IMPORTANCE Maternal overweight, which often results in cesarean delivery, is a strong risk factor for child overweight. Little is known about the joint contribution of birth mode and microbiota in the infant gut to the association between maternal prepregnancy overweight and child overweight.

OBJECTIVE To investigate the association of birth mode with microbiota in the infant gut, and whether this mediates the association between maternal and child overweight.

DESIGN, SETTING, AND PARTICIPANTS An observational study was conducted of 935 full-term infants born between January 1, 2009, and December 31, 2012, in the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort. Maternal prepregnancy body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared using height and weight data taken from medical records or maternal report. Infant gut microbiota were profiled with 16S rRNA sequencing in fecal samples collected at a mean (SD) age of 3.7 (1.0) months. At ages 1 and 3 years, BMI z scores adjusted for age and sex were generated according to World Health Organization criteria. Statistical analysis was conducted from January 29 to June 15, 2017.

EXPOSURES Mothers of normal weight (BMI, 18.5-24.9) and overweight or obese (BMI, ≥25.0) mothers.

MAIN OUTCOME AND MEASURES Risk of overweight and obesity (>97th percentile BMI z scores) among children at ages 1 and 3 years.

RESULTS Of the 935 mother-infant pairs in the study (mean [SD] age, 32.5 [4.5] years) 382 (40.9%) were overweight, 69 of 926 infants (7.5%) were overweight at age 1 year, and 90 of 866 infants (10.4%) were overweight at age 3 years. Compared with being born vaginally to a mother of normal weight, infants born vaginally to overweight or obese mothers were 3 times more likely to become overweight at age 1 year (adjusted odds ratio [OR], 3.33; 95% CI, 1.49-7.41), while cesarean-delivered infants of overweight mothers had a 5-fold risk of overweight at age 1 year (adjusted OR, 5.02; 95% CI, 2.04-12.38). Similar risks were also observed at age 3 years. Multiple mediator path modeling revealed that birth mode and infant gut microbiota (Firmicutes species richness, especially of the Lachnospiraceae family) sequentially mediated the association between maternal prepregnancy overweight and childhood overweight at ages 1 and 3 years. Bacterial genera belonging to the Lachnospiraceae family were more abundant in infants of overweight mothers; however, the participating genera of Lachnospiraceae differed between infants delivered vaginally and those delivered via cesarean birth.

CONCLUSIONS AND RELEVANCE This study found evidence of a novel sequential mediator pathway involving birth mode and Firmicutes species richness (especially higher abundance of Lachnospiraceae) for the intergenerational transmission of overweight.
Childhood obesity is a global health concern. More than 20% of preschool-aged children in Canada are overweight or obese (OWOB). Also on the rise is maternal OWOB during pregnancy and associated higher rates of birth by cesarean delivery. Furthermore, carrying OWOB into pregnancy presents, at minimum, a 2-fold greater risk of obesity in offspring. Some of this excess risk can be attributed to cesarean delivery, as children delivered by this method are 30% more likely to develop OWOB compared with those delivered vaginally. However, while the epidemiologic evidence is strong that prenatal maternal obesity predisposes newborns to develop OWOB, the mechanism behind this intergenerational association has not, to our knowledge, been delineated by known genetic or lifestyle factors shared between mothers and their offspring.

Mother-to-newborn transfer of obesogenic microbes has been put forward as a biological pathway for the intergenerational transmission of OWOB. Substantial changes to the intestinal microbiota of women are observed as pregnancy progresses to parturition. The weight status of women entering pregnancy can modify this process. Compared with their normal-weight counterparts, women with a high prepregnancy body mass index (BMI) have elevated levels of Bacteroides in their third trimester. Because maternal microbiota are the primary source for the first inoculation of newborn infants and microbiota have been implicated in adipogenesis, it is conceivable that prepregnancy weight and the maternal intestinal microbiome influence microbial assembly in the infant gut, as well as OWOB outcomes.

Several studies have investigated maternal OWOB-associated changes in microbiota of the infant gut. Prepregnancy overweight has been found to affect microbial composition in infant stool, as seen in Bacteroides species, at the ages of 1 month, 6 months, and 2 years. Microbial compositional changes associated with maternal OWOB are more evident in newborns after vaginal rather than cesarean delivery, and, for the latter, reductions in Bacteroides are seen. No gut dysbiosis in relation to maternal OWOB has been found in later infancy at ages 9 and 18 months. Although cesarean delivery alters the structure of gut microbiota during early life, it remains to be determined whether birth mode plays a role in maternal OWOB-related changes to the microflora of the infant gut and subsequent risk for OWOB. To address this gap in knowledge, we determined the joint associations of maternal prepregnancy OWOB and birth mode with microbial composition of the infant gut and microbiota interactions at ages 3 to 4 months, and with OWOB outcomes at ages 1 and 3 years. Second, we assessed whether microbiota of the infant gut mediated the association between maternal OWOB and child OWOB, and whether the mediation was dependent on birth mode.

Key Points

Question: Do birth mode and microbiota in the infant gut mediate the association between maternal prepregnancy overweight and childhood overweight?

Findings: In this cohort study of 935 mother-infant pairs, both vaginally and cesarean-delivered infants born to overweight and obese mothers were at greater risk of being overweight at ages 1 and 3 years compared with infants born vaginally to a mother of normal weight. Birth mode and microbiota in the infant gut (especially Lachnospiraceae) act sequentially to mediate the association between maternal prepregnancy overweight and child overweight.

Meaning: Together, birth mode and Lachnospiraceae family microbiota in the infant gut sequentially mediate the intergenerational association of overweight, underscoring their potential contributions in developing child overweight and obesity.

Methods

Study Design

This study involved a subsample of 935 Canadian full-term infants from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort (http://www.childstudy.ca). Mothers of studied infants were enrolled during pregnancy between January 1, 2009, and December 31, 2012. Maternal BMI was calculated as weight in kilograms divided by height in meters squared using measured height and self-reported prepregnancy weight or estimated from measured weight at 1 year post partum. Validation against prenatal records showed that prepregnancy weight was slightly underestimated by maternal recall (mean difference, –1.0 kg; 95% CI, –1.5 to –0.4 kg) and slightly overestimated by measured weight at 1 year post partum (mean difference, 1.3 kg; 95% CI, 0.5–2.2 kg). Maternal BMI was classified as normal weight (BMI, 18.5–24.9 [553 mothers]) and overweight and obese (BMI, ≥25.0 [382 mothers]). Child OWOB was defined as BMI z scores greater than the 97th percentile according to World Health Organization criteria; scores were generated from weight and height measured at ages 1 and 3 years. Data on covariates were obtained from hospital records (birth mode and intrapartum antibiotic prophylaxis) or standardized questionnaires (maternal race/ethnicity, maternal asthma or allergy status, smoking during pregnancy, infant sex, infant direct antibiotic exposure by age 1 year, breastfeeding status before 3 months, siblingship, and pet ownership). The Human Research Ethics boards at the University of Alberta, University of Manitoba, and University of British Columbia approved this study. Written informed consent was obtained from parents at enrollment.

Fecal Microbiota Analysis

Fecal samples of infants were collected at a mean (SD) age of 3.7 (1.0) months using a standard protocol during a planned home visit. Methods of sample collection, DNA extraction and amplification, 16S ribosomal RNA sequencing, and taxonomic classification have been previously described (eAppendix in the Supplement).

Statistical Analysis

Statistical analysis was conducted from January 29 to June 15, 2017. The association between maternal OWOB and cesarean vs vaginal delivery, or a 4-category variable for birth mode
(vaginal without IAP, vaginal with IAP, scheduled cesarean delivery with IAP, and emergency cesarean delivery with IAP), was determined by binary and multinomial logistic regression, adjusting for location, infant sex, maternal race/ethnicity, maternal prenatal asthma, and maternal smoking during pregnancy. Logistic regression models were performed after covariate adjustment to test associations between maternal weight status (OWOB vs normal weight) or joint categories of maternal OWOB and birth mode with childhood OWOB (at ages 1 and 3 years) and microbiota of the infant gut (overall Chao1, Chao1, and Shannon indices of Firmicutes).

The association of maternal OWOB with microbiota of the infant gut (richness, a and β diversity, and relative abundance of taxa) was examined by a nonparametric Kruskal-Wallis test followed by post hoc comparison using the Dunn test. As evaluated by others,29,30 the coexistence of gut microbiota was measured as the Firmicutes to Bacteroidetes and Enterobacteriaceae to Bacteroidaceae ratios. Regression models of gut microbial measures (higher vs lower values based on a median cutoff) were performed against maternal OWOB and birth mode. Mediation analysis was conducted using the Hayes PROCESS macro in SPSS, version 23.0 (SPSS Inc), to permit evaluation of sequential mediators for the maternal-child OWOB association. A multiple mediator path model was evaluated to examine indirect associations of the 4-category variable of birth mode (mediator 1) and a diversity or relative abundance (categorized into tertiles) of microbiota of the infant gut at the family level (mediator 2). Bootstrapping, a nonparametric resampling procedure (5000 bootstrap resamples),31,32 was used to generate 95% CIs in mediation models. Microbial interaction networks by maternal-child OWOB group were built using the Spearman correlation coefficient (ρ > 0.3 or <−0.3) and visualized with Cytoscape, version 3.5.1.33 To identify discriminative biomarkers for maternal OWOB to children, the linear discriminant analysis effect size (LEfSe) was determined with a linear discriminant analysis log score cutoff of 2.34

Results

In this population-based cohort of 935 mother-infant pairs, 382 mothers (40.9%) were OWOB, 69 of 926 infants (7.5%) became OWOB at 1 year, and 90 of 866 infants (10.4%) became OWOB at 3 years (Table). Childhood weight status was associated with maternal weight status. Significant differences in the prevalence of childhood OWOB at age 1 or 3 years were found according to study location, infant sex, maternal prenatal asthma, maternal smoking during pregnancy, and direct exposure of infants to antibiotics. Prepregnancy rates of OWOB were higher in women who gave birth by cesarean delivery and who partially breastfed or did not breastfeed their infants.

Association Between Maternal OWOB and Cesarean Delivery

Almost half of mothers delivering by cesarean delivery had prepregnancy OWOB (Table). After covariate adjustment, maternal OWOB was associated with a 1.50 (95% CI, 1.10-2.07) times greater odds of cesarean delivery. A similar association was also observed for maternal BMI z score (eFigure 1A in the Supplement). Overweight or obese mothers were more likely to undergo scheduled cesarean delivery or to have an emergency cesarean delivery than to deliver vaginally without IAP (eFigure 1B in the Supplement).

Impact of Maternal OWOB on Childhood OWOB at Ages 1 and 3 Years

As seen in Figure 1A and B, infants born to OWOB mothers were more likely to become OWOB at ages 1 year (adjusted odds ratio [OR], 3.80; 95% CI, 1.88-7.66) and 3 years (adjusted OR, 3.79; 95% CI, 2.10-6.84). This association was also significant with the maternal BMI z score (eTable 1 in the Supplement). Compared with vaginal delivery without IAP (reference group), emergency cesarean delivery was associated with a 2-fold greater odds of childhood OWOB at ages 1 and 3 years, but not after covariate adjustment (Figure 1A and B and eTable 1 in the Supplement). Joint associations of maternal weight status and birth mode with childhood OWOB were observed after covariate adjustment (Figure 1C and D). Compared with infants delivered vaginally to normal-weight mothers without IAP (reference group), vaginally delivered infants of OWOB mothers had approximately 3 times greater odds of OWOB at ages 1 year (3.33; 95% CI, 1.49-7.41) and 3 years (3.07; 95% CI, 1.58-5.96), whereas cesarean-delivered infants of OWOB mothers had approximately 5 times greater odds of OWOB at ages 1 year (5.02; 95% CI, 2.04-12.38) and 3 years (5.53; 95% CI, 2.55-12.04). The joint association with maternal OWOB was more prominent for emergency cesarean delivery than scheduled cesarean delivery (Figure 1C and D and eTable 1 in the Supplement).

Association of Maternal OWOB With Microbiota of the Infant Gut

Microbiota β diversity differed by maternal weight status (pseudo F = 3.14; P = .001 for unweighted UniFrac; pseudo F = 2.45; P = .06 for weighted UniFrac). Infants born to OWOB mothers had greater species richness (Chao1) in their gut microbiota, especially within the Firmicutes phyla; the diversity of the Firmicutes phyla was also higher (eTable 2 in the Supplement). Associations with higher Chao1 richness were independent of birth mode (eTable 3 in the Supplement). The Proteobacterial families Enterobacteriaceae and Pasteurellaceae were less abundant in infants born to OWOB vs normal-weight mothers, whereas 4 bacterial families (Coriobacteriaceae, Erysipelotrichaceae, Lachnospiraceae, and Ruminococcaceae) belonging to Actinobacteria and Firmicutes were more abundant (eTable 2 in the Supplement). Only maternal OWOB-associated changes in the Enterobacteriaceae to Bacteroidaceae ratio remained statistically significant after covariate adjustment (eTable 4 in the Supplement). Our LEfSe analysis indicated that several genera, including those of the Lachnospiraceae family, were significantly higher in infants born to OWOB mothers (eFigure 2 in the Supplement).

Joint Associations of Maternal OWOB and Birth Mode With Microbiota of the Infant Gut

Infants of OWOB mothers born via emergency cesarean delivery were twice more likely than vaginally born infants...
of normal-weight mothers to have higher Firmicutes richness (eTable 5 in the Supplement). Jointly, maternal OWOB and emergency cesarean delivery were significantly associated with a higher abundance of fecal Lachnospiraceae in infants (adjusted OR, 2.02; 95% CI, 1.06-3.87) and of several other microbiota at the family level. Few family-level differences in gut microbiota were found after maternal OWOB and vaginal birth.

<table>
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<tr>
<th>Characteristic</th>
<th>Maternal OWOB (n = 382/935 [40.9%])</th>
<th>P Value</th>
<th>Childhood OWOB at 1 y (n = 60/926 [7.5%])</th>
<th>P Value</th>
<th>Childhood OWOB at 3 y (n = 90/866 [10.4%])</th>
<th>P Value</th>
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<td>Winnipeg, Manitoba</td>
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<td>Vaginal, IAP−</td>
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<td>26/202 (12.9)</td>
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<td>9/120 (7.5)</td>
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<td>Partial</td>
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<td>Exclusive</td>
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<td>Only prenatal</td>
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<td>4/67 (6.0)</td>
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<td>Both prenatal and postnatal</td>
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<td>34/401 (8.5)</td>
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<td>46/383 (12.0)</td>
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<td>Maternal prepregnancy weight status, No. (%)</td>
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<td>Normal</td>
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<td>&lt;.001</td>
<td>24/507 (4.7)</td>
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<td>45/371 (12.1)</td>
<td></td>
<td>63/328 (19.2)</td>
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</table>

Abbreviations: IAP−, no intrapartum antibiotic prophylaxis; IAP+, intrapartum antibiotic prophylaxis; NA, not applicable; OWOB, overweight or obese.
Among vaginally born infants (Figure 2), the LEfSe analysis revealed that infants born to OWOB vs normal-weight mothers had a statistically higher abundance of several genera (e.g., Bacteroides, Megasphaera, Blautia, and Oscillospira) but reduced abundance of others (e.g., Haemophilus and Veillonella). After emergency cesarean delivery, genera Coprococcus and Ruminococcus of the Lachnospiraceae family were more abundant in infants born to OWOB mothers than normal-weight mothers.

Sequential Mediators in the Intergenerational Transmission of OWOB

The sequential mediation model (Figure 3A) showed direct associations (path c’) of prepregnancy OWOB with childhood OWOB and indirect associations (path a₁d₂₁b₂) with the sequential mediators, birth mode, and Firmicutes richness of the microbiota of the infant gut. Maternal OWOB was associated with cesarean delivery (path a₁) and cesarean delivery enriched Firmicutes richness (path d₂₁). A positive direct association...
Microbiota Interaction Networks Associated With Child OWOB

Compared with normal-weight infants, complex microbiota interactions in the infant gut had a direct association with maternal OWOB at ages 1 and 3 years regardless of their maternal weight status. However, among OWOB children born to OWOB mothers, the family Lachnospiraceae became more abundant with increasing levels of several other families or orders, including the Lactobacillales (lactic acid bacteria), Ruminococcaceae, and Veillonellaceae. Few of the same interactions for the family Lachnospiraceae were seen among OWOB children after a normal-weight pregnancy, and notably absent was a positive correlation with Lactobacillales (eFigure 3 in the Supplement).

Microbiota Interaction Networks Associated With Child OWOB

Compared with normal-weight infants, complex microbiota interactions in the infant gut had a direct association with maternal OWOB at ages 1 and 3 years regardless of their maternal weight status. However, among OWOB children born to OWOB mothers, the family Lachnospiraceae became more abundant with increasing levels of several other families or orders, including the Lactobacillales (lactic acid bacteria), Ruminococcaceae, and Veillonellaceae. Few of the same interactions for the family Lachnospiraceae were seen among OWOB children after a normal-weight pregnancy, and notably absent was a positive correlation with Lactobacillales (eFigure 3 in the Supplement).

Discussion

In our general population birth cohort of 935 infants, those born to OWOB mothers were more likely to develop OWOB at ages 1 and 3 years, and the magnitude of the risk varied by birth mode. Compared with infants born vaginally after a normal-weight pregnancy, those born vaginally to OWOB mothers were 3.33 times more likely to become OWOB at age 1 year (95% CI, 1.49-7.41), whereas cesarean-delivered infants of OWOB mothers had a 5.02-fold risk of OWOB (95% CI, 2.04-12.38), when adjusted for other covariates. Infants born by emergency cesarean delivery to OWOB mothers were at highest risk for OWOB. Similar associations were found for OWOB at age 3 years. In keeping with the thesis of intergenerational transmission of obesogenic microbes, we found that enrichment of infant gut microbiota with the family Lachnospiraceae at ages 3 to 4 months mediated the association between maternal OWOB and child OWOB through a birth mode pathway. A mediation association for richness of total microbial species was also observed for child OWOB; this association also depended on birth mode, such that several microbial species (eg, Bacteroides) were more abundant in infants born vaginally to OWOB women. Our findings are consistent with those of other reports of overweight risk in preschool children following prenatally overweight women and our knowledge of causal pathways.

Among several emerging theories, the development of OWOB has been attributed to greater energy harvest from short-chain fatty acids produced by gut microbes when the abundance of Firmicutes exceeds that of the Bacteroidetes phylum. This thesis has found support in some, but not all, studies of obese children. We observed higher species richness and diversity within the Firmicutes phylum in infants born vaginally or by cesarean delivery to OWOB mothers, as well as evidence of mediation with this phylum. Within the Firmicutes phylum, experimental evidence is accumulating that the family Lachnospiraceae promotes adiposity, inflammation in body fat, and the development of diabetes.
Figure 3. Sequential Mediation Models of Associations Between Maternal Weight Status, Modes of Delivery, and Microbiota of the Infant Gut

A. Firmicutes species richness and childhood OWOB

B. Lachnospiraceae abundance and childhood OWOB

A. Maternal weight status (normal vs OWOB)

B. Mode of delivery + IAP (VgIAP–, VgIAP+, scheduled-CD, emergency-CD)

C. Gut microbiota (Firmicutes species richness)

D. Childhood OWOB at age 1 y and 3 y

Estimate and bootstrap 95% CI for indirect effect (a1d21b2)

A. Data at age 1 y

B. Data at age 3 y

c' = 1.09b

c' = 1.57a

c' = 1.07b

c' = 1.15c

b2 = 0.22d

b2 = 0.15

b2 = 0.67a

b2 = 0.41d

b2 = 0.13a

b1 = 0.15

b1 = 0.16

b1 = 0.05

b1 = 0.04

a2 = 0.11c

a2 = 0.11c

a2 = 0.04

a2 = 0.05

a1 = 0.19b

a1 = 1.15c

a1 = 0.20c

a1 = 1.15c

a1 = 0.22d

a1 = 0.11c

We found indirect or mediating associations for infant fecal abundance of Lachnospiraceae in the association between maternal OWOB and child OWOB after vaginal or cesarean delivery. Within the Lachnospiraceae, genus Blautia was elevated among infants born vaginally to OWOB mothers, whereas abundance of Coprococcus and Ruminococcus was higher after...
Carbon excretion by infants is another indicator of gut microbiota richness and metabolic capability. Several studies have found increased fecal abundance of coprophilic bacteria, which excrete excess nitrogen, in OWOB children born by cesarean delivery. The dysbiotic shifts of the gut microbiota in OWOB infants are associated with abnormal intestinal function and metabolic fate of nutrients. These shifts manifest in altered fecal metabolite concentrations and altered gut microbiota richness. The compositions of the gut microbiota in OWOB infants are characterized by lower abundances of lactobacillales and higher abundances of coproplasma, coprococcus, and coprothermus. These microbial shifts are associated with increased serum levels of tryptophan and indole, which are known to disrupt the balance of the gut microbiota.

The dysbiotic shifts of the gut microbiota in OWOB infants are associated with abnormal intestinal function and metabolic fate of nutrients. These shifts manifest in altered fecal metabolite concentrations and altered gut microbiota richness. The compositions of the gut microbiota in OWOB infants are characterized by lower abundances of lactobacillales and higher abundances of coproplama, coprococcus, and coprothermus. These microbial shifts are associated with increased serum levels of tryptophan and indole, which are known to disrupt the balance of the gut microbiota.
Intergenerational Maternal Transmission of Overweight and Obesity

ORIGINAL INVESTIGATION

Research

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Study supervision: Gutmann, Becker, Turvey, Kozyrskyj.

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REFERENCES


27. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on

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