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Impact of maternal pre-pregnancy overweight on infant overweight at 1 year of age: associations and sex-specific differences

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Summary

Background: Maternal overweight or obesity (OWOB) is linked to gestational diabetes, fetal macrosomia and higher rates of caesarean delivery.

Objectives: The study aims to assess whether maternal pre-pregnancy OWOB is associated with infant overweight in a sex-dependent manner, independent of microbiota-altering variables.

Methods: Weight and length measurements of 955 mother–infant pairs were obtained from the Canadian Healthy Infant Longitudinal Development cohort. Maternal pre-pregnancy weight was defined as follows: normal, overweight ($25 \leq$ body mass index < 30) and obese (body mass index ≥ 30). Age and sex-adjusted weight-for-length z-scores >97th percentile were classified as infant overweight at age 1 year. Associations between pre-pregnancy and infant overweight were determined by linear and logistic regression, adjusting for covariates.

Results: Maternal pre-pregnancy OWOB were associated with infant weight-for-length and overweight risk at 1 year. Except for pre-pregnancy obesity, these associations were not attenuated appreciably after adjustment for birth mode, exclusivity of breastfeeding, exposure to antibiotics and infant sex. Yet only boys born to mothers with obesity were three times more likely to become overweight at age 1 independent of microbiota-altering variables. Pre-pregnancy obesity was associated with weight-for-length in male and female infants.

Conclusions: Maternal pre-pregnancy OWOB increases the risk of infant overweight, and this association is more evident in male infants.

Keywords: infant, maternal, overweight, pregnancy.

Abbreviations: Canadian Healthy Infant Longitudinal Development, CHILD; Odds ratio, OR.

Introduction

Over the past three decades, the prevalence of overweight and obesity in women of reproductive age has risen substantially, exceeding 30% in some high-income countries (1). According to the 2006–2007 Canadian Maternity Experience Survey, approximately one-third of Canadian women began their pregnancy either overweight or with obesity (2). This leads to a greater risk for gestational diabetes, hypertension and pre-eclampsia, preterm birth, caesarean section delivery and antibiotic use, and failure to initiate or continue breastfeeding (1). Through proposed fetal programming mechanisms, maternal overweight status adversely affects the health of the unborn child. For example, prenatal maternal obesity increases the likelihood of both low and high birthweight, and subsequent child overweight and metabolic dysfunction (3). Strikingly, nearly 20% of preschool children in Canada are now classified as overweight or obese (4).

The influence of maternal pre-pregnancy overweight on offspring overweight has been extensively studied (5), although not at very young ages (6). In a meta-analysis of studies until 2012 by Yu *et al*. (7), which included children aged 3 years and older, pre-pregnancy overweight doubled the risk of subsequent child overweight and

pre-pregnancy obesity tripled the risk. Several studies of large representative populations reported higher risks for overweight among 2–3 year olds born in the USA to mothers with pre-pregnancy obesity in the late 1970s (8) and in 3 year olds born in the UK in 2000 following pre-pregnancy overweight (9). In Latin-based cohorts from Chile, Italy and Portugal, overweight between 2 and 4 years of age was eightfold higher following pre-pregnancy overweight (10). Most recently, a large cohort study of 15,710 mother–infant pairs delivered in 2011 confirmed an association with overweight at age 2 following maternal overweight and reported a 2.3-fold higher risk for maternal obesity (11). To our knowledge, only three studies have tested the impact of pre-pregnancy weight on infants. Infant weight was higher at birth and at 13 months of age following pre-pregnancy overweight in a Finnish study (12). In two Asian cohorts, maternal pre-pregnancy body mass index (BMI) was positively associated with offspring weight for length z-score through the first 12 months of life (13,14).

Sex-specific differences exist among children who are overweight. Foremost, the burden of obesity is much greater for boys than girls within the 5–11 age group (15). Second, prenatal and postnatal exposures seem to primarily influence overweight development in boys, such as maternal smoking during pregnancy and antibiotic use during infancy (16). In addition, exclusive breastfeeding shows greater protection against overweight for boys than girls (17). Finally, sex differences in metabolic biomarkers of overweight have recently been reported in children (18). Despite this emerging evidence, male and female children are often combined in studies on prenatal determinants of overweight.

In summary, there is a limited literature on the impact of pre-pregnancy overweight on overweight in infants, and there are no studies that critically examine the impact of sex differences. Further, from a recent systematic review of putative risk factors for childhood obesity before age 2, less is known about birth or postnatal antibiotic exposure versus other factors that modify infant gut microbiota, such as breastfeeding or caesarean birth (19). Our objective was to assess whether maternal pre-pregnancy overweight and obesity was associated with infant overweight/obesity at age 1 year and whether any sex differences were already apparent. We adjusted these associations for well-known confounding factors, including those known to affect gut microbial composition.

Methods

This was a prospective cohort study of 988 pregnant women and their infants who were enrolled in the Manitoba sub-cohort of the Canadian Healthy Infant Longitudinal Development (CHILD) study, a longitudinal, population-based birth cohort study in Canada (www.childstudy.ca) (20). Women were recruited during the second and third trimester, and the infant deemed eligible for study if a live birth occurred at 35.5 weeks gestation or later. For the current analysis, we excluded home births ($n = 26$) and infants born late preterm ($n = 7$), leaving a total of 955 mother–infant dyads.

Maternal and infant overweight

Maternal BMI (weight in kilograms/height in meters squared) was calculated from measured height and self-reported pre-pregnancy weight ($n = 860$) or estimated from measured weight at 1 year postpartum if mothers could not recall their pre-pregnancy weight ($n = 71$); maternal pre-pregnancy weight was missing in 24 women. Validation against prenatal health records ($n = 224$) showed that pre-pregnancy weight was slightly underestimated by maternal recall (mean difference −1.0 kg, 95% confidence [CI] −1.5 to −0.4) and slightly overestimated by measured weight at 1 year postpartum (mean difference + 1.3 kg, 95%CI 0.5 to 2.2). A three-category variable of pre-pregnancy weight was created according to World Health Organization (WHO) criteria as follows: normal weight ($18.5 < \text{BMI} < 25$), overweight ($25 \leq \text{BMI} < 30$) and obese ($\text{BMI} \geq 30$) (21). Infants were physically assessed at 1 year of age, at which time weight and length were measured by trained study staff according to a standardized protocol. Infant overweight/obesity at 1 year was defined according to the WHO reference standard as weight for length z-score >97th percentile for age and sex (22).

Maternal and infant nutritional assessment

The Food Frequency Questionnaire developed by nutritional epidemiologists at the Fred Hutchinson Cancer Research Center in Seattle, WA, was modified to reflect Canadian ethnic food choices (20). From the Hutchinson Food Frequency Questionnaire food groupings, total daily added sugar consumption by mothers was estimated and a binary variable of 'added sugar' was created based on strong associations in the literature between prenatal added sugar consumption and child overweight (23); the

American Heart Association upper limit of no more than 100 calories per day (24 g of sugar) for women was used as a cut-off (23). Infant diet (exclusively breast fed, partially breast fed or formula fed) was assessed at 3 months by mothers' report.

Other covariates

Mode of delivery from hospital records was defined as vaginal or caesarean section. The presence of gestational diabetes between 24 and 28 weeks of gestation was retrieved from the birth chart. Tobacco smoke exposure (none, prenatal maternal and postnatal household, and only postnatal household) was documented from prenatal and postnatal questionnaires. Birthweight, retrieved from birth chart records, was categorized into high (>4 kg) and normal (≤4 kg) weight. A measure of infant antibiotic exposure was derived from the birth record and infant medication questionnaire as follows: no exposure, indirect only (maternal intrapartum antibiotic prophylaxis), and direct (intravenous antibiotics at birth and/or oral prescription in the first 3 months) with/without indirect exposure.

Statistical analysis

Data were analysed with purposeful stepwise logistic regression modelling using SPSS 24.0 software to determine the association (odds ratio [OR]) between maternal overweight prior to pregnancy and overweight in offspring at age 1. Significance was set at $p < 0.05$. Upon reviewing the frequency distribution of covariates by the exposure and outcome variables, we pursued a systematic approach to modelling by testing the influence of covariates on the association of pre-pregnancy overweight and obesity and infant overweight or obesity. The first model reported the unadjusted odds ratio for pre-pregnancy overweight and infant overweight. The second model was adjusted for maternal pregnancy variables including maternal gestational diabetes, maternal added sugar consumption, smoking history and mode of delivery. The third model was adjusted for infant variables including birthweight. Our final model consisted of covariates, which are known to affect the infant gut microbiome (mode of delivery, breastfeeding status and infant antibiotic exposure). All models were adjusted for infant sex. Sex-specific logistic regression analyses were also conducted. The same analyses were conducted using linear regression models with the continuous measure of age and sex-adjusted weight-for-length z (WFL-z) scores as the outcome variable.

Results

In this study of 955 Canadian women and their offspring from the Manitoba site of the CHILD cohort, almost one quarter of women were overweight (24.0%) and a further one in five had obesity (19.3%). Gestational diabetes was reported by 4.2%, and the majority of women (93.2%) exceeded the recommended daily intake of added sugar. Overall, 19.5% of infants were delivered by caesarean section, 14.3% of infants were born with high birthweight and 10.7% directly received antibiotics before 3 months of age; 24.2% were exposed to maternal prenatal and postnatal smoking, and 18.1% were exposed to postnatal environmental tobacco smoke alone. Over half (57%) were exclusively breastfed for at least 3 months, and 4.7% were classified as overweight or obese at 1 year of age. Pre-pregnancy overweight was crudely associated with several covariates (Table 1). Women who were overweight and/or had obesity were more likely to have gestational diabetes, smoke, deliver by caesarean section and formula feed their infants; their infants were more likely to have high birthweight and be exposed to antibiotics ($p < 0.05$, chi-square test). Formula feeding, high birthweight and exposure to antibiotics were all significantly associated with child overweight/obesity at age 1 year.

A total of 891 mother–infant dyads had complete data on pre-pregnancy overweight and infant overweight risk. Maternal pre-pregnancy overweight and obesity both increased the risk of infant overweight/obesity at age 1 (OR 2.51, 95%CI 1.16–5.44 and 3.33, 95%CI 1.53–7.23, respectively, Model 1, Table 2). Adjustment for gestational diabetes, high sugar consumption, pre/postnatal smoking exposures ('Pregnancy variables', Model 2) and infant sex reduced the magnitude of the association between maternal obesity and infant overweight/obesity (adjusted OR 2.62, 95%CI 1.10–6.22). Controlling for pregnancy-related variables did not alter the risk from maternal overweight alone. Adjustment for the intermediate outcome (24), high birthweight status (Model 3), also lowered the risk for child overweight if the mother was overweight but did not have obesity (adjusted OR 2.38, 95% CI: 1.09–5.22). In this model, risk of overweight was fourfold higher in high birthweight infants. In a model, which included mode of delivery, exclusive breast feeding and infant antibiotic exposure ('Microbiota variables', Model 4), associations between maternal overweight and obesity and infant overweight were attenuated (adjusted OR 2.20, 95%CI:1.00–4.83

Table 1 Frequency distribution of maternal pre-pregnancy and infant overweight according to study covariates

	Overall prevalence		Maternal pre-pregnancy weight status						Overweight or obese at 1 year of age			
			Total count	Overweight		Obese			Total count			
	N	%	*N*	*N*	%	*N*	%	*p*	*N*	*N*	%	*p*
Race/Ethnicity												
White	721	77.5	705	171	24.3	134	19.0	0.26	695	25	3.6	<0.01
Asian	88	9.5	86	18	20.9	9	10.5		84	4	4.8	
Other	121	13.0	118	32	27.1	34	28.8		106	12	11.3	
Maternal gestational diabetes (GDM)												
Yes	40	4.2	38	12	31.6	17	44.7	<0.001	36	2	5.6	0.77
No	908	95.8	891	219	24.6	163	18.3		864	39	4.5	
Maternal prenatal diet (added sugar exceeds daily recommendations)												
Yes (>24 g)	816	93.2	798	191	23.9	156	19.5	0.23	785	35	4.5	0.38
No (≤24 g)	60	6.8	59	20	33.9	10	16.9		57	4	7.0	
Maternal/household smoke exposure												
None	528	57.6	517	124	24.0	70	13.5	<0.001	519	19	3.7	0.15
Pre + Postnatal	222	24.2	220	55	25.0	61	27.7		200	14	7.0	
Postnatal only	166	18.1	161	46	28.6	39	24.2		163	7	4.3	
Caesarean section delivery												
Yes	185	19.5	180	47	26.1	54	30.0	<0.001	176	11	6.3	0.27
No	765	80.5	746	182	24.4	125	16.8		722	31	4.3	
Birthweight												
High (>4 kg)	135	14.3	131	36	27.5	35	26.7	0.02	130	16	12.3	<0.001
Normal (≤4 kg)	811	85.7	791	192	24.3	142	18.0		764	25	3.3	
Breastfeeding status at 3 months												
Exclusive	534	57.0	519	122	23.5	72	13.9	<0.001	518	13	2.5	<0.001
Partial	210	22.4	209	60	28.7	39	18.7		204	10	4.9	
None	193	20.6	188	47	25.0	64	34.0		175	18	10.3	
Infant antibiotic exposure												
None	513	54.3	501	114	22.8	70	14.0	<0.001	485	15	3.1	0.04
Indirect ONLY	330	35.0	320	87	27.2	79	24.7		313	17	5.4	
Direct or direct + indirect	101	10.7	99	27	27.3	26	26.3		94	8	8.5	
Infant sex												
Female	471	49.3	457	119	26.0	98	21.4	0.11	443	17	3.8	0.26
Male	484	50.7	474	112	23.6	82	17.3		460	25	5.4	

Table 2 Associations between maternal pre-pregnancy overweight and infant risk of overweight/obesity at 1 year of age

Odds ratio (OR), 95%CI	Reference category	*N* (for crude model)	Model 1 Unadjusted	Model 2 *N* = 820 Adjusted for sex and maternal pregnancy variables	Model 3 *N* = 882 Adjusted for sex and infant birthweight	Model 4 *N* = 875 Adjusted for sex and microbiota-associated variables
Pre-pregnancy weight:						
Overweight (25 ≤ BMI < 30)	Normal weight	891	2.51 (1.16–5.44)*	2.51 (1.11–5.67)*	2.38 (1.09–5.22)*	2.20 (1.00–4.83)*
Obese (BMI ≥ 30)			3.33 (1.53–7.23)**	2.62 (1.10–6.22)*	2.77 (1.24–6.21)*	2.13 (0.92–4.91)
Maternal gestational diabetes	No GDM	900	1.24 (0.29–5.37)	1.03 (0.22–4.73)		
Maternal diet (added sugar >24 g)	≤24 g/day	842	0.62 (0.21–1.81)	0.65 (0.21–1.97)		
Smoking – pre + postnatal	No household smoking	882	1.98 (0.97–4.03)	1.75 (0.81–3.75)		
Smoking – postnatal only			1.18 (0.49–2.86)	0.97 (0.37–2.55)		
High birthweight (>4 kg)	Normal birthweight	894	4.14 (2.15–8.01)***		3.77 (1.91–7.43)***	
Caesarean section delivery	Vaginal delivery	898	1.49 (0.73–3.02)			0.91 (0.38–2.16)
Exclusively breastfed at 3 months	No exclusive breastfeeding at 3 months	897	0.32 (0.17–0.63)***			0.32 (0.16–0.67)**
Infant antibiotic exposure:						
Indirect ONLY	No antibiotics	892	1.80 (0.88–3.66)			1.55 (0.67–3.60)
Direct or direct + indirect			2.92 (1.20–7.09)*			2.35 (0.91–6.06)
Male sex	Female	903	1.44 (0.77–2.71)	1.85 (0.92–3.74)	1.37 (0.70–2.66)	1.32 (0.67–2.59)

Outcome variable: child overweight/obesity at 1 year; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 3 Associations between maternal pre-pregnancy overweight and risk of overweight/obesity at 1 year of age for male and female infants

Odds ratio (OR), 95%CI	Reference Category	*N* for crude model	Model 1 (Males) Unadjusted crude OR	Model 4 (Males) *N* = 446 Adjusted for microbiota-associated variables	*N* for crude model	Model 1 (Females) Unadjusted crude OR	Model 4 (Females) *N* = 429 Adjusted for microbiota-associated variables
Pre-pregnancy weight:							
Overweight (25 ≤ BMI < 30)	Normal weight	453	3.03 (1.07–8.58)*	2.66 (0.92–7.64)	438	2.05 (0.65–6.49)	1.65 (0.50–5.45)
Obese (BMI ≥ 30)			5.31 (1.95–14.44)**	3.32 (1.13–9.75)*		1.72 (0.48–6.26)	1.09 (0.28–4.23)
Caesarean section delivery	Vaginal delivery	458	2.17 (0.93–5.08)	1.64 (0.51–5.32)	440	0.61 (0.14–2.72)	0.36 (0.07–1.80)
Exclusively breastfed at 3 months	No exclusive breastfeeding	457	0.38 (0.16–0.91)*	0.43 (0.17–1.08)	440	0.26 (0.09–0.76)*	0.22 (0.07–0.70)*
Infant antibiotic exposure:							
Indirect ONLY	No antibiotics	455	1.58 (0.61–4.07)	0.93 (0.27–3.26)	437	2.13 (0.72–6.25)	2.56 (0.78–8.42)
Direct or direct + indirect			2.19 (0.71–6.79)	1.42 (0.42–4.83)		4.30 (1.02–18.17)*	5.91 (1.29–27.20)*

Outcome variable: child overweight/obesity at 1 year; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

and 2.13, 95%CI 0.92–4.91 respectively). Exclusive breastfeeding independently lowered the risk of infant overweight by 68% in this model (adjusted OR 0.32, 95%CI 0.16–0.67).

In the sex-specific regression models (Table 3), boys born to mothers with obesity were three times more likely to become overweight or have obesity at age 1, independent of mode of delivery, infant diet and antibiotic exposure (adjusted OR: 3.32, 95%CI:1.13–9.75). Additional adjustment for maternal ethnicity did not change this association (data not shown). Breastfeeding status lost statistical significance in the sex-specific model for boys, but not girls. In contrast, the increased prevalence of overweight in female infants following maternal pre-pregnancy overweight or obesity was not statistically significant (unadjusted OR: 2.05; 95%CI: 0.65–6.49 and 1.72, 95%CI 0.48–6.26). This association further approached the null after adjustment for the 3 microbiota-related covariates. Overweight risk was significantly reduced among female infants who were exclusively breastfed, independent of maternal overweight, caesarean section and antibiotic exposure (adjusted OR: 0.22; 95% CI:0.07–0.70). Only in female infants was there an independent association between overweight and antibiotic treatment by age 3 months, with or without maternal intrapartum antibiotic prophylaxis.

Using child WFL z-score as the outcome (Table 4), crude associations were observed with pre-pregnancy overweight, obesity and maternal pre-postnatal smoking. Adjustment for pregnancy, infant or gut microbiota related variables did not alter the association with maternal overweight/obesity in all children. Significant sex-specific associations with infant overweight were observed for pre-pregnancy obesity but not overweight (Table 5); the association remained in both sexes following adjustment for microbiota-affecting variables. Additional adjustment for maternal ethnicity strengthened the association between maternal obesity and WFL z-score in male infants (beta-coefficient, 0.53, $p < 0.0001$) and in female infants (beta-coefficient, 0.34, $p = 0.01$). In this adjusted model, breastfeeding was inversely related with WFL z-score in female but not male infants.

Discussion

In a cohort of 955 pregnant women, of whom over 40% were overweight or had obesity prior to pregnancy, an association between pre-pregnancy overweight/obesity and child overweight (>97th centile WFL z-score) was already evident at 1 year of age. Maternal pre-pregnancy obesity presented

more than a threefold risk for infant overweight (OR 3.33, 95%CI 1.53–7.23). This association was independent of maternal gestational diabetes or high sugar consumption, tobacco smoking exposure and high birthweight, although adjustment for these factors attenuated the association. Our results are consistent with the Bider-Canfield *et al*. study on childhood overweight at age 2 years (11); they also align with results from two Asian cohorts, in which pre-pregnancy BMI was positively associated with infant overweight/obesity status and WFL z-score at 12 months of age (13,14). In our study, when breastfeeding or antibiotic exposure by 3 months of age and birth mode were taken into account, the magnitude of the association with child overweight was diminished to a much greater extent following maternal obesity than maternal overweight. Hence, our findings indicate that caesarean delivery, maternal or infant antibiotic use, and absence of early breastfeeding, which are common outcomes for women with obesity (1) and are known to cause infant gut dysbiosis (25), are factors in the pathway between extremes in maternal overweight during pregnancy and overweight status in infants.

On the other hand, similar to Li *et al*. (14), a diminishment in statistical association was not observed with maternal overweight or obesity following adjustment for microbiota-altering variables when the outcome variable was WFL z-score rather than extreme values beyond the 97th centile cut-off for overweight. Because our findings for WFL z-score were found equally in male and female infants and were found to be independent of birth and postnatal microbiota-altering events, it is likely that this propensity for higher WFL commences *in utero*. Fetal programming of offspring adiposity is posited to manifest through impaired glucose tolerance, insulin resistance, leptin resistance, elevated hepatic lipogenesis and ectopic lipid deposition in the liver and pancreas (3,26). *In utero* pathways may also involve the maternal vaginal and gut microbiomes, which undergo change during pregnancy (16) and the transfer of microbial metabolites, the short-chain fatty acids, which can alter energy harvest, metabolic signalling or inflammation (27).

In our study population, the association between pre-pregnancy overweight or obesity and child overweight at age 1 was largely driven by male infants because associations observed for 1-year-old infant were not statistically significant. The risk for overweight in male infants was threefold higher following pre-pregnancy obesity independent of birth and postnatal microbiota-affecting variables. Sex hormones such as testosterone, which are elevated to a greater extent in boys than girls before 3 months of age, have the capacity to influence growth (28). On the other hand, leptin, an appetite suppressant, is also present at higher levels in female infants than in male infants at birth and 3 months later (29). Both hormones are elevated with pregnancy overweight (26,30). Finally, obesity-related microbes, metabolites or hormones that preferentially affect the weight of male fetuses, may also influence postnatal gut microbial composition (16). This finding offers an explanation for why pregnancy and postnatal microbiota risk factors for overweight might be inter-related in male infants and why adjustment with microbiota-affecting variables reduced the crude fivefold risk associated with maternal obesity.

Consistent with older studies (19), exclusive breastfeeding until 3 months of age was inversely associated with infant WFL z-score; it substantially lowered the risk of child overweight at 1 year in male and especially in female infants. More recently, a study of Asian infants found breastfeeding to be more protective against overweight in male infants (17). Several studies have now linked infant antibiotic use and child overweight, including one by Saari *et al*. that reported an association with overweight development during the first 24 months of life (19). In our study, postnatal (with or without maternal intrapartum) antibiotic use by 3 months of age was the sole factor in female infants to raise the likelihood of the extreme overweight phenotype. This association was absent in male infants, inconsistent with the disproportionate influence of antibiotic treatment on overweight among male children in later life (16). As noted earlier, breastfeeding or caesarean section associations with overweight were not independent of maternal overweight in our male infants. Finally, as shown by others, the association between pre-pregnancy overweight and infant overweight was independent of gestational diabetes (11).

Strengths of this research include a large sample size of mother–infant pairs from a general population cohort, which permitted sex-specific analyses and assessment of overweight phenotypic extremes in the mother and infant. Anthropometric measures of infants were standardized, following precise and detailed measurement protocols, and calculated according to the WHO age-appropriate classification for WFL (23). Trained staff retrieved pre-pregnancy anthropometric data from birth chart reviews. Information on maternal prenatal diet, smoking habits and gestational diabetes was prospectively collected for the duration of the pregnancy and postnatally, so there was no time lag leading to

Table 4 Linear relationships between maternal pre-pregnancy overweight and infant WFL z-score at 1 year

β (beta coefficient), 95%CI	Reference category	*N* (for crude model)	Model 1 Unadjusted	Model 2 *N* = 820 Adjusted for sex and maternal pregnancy variables	Model 3 *N* = 882 Adjusted for sex and infant birthweight	Model 4 *N* = 875 Adjusted for sex and microbiota-associated variables
Pre-pregnancy weight:						
Overweight (25 ≤ BMI < 30)	Normal weight	891	0.09 (0.05 to 0.39)*	0.09 (0.05 to 0.40)*	0.08 (0.02 to 0.36)*	0.08 (0.02 to 0.37)*
Obese (BMI ≥ 30)			0.19 (0.35 to 0.72)***	0.17 (0.27 to 0.66)***	0.17 (0.28 to 0.65)***	0.17 (0.27 to 0.66)***
Maternal gestational diabetes	No GDM	900	0.05 (−0.11 to 0.62)	0.02 (−0.26 to 0.49)		
Maternal diet (added sugar >24 g)	≤24 g/day	842	−0.01 (−0.35 to 0.23)	−0.01 (−0.32 to 0.26)		
Smoking – pre + postnatal	No household	882	0.10 (0.08 to 0.43)**	0.07 (−0.01 to 0.35)		
Smoking – postnatal only	smoking		0.05 (−0.06 to 0.32)	0.01 (−0.16 to 0.23)		
High birthweight (>4 kg)	Normal birthweight	894	0.19 (0.39 to 0.79)***		0.17 (0.34 to 0.74)***	
Caesarean section delivery	Vaginal delivery	898	−0.001 (−0.18 to 0.18)			−0.06 (−0.36 to 0.06)
Exclusively breastfed at 3 months	No exclusive breastfeeding at 3 months	897	−0.14 (−0.44 to −0.16)***			−0.12 (−0.40 to −0.11)**
Infant antibiotic exposure:						
Indirect ONLY	No antibiotics	892	0.03 (−0.09 to 0.22)			0.03 (−0.11 to 0.26)
Direct or direct + indirect			0.05 (−0.06 to 0.43)			0.04 (−0.12 to 0.38)
Male sex	Female	903	0.01 (−0.11 to 0.17)	0.04 (−0.07 to 0.22)	0.004 (−0.13 to 0.15)	0.02 (−0.11 to 0.18)

Outcome variable: Weight-for-length (WFL) z-score at 1 year; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 5 Linear relationships between maternal pre-pregnancy overweight and WFL z-score at 1 year for male and female infants

β (beta coefficient), 95%CI	Reference category	*N* for crude model	Model 1 (Males) Unadjusted	Model 4 (Males) *N* = 446 Adjusted for microbiota-associated variables	*N* for crude model	Model 1 (Females) Unadjusted	Model 4 (Females) *N* = 429 Adjusted for microbiota-associated variables
Pre-pregnancy weight:							
Overweight (25 ≤ BMI < 30)	Normal weight	453	0.09 (−0.12 to 0.48)	0.08 (−0.05 to 0.45)	438	0.09 (−0.03 to 0.43)	0.08 (−0.05 to 0.41)
Obese (BMI ≥ 30)			0.22 (0.38 to 0.93)***	0.19 (0.29 to 0.86)***		0.17 (0.18 to 0.68)**	0.14 (0.10 to 0.63)**
Cesarean delivery	Vaginal delivery	458	0.02 (−0.21 to 0.30)	−0.04 (−0.42 to 0.20)	440	−0.02 (−0.32 to 0.20)	−0.07 (−0.49 to 0.12)
Exclusively breastfed at 3 months	No exclusive breastfeeding	457	−0.11 (−0.45 to −0.03)*	−0.08 (−0.40 to 0.02)	440	−0.17 (−0.56 to −0.16)***	−0.15 (−0.53 to −0.12)**
Infant antibiotic exposure:							
Indirect ONLY	No antibiotics	455	0.01 (−0.20 to 0.26)	0.01 (−0.26 to 0.29)	437	0.05 (−0.10 to 0.32)	0.06 (−0.12 to 0.37)
Direct or direct + indirect			0.07 (−0.10 to 0.53)	0.04 (−0.19 to 0.45)		0.03 (−0.29 to 0.50)	0.03 (−0.29 to 0.53)

Outcome variable: WFL z-score at 1 year; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

recall bias. We also pursued a systematic approach to logistic regression modelling by adjusting for covariates, including exposures that strongly affected the gut microbiome. On the other hand, pre-pregnancy maternal weight was derived from maternal recall or medical records rather than by actual measurements.

In conclusion, while other studies have been conducted on pregnancy overweight and child overweight in Canada (15), ours is the first to report on the impact of maternal overweight and obesity prior to pregnancy on overweight in Canadian children as early as 1 year of age. Interesting sex differences were seen, with male infants being disproportionately affected, and they require further study. Evidence that maternal pre-pregnancy overweight has an impact on early infant growth, with a potential for later development of chronic diseases, is essential to inform interventions that target excess weight in women of reproductive age. These same interventions will also be beneficial in reducing perinatal complications such as gestational diabetes, hypertensive disorders of pregnancy and large for gestational age birthweights.

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Conflict of interest statement

No conflict of interest was declared.

References

1. Poston L, Caleyachetty R, Cnattingius S, *et al*. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol* 2016; 4: 1025–1036.
2. Public Health Agency of Canada. What mothers say: the Canadian Maternity Experiences Survey 2009; [WWW document] URL http://www.publichealth.gc.ca/mes. Accessed 2017
3. Penfold NC, Ozanne SE. Developmental programming by maternal obesity in 2015: outcomes, mechanisms, and potential interventions. *Horm Behav* 2015; 76: 143–152.
4. Shields M. Overweight and obesity among children and youth. *Health Rep* 2006; 17: 27–42.
5. Godfrey KM, Reynolds RM, Prescott SL, *et al*. Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol* 2017; 5: 53–64.
6. Weng SF, Redsell SA, Swift JA, Yang M, Glazebrook CP. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. *Arch Dis Child* 2012; 97: 1019–1026.
7. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PLoS One* 2013; 8: e61627.
8. Salsberry PJ, Reagan PB. Dynamics of early childhood overweight. *Pediatrics* 2005; 116: 1329–1338.
9. Hawkins SS, Cole TJ, Law C. An ecological systems approach to examining risk factors for early childhood overweight: findings from the UK Millennium Cohort Study. *J Epidemiol Community Health* 2009; 63: 147–155.
10. Pizzi C, Cole TJ, Richiardi L, dos-Santos-Silva I, Corvalan C, De Stavola B. Prenatal influences on size, velocity and tempo of infant growth: findings from three contemporary cohorts. *PLoS One* 2014; 9.
11. Bider-Canfield Z, Martinez MP, Wang X, *et al*. Maternal obesity, gestational diabetes, breastfeeding and childhood overweight at age 2 years. *Pediatr Obes* 2016; 12: 171–178.
12. Makela J, Lagstrom H, Kaljonen A, Simell O, Niinikoski H. Hyperglycemia and lower diet quality in pregnant overweight women and increased infant size at birth and at 13 months of age – STEPS study. *Early Hum Dev* 2013; 89: 439–444.
13. Zalbahar N, Jan Mohamed HJ, Loy SL, Najman J, McIntyre HD, Mamun A. Association of parental body mass index before pregnancy on infant growth and body composition: evidence from a pregnancy cohort study in Malaysia. *Obes Res Clin Pract* 2016; 10: S35–s47.
14. Li N, Liu E, Guo J, *et al*. Maternal prepregnancy body mass index and gestational weight gain on offspring overweight in early infancy. *PLoS One* 2013; 8: e77809.
15. Roberts KC, Shields M, de Groh M, Aziz A, Gilbert J-A. Overweight and obesity in children and adolescents: results from the 2009 to 2011 Canadian Health Measures Survey. *Health Rep* 2012; 23: 37–41.
16. Kozyrskyj AL, Kalu R, Koleva PT, Bridgman SL. Fetal programming of overweight through the microbiome: boys are disproportionately affected. *J Dev Orig Health Dis* 2016; 7: 25–34.
17. Zheng JS, Liu H, Li J, *et al*. Exclusive breastfeeding is inversely associated with risk of childhood overweight in a large Chinese cohort. *J Nutr* 2014; 144: 1454–1459.
18. Newbern D, Gumus Balikcioglu P, Balikcioglu M, *et al*. Sex differences in biomarkers associated with insulin resistance in obese adolescents: metabolomic profiling and principal components analysis. *J Clin Endocrinol Metab* 2014; 99: 4730–4739.
19. Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk factors for childhood obesity in the first 1,000 days: A Systematic Review. *Am J Prev Med* 2016; 50: 761–779.

20. Canadian Healthy Infant Longitudinal Development (CHILD) study 2013; [WWW document] URL http://www.childstudy.ca/methods.html. Accessed 2017.

21. Eveleth PB. Physical status: the use and interpretation of anthropometry. report of a WHO Expert Committee-WHO. *Am J Hum Biol* 1996; 8: 786–787.

22. Group WHOMGRS. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* 2006; 450: 76–85.

23. Johnson RK, Appel LJ, Brands M, *et al*. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 2009; 120: 1011–1020.

24. Giles LC, Whitrow MJ, Davies MJ, Davies CE, Rumbold AR, Moore VM. Growth trajectories in early childhood, their relationship with antenatal and postnatal factors, and development of obesity by age 9 years: results from an Australian birth cohort study. *Int J Obes (Lond)* 2015; 39: 1049–1056.

25. Kozyrskyj AL, Bridgman SL, Tun MH. Chapter 4 The impact of birth and postnatal medical interventions on infant gut microbiota. In: Browne PD, Claassen E, Cabana MD (eds). *Microbiota in Health and Disease: From Pregnancy to Childhood*, 2017, pp. 79–104.

26. Briffa JF, McAinch AJ, Romano T, Wlodek ME, Hryciw DH. Leptin in pregnancy and development: a contributor to adulthood disease? *Am J Physiol Endocrinol Metab* 2015; 308: E335–E350.

27. Kumari M, Kozyrskyj AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev* 2017; 18: 18–31.

28. Winter JS, Hughes IA, Reyes FI, Faiman C. Pituitary-gonadal relations in infancy: 2. Patterns of serum gonadal steroid concentrations in man from birth to two years of age. *J Clin Endocrinol Metab* 1976; 42: 679–686.

29. Trevino-Garza C, Bosques-Padilla FJ, Estrada-Zuniga CM, *et al*. Typical leptin fall is mitigated by breastfeeding in female infants. *Arch Med Res* 2010; 41: 373–377.

30. Maliqueo M, Cruz G, Espina C, *et al*. Obesity during pregnancy affects sex steroid concentrations depending on fetal gender. *Int J Obes (Lond)* 2017. https://doi.org/10.1038/ijo.2017.159.