietary instrument's inability to distinguish between the nicotinamide form of niacin and the nicotinic acid form, both of which are derived from the diet. Nicotinic acid is not physiologically equivalent to nicotinamide and is not known to inhibit SIRT1. Therefore, the sensitivity of total dietary niacin estimates derived from self-reported diet as a proxy for dietary nicotinamide exposure may not be optimal. This could have biased a potential effect of niacin on neonatal adiposity in our study toward the null. In future studies, urine analysis of nicotinamide metabolites in conjunction with diet data may provide a more specific exposure estimate. Further, in our analysis of UCT SIRT1 protein levels we did not find that maternal dietary niacin was associated with neonatal SIRT1 levels or that neonatal SIRT1 levels were related to adiposity at birth. It is possible that SIRT1 protein levels may not accurately measure the *in-vivo* impact of nicotinamide on SIRT1 protein *activity* and therefore not fully capturing the effect on neonatal adiposity. It is the *activity* of the SIRT1 protein, not the *level* of protein, which is responsible for controlling adipogenesis. Given the heterogeneous cell populations contained in UCT, it is also possible that the SIRT1 protein levels in the umbilical cord are not representative of the SIRT1 protein content in the progenitor cells (mesenchymal stem cells), the multipotent cell population with the capacity to undergo adipogenesis. Further, it is possible that other tissue types in the umbilical cord that are not niacin sensitive could have contributed to the lack of an association between SIRT1 and niacin intake. We do not believe that the lack of an association is due to sample bias introduced through our convenience sampling design; the subsample of UCT did not differ from the final analytic cohort with respect to maternal and infant characteristics, such as maternal pre-pregnancy BMI and neonatal adiposity. Despite these limitations, our analysis is the first to investigate the relationships between maternal niacin intake and HFD with neonatal body composition in a large cohort, as well as with SIRT1 protein in the umbilical cord tissue.

Our results showing the significant association between a HFD during pregnancy and neonatal adiposity at birth support the findings of other studies showing that a *generally* unhealthy diet has a negative impact on offspring health (Okubo et al., 2012; Shapiro et al., 2016; Timmermans et al., 2012). Specifically, this additional knowledge may help to inform future intervention efforts among pregnant women and women of reproductive age with the intention to become pregnant. For example, reducing fat intake during pregnancy may be important for reducing fetal fat accretion and newborn adiposity, which may be associated with future childhood obesity risk.

In conclusion, our results from this large pre-birth cohort suggest that maternal HFD during pregnancy increases neonatal adiposity, independent of maternal obesity and other relevant confounders. While we were unable to detect an effect of dietary niacin or SIRT1 protein, our study suggests further refinements that will allow other researchers to revisit the issue.

Finally, further studies are needed determine the mechanisms responsible for these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE

What is already known on this subject?

Fetal over-nutrition, commonly attributed to exposure to diabetes during pregnancy, maternal obesity, or excess dietary carbohydrate or fat, often results in excess fetal growth and is implicated in child obesity risk. However, it is not known whether excess of specific micronutrients, such as niacin, which are involved in adipogenic pathways could also contribute to increased fetal growth and further, whether this could be compounded by a maternal high-fat diet (HFD).

What this study adds?

Our study is the first to test whether consumption of niacin (as a proxy for dietary nicotinamide) during pregnancy is associated with higher infant adiposity and whether this relationship is augmented by maternal HFD during pregnancy. We did not find an association between maternal dietary niacin consumption during pregnancy and neonatal adiposity; however, maternal HFD was a significant, independent predictor of adiposity in the neonate. Mechanisms responsible for these potential effects on fat development need further exploration.

Table 1

Demographic and descriptive characteristics by pre-pregnant BMI status

	Pre-pregnant BMI Status			*p*[2]
	Normal (n=582)	**Overweight (n=258)**	**Obese (n=200)**	
Maternal				
Age at delivery in years, mean (SD)	27.9 (6.1)	27.8 (6.2)	27.9 (6.0)	0.9
Race/ethnicity, n (%):				<0.001
NHW[1]	373 (64.1)	120 (46.5)	77 (38.5)	
Hispanic	98 (16.8)	90 (34.9)	68 (34.0)	
NHB[1]	72 (12.4)	37 (14.3)	44 (22.0)	
Other	39 (6.7)	11 (4.3)	11 (5.5)	
Gravidity, mean (SD)	1.0 (1.3)	1.5 (1.7)	2.1 (1.8)	<0.001
IOM recommended GWG, n (%):				<0.001
Inadequate	146 (25.1)	36 (13.9)	48 (24.0)	
Adequate	198 (34.0)	57 (22.1)	42 (21.0)	
Excessive	238 (40.9)	165 (63.9)	110 (55.0)	
GA at birth (weeks), mean (SD)	39.6 (1.1)	39.6 (1.1)	39.4 (1.1)	0.07
Cesarean section, n (%)	98 (16.9)	61 (23.9)	51 (26.3)	0.01
Smoking in pregnancy, n (%)	49 (8.4)	17 (6.6)	24 (12.0)	0.12
Household income, n (%):				<0.001
< $20,000	58 (10.0)	36 (13.9)	55 (27.5)	
$20,000 – $40,000	68 (11.7)	41 (15.9)	35 (17.5)	
$40,000 – $70,000	106 (18.2)	59 (22.9)	32 (16.0)	
> $70,000	241 (41.4)	75 (29.1)	35 (17.5)	
Don’t know	109 (18.7)	47 (18.2)	43 (21.5)	
Energy expenditure (mets/week), mean (SD)	184.5 (85.0)	188.3 (82.2)	188.9 (80.7)	0.73
HFD (yes), n (%)	199 (34.2)	85 (32.9)	75 (37.5)	0.58
Niacin (mg/day), mean (SD)	21.7 (7.6)	20.8 (7.1)	20.7 (7.9)	0.14
Offspring				
Female, n (%)	299 (51.4)	120 (46.5)	92 (46.0)	0.13
Birth weight (g), mean (SD)	3254 (417)	3311 (454)	3331 (444)	0.04
Length (cm), mean (SD)	49.3 (2.8)	49.5 (2.5)	49.5 (2.3)	0.11
% FM, mean (SD)	8.8 (3.9)	9.1 (3.9)	10.1 (4.1)	<0.001

	Pre-pregnant BMI Status			*P*[2]
	Normal (n=582)	**Overweight (n=258)**	**Obese (n=200)**	
FM[1] (g), mean (SD)	282 (147)	299 (153)	334 (164)	<0.001
FFM[1] (g), mean (SD)	2838 (324)	2876 (367)	2864 (330)	0.28

[1] NHW – non-Hispanic white; NHB – non-Hispanic Black; FM – fat mass; FFM – fat-free mass.

[2] p-values generated using Cochran-Mantel Haenszel test for categorical characteristics and ANOVA for continuous characteristics

Table 2

Associations between maternal dietary niacin, high-fat diet and neonatal body composition, adjusted for covariates.

	%FM β (95% CI)	FM β (95% CI)	FFM β (95% CI)
Dietary niacin (mg/day)	0.01 (−0.03, 0.05)	0.4 (−1.2, 1.9)	−1.2 (−4.2, 1.8)
HFD[a]:			
Yes	0.8 (0.1, 1.4)[3]	32.4 (6.7, 58.0)[2]	28.0 (−21.9, 77.9)
No	ref.	ref.	ref.
Pre-pregnant BMI[β]:			
Normal	ref.	ref.	ref.
Overweight	0.4 (−0.1, 1.0)	19.6 (−2.3, 41.5)	34.3 (−8.4, 76.9)
Obese	1.5 (0.9, 2.2)[1]	60.5 (35.9, 85.0)[1]	53.4 (5.7, 101.1)[3]
Race/ethnicity:			
NHW	ref.	ref.	ref.
Hispanic	0.1 (−0.6, 0.7)	4.6 (−19.1, 28.3)	6.4 (−39.6, 52.5)
NHB	−0.2 (−0.9, 0.5)	−23.7 (−51.9, 4.5)	−167.6 (−222.4, 112.7)[1]
Other	−0.7 (−1.7, 0.3)	−24.1 (−63.1, 14.9)	−35.0 (−110.9, 40.8)
Maternal age	0.1 (0.01, 0.1)[2]	2.4 (0.8, 4.1)[2]	3.0 (−0.1, 6.1)
Total energy (kcal/day)	0.002 (−0.003, 0.01)	0.1 (−0.1, 0.3)	0.1 (−0.3, 0.4)
GA at birth (weeks)	0.5 (0.3, 0.7)[1]	28.8 (20.6, 37.0)[1]	128.7 (112.9, 144.7)[1]
Infant sex:			
Female	1.5 (1.0, 2.0)[1]	35.1 (17.1, 53.0)[1]	−191.0 (−225.9, −156.2)[1]
Male	ref.	ref.	ref.

[1] p-value < 0.001.

[2] p-value < 0.01.

[3] p-value < 0.05