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Intrapartum antibiotic exposure for group B streptococcus prevention and body mass index trajectory in a population-based cohort of California children

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Abstract

Importance: Intrapartum antibiotics greatly reduce a newborn's risk of group B streptococcal infection (GBS) but may increase the risk of obesity during childhood due to disruption of microbiome formation.

Objective: To examine the association between GBS intrapartum antibiotics and body mass index (BMI) trajectory during the first 5 years after birth.

Design, Setting, and Participants: Retrospective cohort study in an integrated health care system in Southern California of 223,431 singleton-birth infants with >12 months of follow-up between 2007 and 2015.

Exposure: We compared children exposed to GBS intrapartum antibiotic prophylaxis (IAP) defined as administration of penicillin G, ampicillin, cefazolin, clindamycin or vancomycin ≥4 hours before delivery to those unexposed or exposed to any other type or duration of antibiotics within 48 hours before delivery. Reference for vaginal delivery were unexposed children. Because virtually all children born by Cesarean delivery are exposed, other antibiotics were used as reference.

Main Outcome and Measure: BMI measured during routine visits between 0 and 5 years of age was compared between exposure groups using non-linear multivariable models with B-spline functions (knots 0.4, 1.2, and 2.7 years of age), stratified by delivery mode (vaginal or Cesarean),

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and adjusted for demographic, maternal and birth-related factors, breastfeeding and childhood antibiotic exposure.

Results: The mean follow-up time was 4.94 (SD 2.71) years (1,103,569 person-years) with 13.4 (SD 5.3) BMI measures per child; 20.0% (31,263/156,381) of vaginal and 12.5% (8,366/67,050) of Cesarean deliveries were exposed to GBS IAP. In vaginally delivered infants, GBS IAP, but not other intrapartum antibiotics, were associated with increased BMI at age 5 (0.12 kg/m^2, 95% CI 0.07 to 0.16 kg/m^2, P<0.001), compared to no antibiotics. In Cesarean deliveries, GBS IAP was associated with increased BMI at age 5 (0.24 kg/m^2, 95% CI 0.14 to 0.34 kg/m^2, P<0.001) compared to other antibiotics. Breastfeeding did not modify these associations.

Conclusions and Relevance: With GBS IAP used in 1 in 3 U. S. births, the potential increase in BMI on a population level, although small, is relevant. While this does not support changing current practice, it is important to also pursue preventive strategies such as maternal GBS immunization.

Keywords

Perinatal group B streptococcus disease; intrapartum antibiotic prophylaxis; childhood obesity; body mass index

INTRODUCTION

Since the early 1990s, intrapartum antibiotic prophylaxis (IAP) to prevent the vertical transmission of group B *Streptococcus* (GBS) has resulted in an approximate 80% decline in early-onset GBS sepsis, a leading cause of neonatal sepsis in the United States.[1] At the same time, the proportion of infants exposed to intrapartum antibiotics increased from 12% in the early 1990s to over 30% in 2014.[2–4]

Animal studies indicate that antibiotics at young age lead to long-term increases in body weight by altering the intestinal microbiota.[5] GBS IAP is associated with a decreased bacterial diversity of a newborn's microbiome.[6–11] Recent meta-analyses and systematic reviews suggested a link between antibiotic use in early childhood and increased prevalence of overweight and obesity.[12,13] However, the effect of intrapartum exposure to antibiotics on the risk of excess weight gain in offspring is unclear.

We examined the association between GBS IAP and body mass index (BMI) trajectory during the first 5 years of life. Additionally, we investigated whether breastfeeding modified the association.

PATIENTS AND METHODS

Study Setting and Design

Kaiser Permanente Southern California (KPSC) is a large, integrated health care delivery organization that serves approximately 4.3 million members throughout Southern California (~17% of the population) including approximately 40,000 births each year. The membership is diverse and similar in socioeconomic characteristics to the region's census demographics.[14] We conducted a retrospective cohort study among infants born to health

plan members. The KPSC Institutional Review Board (IRB) approved the study and granted a waiver for informed consent. A separate IRB review of the Centers for Disease Control and Prevention (CDC) was not required because CDC staff was not engaged in human subject research.

Study population

We identified singleton infants born in KPSC hospitals between January 01, 2007 and December 31, 2015 (n=302,732). We excluded infants whose mothers did not have at least 3 months continuous health plan enrollment before delivery (n=19,443), who did not remain health plan members for 12 months after birth to allow follow-up (n=58,717) and those born before 22 weeks of gestation (n=167). The analytical cohort for this study consisted of 223,431 (74.8%) infants (eFigure 1).[15] The population was a priori stratified by delivery mode (vaginal or Cesarean section).

Antibiotic Exposure

Exposure to antibacterial agents (oral, intramuscular, or intravenous) was extracted from maternal electronic medical records. We defined intrapartum as the time between maternal admission and delivery. For mothers with longer or multiple inpatient stays before delivery, we defined intrapartum as 48 hours before delivery to exclude stays for false labor or maternal observation. The intrapartum exposure to antibiotics was calculated as time from first administration to delivery and classified as: 1) no intrapartum exposure to antibiotics, 2) antibiotic prophylaxis for perinatal GBS disease (GBS IAP) defined as administration of penicillin G, ampicillin, cefazolin, clindamycin and/or vancomycin for ≥4 hours before delivery,[16] or 3) any other type or duration of intrapartum antibiotic administration. Because of universal Cesarean prophylaxis (typically intravenous cefazolin administered within 60 mins before delivery), all infants delivered via Cesarean section were exposed to intrapartum antibiotics.

Follow-up for childhood body mass index

Body weight, measured by trained staff on calibrated scales at routine medical office visits during the first five years of childhood, was obtained from electronic medical records.[17] Height was measured by calibrated stadiometer or horizontal length board on the same day. After data entry by staff, weight and height were visualized in growth charts with previous measurements to highlight data entry errors. In 2007 and 2008, the error rates in weight and height data of children aged <2 and 2–5 years were 0.4% and 0.7%, respectively.[18] To transform recumbent length into standing height, we subtracted 0.8 cm from recumbent length in children under the age of 18 months.[19] BMI was calculated as weight in kilograms divided by the square of height in meters. Children were followed for a maximum of 5 years through February 08, 2018. BMI was analyzed from birth until the first occurrence of one of the following events: reaching 5 years of age, end of KPSC health care coverage, death, or the end of follow-up.

Covariates

Data regarding demographic, maternal, birth-related, and childhood factors were obtained from validated research databases derived from health plan electronic medical records, administrative records, and birth records (eTable 1).[18,20–23] Covariates included antepartum and postpartum exposure to antibacterial agents.[18,20–23]

Statistical Analysis

We compared clinical and demographic characteristics among intrapartum antibiotic exposure groups using descriptive statistical methods including Pearson chi-square test for categorical variables and analysis of variance (ANOVA), the Kruskal-Wallis, student's T, or the Wilcoxon rank sum tests. For summary tables, children at age 5 were categorized based on the sex-specific BMI-for-age growth charts developed by the Centers for Disease Control and Prevention (CDC) as underweight (BMI-for-age $<5^{th}$ percentile), normal weight (BMI-for-age $\geq 5^{th}$ to $<85^{th}$ percentile), overweight (BMI-for-age ≥85th to $<95^{th}$ percentile), or obesity (BMI-for age ≥95th).[24]

Missing values in pre-pregnancy weight (n=28,420, 12.7%) and gestational weight gain (n=22,372, 10.0%) were imputed by performing a single regression imputation adjusting for race/ethnicity and parity (eTable 1).[25]

We examined the association between intrapartum antibiotic exposure (None, GBS IAP, Other) and longitudinal BMI using non-linear multivariable models stratified by delivery mode. B-spline functions were fitted to allow for flexible modelling of BMI trajectories over time and for varying fit by exposure group. Quadratic splines with 3 knots were selected based on initial unadjusted plots and model fit. BMI trajectories over time were similar when comparing the entire cohort, children with more than 4 BMI measurements or over at least 4 years (data not shown). For all models, we set spline knots at 0.4, 1.2, and 2.7 years of age, based on best model fit but consistent with 2000 CDC growth charts.[24] We used marginal models with robust standard errors[26] accounting for the repeated measures within each child to determine the mean BMI at each time point and to calculate the difference in mean population BMI between the intrapartum antibiotic exposure and the reference category. We evaluated above models against unadjusted and fully adjusted mixed effect regression models for each delivery method including a random effect to accommodate within child correlation over time with comparable results; for the latter, missing outcome data were handled through maximum likelihood estimation under the assumption of missing at random. We adjusted for demographics, maternal and birth-related covariates (eTable 1; referred to as 'Birth Model') and childhood covariates (referred to as 'Full Model'). The selection of adjustment variables was informed by the development of a directed acyclic graph and the Bayesian information criterion.[27] We also present comparisons of parameter estimates for antibiotic exposure antepartum (trimester 1/2, trimester 3) and postpartum (neonatal, lactation, childhood). Separate two-way interaction terms with exposure were tested for breastfeeding, maternal pre-pregnancy weight class, maternal diabetes, maternal hypertension, and chorioamnionitis. For meaningful figures of BMI trajectories, model covariates were set at the population mean for continuous and mode for categorical variables.

To translate BMI differences into weight gain differences, we transformed predicted BMIs from the fully adjusted model into weight (kg) = predicted BMI * height in m^2 to determine weight in kg at age 5 years. We used the mean height at baseline and age 5 for each exposure category and delivery method from the unadjusted data. Confidence intervals (95% CI) were constructed using the standard error of the difference.

We conducted several sensitivity analyses (see eTable 2) including: 1) restricting to healthy term-born children,[20,21] 2) limiting the GBS IAP antibiotics to children who received no additional non-GBS agents, 3) creating antibiotic exposure groups that were homogenous with regard to GBS colonization, and 4) excluding children exposed to antibiotics during pregnancy. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and R version 3.5.3.[28]

RESULTS

Cohort description

Of the 223,431 children included in this study, 70.0% were delivered vaginally and 30.0% were delivered via Cesarean section (Table 1). The cohort contained 1,103,569 person-years, with a mean follow-up time of 4.94 years (SD 2.71 years). A total of 122,708 (54.9%) children completed follow-up to 5 years of age (eFigure 1). Children had an average of 13.4 (SD 5.3) BMI measures during follow-up. Among vaginal deliveries, 113,693 (72.7%) were unexposed to antibiotics during the intrapartum period, 31,263 (20.0%) were exposed to GBS IAP, and 11,425 (7.3%) were exposed to other intrapartum antibiotics. Among Cesarean deliveries, 8,366 (12.5%) were exposed to GBS IAP, and 58,684 (87.5%) were exposed to antibiotics of other type or duration including antibiotic prophylaxis to prevent maternal post-Cesarean infection (eTable 3).

Infants born to mothers exposed to GBS IAP were more likely to be born preterm (P <0.001 for vaginal and Cesarean section deliveries), born to a mother with diabetes (P < 0.001 for vaginal, P =0.010 for CS), or of Black race (P <0.001 for both delivery methods) than were infants exposed to no or other intrapartum antibiotics. They were also more likely to be exposed to antibiotics antepartum for both delivery methods (P <0.001 for both), during the neonatal period for Cesarean section deliveries (P < 0.001), and more likely to be on a state subsidized health plan for vaginal deliveries (P< 0.001).

Vaginal delivery

We observed significant differences in BMI between the GBS IAP and unexposed groups (unadjusted Δ BMI at age 5 = 0.09 kg/m^2, 95% CI 0.04 kg/m^2 to 0.13 kg/m^2, P<0.001, Table 2, crude models, eFigure 2). BMI did not differ between the other intrapartum antibiotic and unexposed groups. Adjustment for sociodemographic, maternal and delivery-related factors (Birth Model – covariates up to delivery), breastfeeding, and exposure to antibiotics during childhood (Full Model – covariates through childhood) slightly strengthened the association between GBS IAP and BMI starting after the age of 0.5 years (Full Model, adjusted Δ BMI at age 5 = 0.12 kg/m^2, 95% CI 0.07 kg/m^2 to 0.16 kg/m^2, P<0.001, Figure 1a). No significant interactions between breastfeeding and other covariates with antibiotic

exposure were observed, indicating that breastfeeding and other covariates did not modify the association of antibiotic exposure and BMI.

Our results translated into a difference in attributable weight gain from birth to 5 years of age of 0.32 kg (95% CI 0.31 kg to 0.33 kg, $P<0.001$) for GBS IAP and 0.16 kg (95% CI 0.15 kg to 0.18 kg, $P<0.001$) for other intrapartum antibiotics compared to no antibiotics (Table 3).

In contrast, antepartum exposure to antibiotics was associated with an adjusted BMI of 0.01 kg/m^2 (95% CI 0.00 kg/m^2 to 0.02 kg/m^2, $P=0.178$) for the first or second trimester of pregnancy and 0.04 kg/m^2 (95% CI 0.02 kg/m^2 to 0.06 kg/m^2, $P<0.001$) for the third trimester of pregnancy (Figure 2a). The indirect antibiotic exposure during lactation with an adjusted Δ BMI of 0.08 kg/m^2 (95% CI 0.06 kg/m^2 to 0.10 kg/m^2, $P<0.001$) during the first 3 months of life and of 0.04 kg/m^2 (95% CI 0.01 kg/m^2 to 0.06 kg/m^2, $P<0.012$) during the first 3 to 6 months of life. Each 14-day antibiotic treatment episode during follow-up was associated with an adjusted Δ BMI of 0.04 kg/m^2 (95% CI 0.03 kg/m^2 to 0.05 kg/m^2, $P<0.001$).

Cesarean delivery

Children delivered via Cesarean section had a significantly higher BMI if exposed to GBS IAP compared to children exposed to other intrapartum antibiotics (unadjusted Δ BMI at age 5 = 0.18 kg/m^2, 95% CI 0.09 kg/m^2 to 0.28 kg/m^2, $P<0.001$, Table 2, crude analysis). Further adjustment for covariates slightly strengthened the association between GBS IAP and childhood BMI after the age of 0.7 years (Full Model adjusted Δ BMI at age 5 = 0.24 kg/m^2, 95% CI 0.14 kg/m^2 to 0.34 kg/m^2, $P<0.001$, Figure 1b). No significant interactions between breastfeeding and other covariates with antibiotic exposure were observed ($P>0.150$).

This translated into a difference in attributable weight gain from birth to 5 years of age of 0.43 kg (95% CI 0.41 kg to 0.45 kg, $P<0.001$) for GBS IAP compared to other intrapartum antibiotics (Table 3).

The association between GBS IAP and childhood BMI was stronger than the association observed with exposure to antibiotics at other time points during pregnancy and childhood (Figure 2b).

Sensitivity analyses

Restricting the cohort to healthy, term children slightly attenuated the association between GBS IAP and childhood BMI for vaginally delivered children (sensitivity analyses 1, full model adjusted Δ BMI at age 5 = 0.16 kg/m^2, 95% CI 0.15 kg/m^2 to 0.17 kg/m^2, $P<0.001$, eTable 4, 5 and eFigures 2 and 3) and children delivered by Cesarean section (full model adjusted Δ BMI at age 5 = 0.23 kg/m^2, 95% CI 0.21 kg/m^2 to 0.26 kg/m^2, $P<0.001$). In contrast to the main cohort, the association between exposure to antibiotics during the neonatal period and childhood BMI was not significant. Sensitivity analysis limiting the GBS IAP antibiotics to children who received no additional non-GBS agents, creating

homogenous exposure groups with regard to GBS colonization, or excluding infants who were exposed to antibiotics antepartum did not alter the results (eTable 4).

DISCUSSION

This is currently the largest study investigating the impact of intrapartum antibiotic exposure as recommended for perinatal GBS disease prevention on childhood BMI. Exposure to GBS IAP was associated with a higher BMI starting at 5 to 7 months of age, depending on the delivery mode and translated at 5 years of age into an excess weight gain of 0.12 to 0.24 kg/m^2. Our study was conducted in parallel with a retrospective cohort study in Philadelphia (N =13,804) using the same exposure definition and a similar analysis approach.[29] In that study, GBS IAP was associated with an adjusted attributable difference in BMI gain from birth to age 5 years of 0.24 kg (95% CI 0.04 kg to 0.44 kg) for vaginal deliveries and 0.60 kg (95% CI 0.32 kg to 0.88 kg) for Cesarean deliveries.[29]

Small changes in BMI at the individual level can have significant effects at the population level.[30,31] Early childhood BMI trajectories are crucial factors in the development of adult obesity from early youth. Several studies suggest that the majority of excess body weight in children who develop obesity is often gained before age 5 or 6 years.[32,33] A recent modeling study also suggested that the chance a child with obesity at age 2 years resolves their obesity decreases with every year that they have obesity,[34] underscoring the importance of preventing early excess weight gain.

Associations between antibiotic exposure in early childhood and childhood obesity have received recent attention.[12,13] Our findings suggest the association between GBS IAP and childhood BMI was stronger than for other (primarily shorter) intrapartum exposures as well as antepartum and postpartum antibiotic exposures. This may be consistent with hypotheses that disruptions at the time of initial microbiome formation may have lasting effects.[35–40]

It is currently believed that an infant's microbiome is seeded by selected maternal bacteria.[41] GBS colonization of the mother as well as GBS IAP are associated with a shift in microbiome composition[42] and a decreased bacterial diversity in a newborn's microbiome.[6–11,43] Rodent studies indicate that antibiotics at young age lead to long-term increases in body weight by altering the intestinal microbiota in a way that may cross generations.[5,44] These downstream health consequences may be intensified when combined with other factors associated with microbiome disruption such as Cesarean delivery[9,11,45–48] and formula feeding.[9,11] While results from our study showed stronger associations between GBS IAP and childhood BMI in children born via Cesarean delivery, breastfeeding did not alter the association. Our sensitivity analyses suggested that GBS colonization alone was not an important factor in the association between antibiotic exposure and childhood BMI. Prospective studies are necessary to examine if the early life disruption in an infant's microbiome caused by GBS IAP may lead to strong or sustained shifts in microbiome composition or microbiome diversity and to understand how these may lead to an increase in BMI.[35–38]

Strengths of the study include medical record data from a large, community-based, average risk population with a high screening rate for GBS colonization.[2] The study population is generally reflective of Southern California and includes a high proportion of children born to low income families.[14] The cohort study design reduced the chance of possible bias inherent in case-control and hospital-based studies. An extensive number of potential covariates was available including demographics, maternal health, birth-related factors, and childhood information with a high proportion of children who remained in the study for over 4 years. Exposure to antibiotics antepartum, intrapartum, and postpartum was captured comprehensively via electronic medical records, enabling adjustment for the contributions of antibiotic exposure during pregnancy and childhood. Antibiotic exposure groups were compared by delivery mode with unexposed infants from the same background population. The study benefitted from the high frequency of BMI measures throughout childhood, a high quality of weight and height measured due to rigorous training.[17] The large sample size enabled evaluation of the BMI trajectories with higher precision than previous studies and allowed us to estimate continuous differences in BMI rather than risk of obesity as binary outcome.

Limitations include the possibility of residual confounding inherent to the observational design, including the possibility of differential distribution of unmeasured or incompletely measured confounders. Assessment of the duration of intrapartum antibiotic exposure from electronic medical records may have resulted in reduced capture of women who received GBS IAP due to underestimation of the antibiotic exposure duration.

Conclusions

Exposure of infants to GBS IAP compared to no intrapartum antibiotics was associated with a small but statistically significant and sustained increase in BMI starting at a very early age. On an individual level, the benefit from GBS intrapartum antibiotic prophylaxis to decrease the risk of neonatal sepsis may outweigh the potential risk of weight gain later. On a population level, the potential increase in body weight may be more relevant as GBS IAP is used in 1 in 3 U. S. births. While the potential effects do not support changing current practice, it is important to also pursue preventive strategies such as maternal GBS immunization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or Kaiser Permanente Community Benefit Funds.

Abbreviations:

BMI	body mass index
GBS	Group B Streptococcus
KPSC	Kaiser Permanente Southern California

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Key Points

Question

Do children exposed to intrapartum antibiotics for the prevention of group B streptococcal (GBS) infection have a higher body-mass index (BMI) than unexposed children?

Findings

In this population-based study of 223,431 singleton-births, children exposed to GBS intrapartum antibiotic prophylaxis had a higher BMI at 5 years of age compared to unexposed children, after controlling for key covariates including maternal BMI and breastfeeding. The increase was more pronounced in children delivered via Cesarean section (0.24 kg/m^2) than in those delivered vaginally (0.12 kg/m^2).

Meaning

GBS intrapartum antibiotic prophylaxis was associated with a small but statistically significant and sustained increase in BMI starting at a very early age.

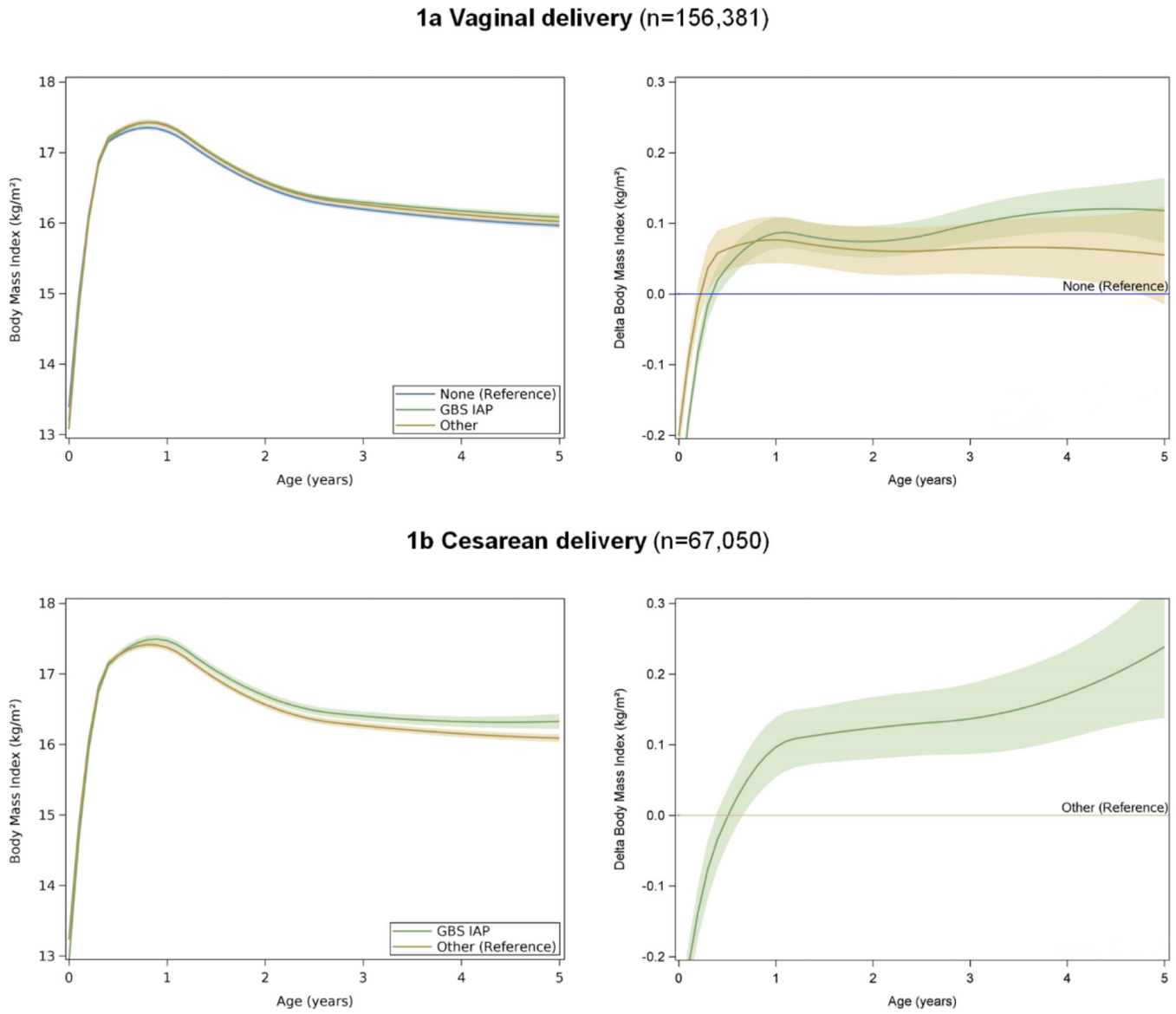

Figure 1:

Adjusted body mass index (BMI), delta BMI, and their 95% CIs for children unexposed to intrapartum antibiotics (None), children exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS) and any other type or duration of intrapartum antibiotic administration (Other) stratified by delivery mode

Covariate adjustments included demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant's race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, any breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.

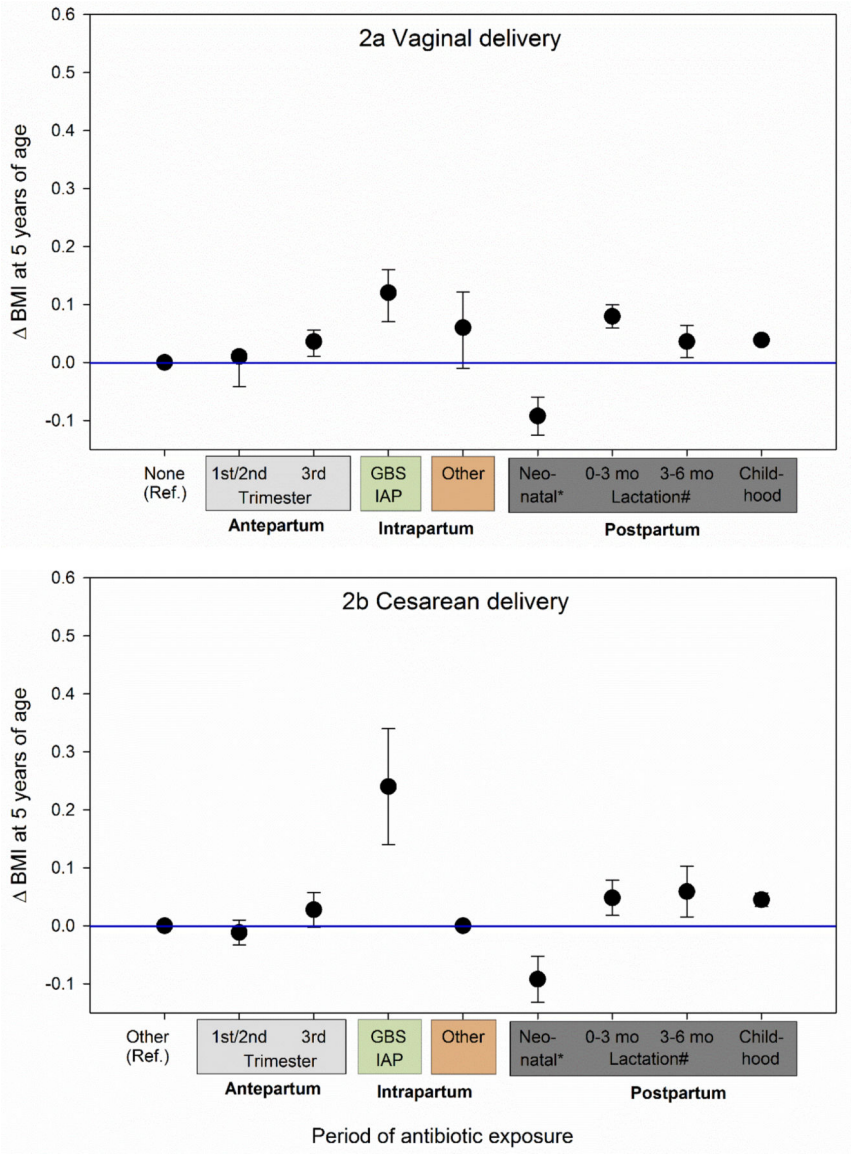

Figure 2:

Comparison of adjusted excess BMI at 5 years of age associated with exposure to antibiotics during antepartum, intrapartum and postpartum periods

*Δ BMI attributable to neonatal antibiotics is no longer significant when excluding children with low or high birth weight and/or complex care conditions (Vaginal delivery: −0.05 kg/m^2, 95% CI −0.11 kg/m^2 to 0.01 kg/m^2, P=0.090; Cesarean delivery: 0.02 kg/m^2, 95% CI −0.04 kg/m^2 to 0.09 kg/m^2, P=0.499; see eFigure 3).

#Indirect antibiotic exposure through breastfeeding by a mother using antibiotics during the first 3 months after birth. The estimate for childhood exposure is per 14-day episode of antibiotic use.

Covariates adjusted for included demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant's race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center

of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, any breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.

The reference point reflects a population mean BMI at age 5 of 15.97 (SD 0.018) kg/m^2 for vaginally delivered children unexposed to intrapartum antibiotics (None) and 16.09 (SD 0.028) kg/m^2 for children delivered by Cesarean section and exposed to other intrapartum antibiotics (Other).

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Table 1:

Demographic, maternal, birth-related, and childhood characteristics by delivery mode and intrapartum antibiotic exposure *

	Total Cohort	Vaginal delivery				Cesarean delivery		
Antibiotic exposure:		**None**	**GBS**	**Other**	**P value**	**GBS**	**Other**	**P value**
N	**223431**	**113693**	**31263**	**11425**		**8366**	**58684**	
Children within delivery mode (%)		72.7	20.0	7.3		12.5	87.5	
Total follow-up, y					<0.001			<0.001
Mean	4.9 (2.71)	5.1 (2.80)	4.5 (2.43)	4.7 (2.47)		4.6 (2.44)	5.0 (2.74)	
Median (IQR)	4.4 (2.7, 7.0)	4.6 (2.7, 7.2)	4.0 (2.6, 6.4)	4.2 (2.7, 6.5)		4.1 (2.6, 6.4)	4.5 (2.7, 7.1)	
Demographics								
Sex,					<0.001			<0.001
Male	108967 (48.8)	56801 (50.0)	15198 (48.6)	5551 (48.6)		3682 (44.0)	27735 (47.3)	
Female	114464 (51.2)	56892 (50.0)	16065 (51.4)	5874 (51.4)		4684 (56.0)	30949 (52.7)	
Race/Ethnicity					<0.001			<0.001
White	63085 (28.2)	32554 (28.6)	8494 (27.2)	2946 (25.8)		2112 (25.2)	16979 (28.9)	
Hispanic	105699 (47.3)	55662 (49.0)	14200 (45.4)	5475 (47.9)		3701 (44.2)	26661 (45.4)	
Black	18934 (8.5)	8157 (7.2)	3277 (10.5)	989 (8.7)		1080 (12.9)	5431 (9.3)	
Asian/Pacific Islander	27937 (12.5)	13394 (11.8)	4123 (13.2)	1632 (14.3)		1187 (14.2)	7601 (13)	
Other, unknown	7776 (3.5)	3926 (3.5)	1169 (3.7)	383 (3.4)		286 (3.4)	2012 (3.4)	
State-subsidized health plan	20071 (9.0)	10273 (9.0)	3275 (10.5)	1082 (9.5)	<0.001	688 (8.2)	4753 (8.1)	0.697
Maternal and pregnancy-related factors								
Maternal education					<0.001			0.002
Less than HS	10969 (4.9)	6275 (5.5)	1263 (4.0)	547 (4.8)		295 (3.5)	2589 (4.4)	
High School	55668 (25.0)	29347 (25.9)	7857 (25.2)	2874 (25.2)		1921 (23.0)	13669 (23.3)	
Some college	67772 (30.4)	33994 (30.0)	9783 (31.3)	3426 (30.0)		2608 (31.2)	17961 (30.6)	
Bachelor degree or higher	86037 (38.5)	42565 (37.5)	11950 (38.2)	4418 (38.7)		3423 (41.0)	23681 (40.4)	
Unknown	2985 (1.2)	1512 (1.1)	410 (1.3)	160 (1.3)		119 (1.3)	784 (1.3)	
Parity					<0.001			<0.001
1	168219 (75.3)	83883 (73.8)	24256 (77.6)	8440 (73.9)		7468 (89.3)	44172 (75.3)	
2	36208 (16.2)	19336 (17.0)	4353 (13.9)	1938 (17.0)		578 (6.9)	10003 (17.0)	

	Total Cohort	Vaginal delivery				Cesarean delivery		
Antibiotic exposure:		**None**	**GBS**	**Other**	**P value**	**GBS**	**Other**	**P value**
N	**223431**	**113693**	**31263**	**11425**		**8366**	**58684**	
3+	19004 (8.5)	10474 (9.2)	2654 (8.5)	1047 (9.2)		320 (3.8)	4509 (7.7)	
Diabetes	13542 (6.1)	4962 (4.4)	2104 (6.7)	671 (5.9)	<0.001	791 (9.5)	5014 (8.5)	0.010
Pre-pregnancy BMI (kg/m^2)								
Mean (SD)	26.9 (6.15)	26.2 (5.64)	26.9 (6.23)	26.3 (5.79)	<0.001	28.6 (7.12)	28.2 (6.70)	<0.001
Pregnancy weight gain (lbs)								
Mean (SD)	27.5 (13.53)	27.6 (12.86)	26.8 (14.11)	27.2 (13.25)	<0.001	28.0 (15.41)	27.6 (14.22)	<0.001
Chorioamnionitis	10869 (4.9)	1203 (1.1)	2213 (7.1)	2604 (22.8)	<0.001	1806 (21.6)	3043 (5.2)	<0.001
Smoking during pregnancy	24231 (10.8)	11610 (10.2)	3644 (11.7)	1177 (10.3)	<0.001	1075 (12.8)	6725 (11.5)	<0.001
GBS culture status					<0.001			<0.001
Negative	163026 (73.0)	106423 (93.6)	4662 (14.9)	5384 (47.1)		2173 (26)	44384 (75.6)	
Positive	38258 (17.1)	3204 (2.8)	19535 (62.5)	4305 (37.7)		4469 (53.4)	6745 (11.5)	
Unknown	22147 (9.9)	4066 (3.6)	7066 (22.6)	1736 (15.2)		1724 (20.6)	7555 (12.9)	
Antibiotic exposure								
Antepartum, trimester 1/2	65276 (29.2)	30040 (26.4)	11055 (35.4)	3567 (31.2)	<0.001	2976 (35.6)	17638 (30.1)	<0.001
Antepartum, trimester 3	26710 (11.9)	12053 (10.6)	4589 (14.7)	1502 (13.1)	<0.001	1319 (15.8)	7247 (12.3)	<0.001
Birth								
Birth weight (g)								
Mean (SD)	3346 (546)	3374 (458)	3252 (577)	3281 (543)	<0.001	3261 (760)	3364 (634)	<0.001
Gestational age (weeks)								
Mean (SD)	38.7 (1.81)	39.0 (1.33)	38.4 (2.21)	38.6 (2.02)	<0.001	38.2 (2.95)	38.5 (2.04)	<0.001
Preterm birth (<37th week)	17191 (7.7)	3638 (3.2)	4880 (15.6)	1173 (10.3)	<0.001	1546 (18.5)	5954 (10.1)	<0.001
Childhood								
Any Breastfeeding								
at 3 months of age	147716 (66.1)	75710 (70.3)	21236 (70.1)	7817 (70.6)	0.717	5481 (68.0)	37472 (67.8)	0.634
at 6 months of age	125523 (56.2)	64469 (59.8)	18182 (60.1)	6720 (60.6)	0.232	4644 (57.6)	31508 (57)	0.262
Antibiotic exposure								
Neonatal								
first 4 days (72 h)	12953 (5.8)	2528 (2.2)	2851 (9.1)	1360 (11.9)	<0.001	1534 (18.3)	4680 (8.0)	<0.001

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	Total Cohort	Vaginal delivery				Cesarean delivery		
Antibiotic exposure:		**None**	**GBS**	**Other**	**P value**	**GBS**	**Other**	**P value**
N	**223431**	**113693**	**31263**	**11425**		**8366**	**58684**	
4–28 days	7438 (3.3)	2415 (2.1)	1358 (4.3)	548 (4.8)	<0.001	691 (8.3)	2426 (4.1)	<0.001
Indirect during lactation								
0–3 mo	30232 (13.5)	13392 (11.8)	4389 (14.0)	1716 (15)	<0.001	1742 (20.8)	8993 (15.3)	<0.001
3–6 mo	13473 (6.0)	6417 (5.6)	2072 (6.6)	706 (6.2)	0.736	528 (6.3)	3750 (6.4)	0.782
Cumulative childhood episodes								
Mean (SD)	2.7 (3.11)	2.7 (3.04)	2.6 (2.99)	2.6 (2.95)	0.153	2.9 (3.26)	2.9 (3.32)	0.159
BMI class at age 5[#]					<0.001			0.014
N	104394	55005	12714	4945		3556	28174	
Underweight	4011 (3.8)	2171 (3.9)	509 (4.0)	215 (4.3)		147 (4.1)	969 (3.4)	
Normal weight	73214 (70.1)	39439 (71.7)	8863 (69.7)	3477 (70.3)		2326 (65.4)	19109 (67.8)	
Overweight	14164 (13.6)	7185 (13.1)	1781 (14.0)	678 (13.7)		524 (14.7)	3996 (14.2)	
Obesity	13005 (12.5)	6210 (11.3)	1561 (12.3)	675 (11.6)		559 (15.7)	4100 (14.6)	

[*] Antibiotic exposure: none, no intrapartum exposure to antibiotics; GBS, GBS intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease; other, any other type or duration of intrapartum antibiotic administration

[#] Extrapolated based on the nearest 2 weight measures within 6 months of a child's 5th birthday (N=104394).

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Table 2:

Body mass index difference between children unexposed to intrapartum antibiotics (None), children exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS) and any other type or duration of intrapartum antibiotic administration (Other) stratified by delivery mode.

	Vaginal delivery			Cesarean delivery	
Child's age (years)	**None (BMI, kg/m^2)**	**GBS (Δ BMI, kg/m^2)**	**Other (Δ BMI, kg/m^2)**	**Other (BMI, kg/m^2)**	**GBS (Δ BMI, kg/m^2)**
Total cohort, N	113693	31263	11425	58684	8366
Crude model	Reference			Reference	
0.0	13.35 (0.004)	−0.36 (−0.38, −0.34)	−0.26 (−0.29, −0.23)	13.29 (0.007)	−0.37 (−0.41, −0.32)
1.0	17.29 (0.005)	0.05 (0.03, 0.07)	0.02 (−0.01, 0.05)	17.46 (0.007)	0.04 (0.00, 0.08)
2.0	16.53 (0.005)	0.03 (0.01, 0.06)	0.01 (−0.03, 0.04)	16.69 (0.007)	0.07 (0.03, 0.11)
3.0	16.23 (0.006)	0.06 (0.04, 0.08)	0.01 (−0.03, 0.04)	16.43 (0.008)	0.08 (0.04, 0.13)
4.0	16.11 (0.007)	0.08 (0.05, 0.11)	0.01 (−0.03, 0.05)	16.35 (0.010)	0.12 (0.06, 0.18)
5.0	16.03 (0.010)	0.09 (0.04, 0.13)	0.00 (−0.07, 0.07)	16.31 (0.015)	0.18 (0.09, 0.28)
Birth Model (adjusting for covariates through delivery) [#]					
0.0	13.25 (0.014)	−0.31 (−0.33, −0.29)	−0.20 (−0.23, −0.18)	13.11 (0.021)	−0.31 (−0.36, −0.27)
1.0	17.17 (0.014)	0.08 (0.06, 0.10)	0.07 (0.04, 0.10)	17.25 (0.021)	0.09 (0.05, 0.13)
2.0	16.40 (0.014)	0.07 (0.05, 0.09)	0.06 (0.02, 0.09)	16.49 (0.021)	0.12 (0.07, 0.16)
3.0	16.11 (0.014)	0.09 (0.07, 0.12)	0.06 (0.02, 0.09)	16.23 (0.021)	0.13 (0.08, 0.18)
4.0	15.98 (0.014)	0.12 (0.09, 0.15)	0.06 (0.01, 0.10)	16.15 (0.022)	0.16 (0.10, 0.23)
5.0	15.91 (0.016)	0.12 (0.07, 0.16)	0.05 (−0.02, 0.12)	16.12 (0.025)	0.23 (0.13, 0.33)
Full Model (adjusting for covariates through childhood) [$]					
0.0	13.38 (0.015)	−0.31 (−0.33, −0.29)	−0.20 (−0.23, −0.17)	13.23 (0.023)	−0.31 (−0.35, −0.27)
1.0	17.30 (0.015)	0.09 (0.06, 0.10)	0.08 (0.04, 0.11)	17.37 (0.023)	0.10 (0.05, 0.14)
2.0	16.51 (0.015)	0.07 (0.05, 0.10)	0.06 (0.03, 0.09)	16.56 (0.023)	0.12 (0.08, 0.17)
3.0	16.20 (0.016)	0.10 (0.07, 0.12)	0.06 (0.03, 0.10)	16.26 (0.024)	0.14 (0.09, 0.19)
4.0	16.05 (0.016)	0.12 (0.09, 0.15)	0.07 (0.02, 0.11)	16.15 (0.025)	0.17 (0.11, 0.23)
5.0	15.97 (0.018)	0.12 (0.07, 0.16)	0.06 (−0.01, 0.12)	16.09 (0.028)	0.24 (0.14, 0.34)

[#]Birth Model (covariates through delivery) adjustment for demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant's race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure.

[$] Full Model (covariates through childhood) adjustment included previously listed Birth Model variables plus neonatal antibiotic exposure, breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.

[#] Sensitivity analysis cohort excludechildren with a birth weight above and below the 5th percentile, born before 37th week of gestation, infants with a positive blood or cerebrospinal fluid culture in first 72 hours with > 5 days of antibiotic therapy, prolonged birth admission (ICU admission > 5 days or total stay > 7 days, infants with any pediatric complex care conditions during follow-up.

Table 3:

Attributable body weight difference from birth to 5 years of age in children unexposed to intrapartum antibiotics (None), children exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS) and any other type or duration of intrapartum antibiotic administration (Other) stratified by delivery mode.

	Vaginal delivery			Cesarean delivery	
	None (weight gain, kg)	**GBS (Δ weight gain, kg)**	**Other (Δ weight gain, kg)**	**Other (weight gain, kg)**	**GBS (Δ weight gain, kg)**
Total cohort, N	113693	31263	11425	58684	8366
	Reference			Reference	
Crude model	16.08	0.30 (0.29, 0.30)	0.12 (0.10, 0.13)	16.47	0.38 (0.36, 0.39)
Full Model	16.00	0.32 (0.31, 0.33)	0.16 (0.15, 0.18)	16.21	0.43 (0.41, 0.45)

Using the Full Model (Covariates through childhood) adjustment for demographics, maternal and birth-related factors included infant sex, gestational age at birth, birth weight, infant's race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.