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Prenatal Antimicrobial Use and Early Childhood Body Mass Index

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Abstract

Background/Objectives—Growing evidence suggests antibiotic use is associated with childhood body mass index (BMI), potentially via mechanisms mediated by gut microbiome alterations. Less is known on the potential role of prenatal antimicrobial use in offspring obesity risk. We examined if prenatal antibiotic or antifungal use was associated with BMI at age 2 years in 527 birth cohort participants.

Methods/Subjects—Antimicrobial use was obtained from the prenatal medical record. Height and weight were measured at age 2 years. Overweight/obesity was defined as a BMI 85th percentile.

Results—A total of 303 (57.5%) women used antibiotics and 101 (19.2%) used antifungals during pregnancy. Prenatal antifungal use was not associated with child BMI at age 2 years. In the fully-adjusted model, prenatal antibiotic use was associated with a 0.20 ± 0.10 ($P=0.046$) higher mean BMI Z-score at age 2 years. Associations between prenatal antibiotic use and childhood BMI varied by trimester of exposure, with 1st or 2nd trimester exposure more strongly associated with larger BMI at age 2 years for both BMI Z-score (interaction $P=0.032$) and overweight/obesity (interaction $P=0.098$) after covariate adjustment.

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Conclusions—Prenatal antibiotic, but not antifungal, use is associated with larger BMI at age 2 years; associations were stronger for antibiotic exposures in earlier trimesters. Future studies examining if these associations are due to alterations in the maternal and/or infant microbiome are necessary. Children who are overweight at age 2 years are at higher risk for overweight as they age; prenatal antibiotic use is a potentially modifiable exposure that could reduce childhood obesity.

Introduction

Rates of childhood overweight and obesity continue to rise in the United States.¹ Rates of medication use in pregnancy have also increased, with antibiotics being among the most commonly administered prescription drugs.² In the Project Women and Infants Starting Healthy Study conducted in San Francisco between 2001 and 2002, over half of all women were prescribed a prescription drug during pregnancy, with 62% of those prescriptions being antibiotics.³

Because of the established impact of antimicrobials on the gut microbiome,⁴ and murine studies demonstrating that administration of sub-therapeutic concentrations increases adiposity,⁵ their administration during pregnancy has the potential to be obesogenic.⁶ Antibiotics have been used in animal husbandry for over 6 decades to increase livestock weight gain, with administration to young, but not mature animals, resulting in increased weight.^{6–8} Antibiotic exposure in infancy is associated with increased childhood body mass index (BMI) and/or risk of overweight/obesity.^{9, 10} There is limited, and conflicting evidence exploring prenatal antibiotic use with childhood obesity. Two studies have shown positive associations between prenatal antibiotic use and overweight/obesity at age 7 years¹¹ or ages 7–16 years¹²; in contrast, in another study, prenatal antibiotic orders were not associated with child BMI Z-score at age 3 years.¹³

Fungal species also impact gut symbiosis.¹⁴ However, in contrast to antibiotics, antifungals have not been shown to impact weight in animals.⁸ Antifungal medications are commonly used by pregnant women, most often for vaginal candidiasis.¹⁵ In non-pregnant, reproductive age women, topical antifungal treatment of *Candida* infection alters the bacterial vaginal microbiome,¹⁶ suggesting that use of these agents during pregnancy could potentially alter offspring's risk of obesity via vertical transmission of an altered vaginal microbiome during the birthing process.

To our knowledge, however, no study has examined the association of prenatal antimicrobial use (antibiotic or antifungal use, separately) with BMI in early childhood, overall and within each trimester. We examined the association of prenatal antimicrobial use with childhood BMI at age 2 years in the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) birth cohort.^{17, 18}

Materials/Subjects and Methods

WHEALS recruited pregnant women who delivered from September 2003 through December 2007, and who were seeing a Henry Ford Health System (HFHS) obstetrics practitioner at one of five clinics.^{17, 18} All women were in their second trimester or later, age

21–49 years, and lived in a predefined geographic area that was selected to encourage racial and socioeconomic diversity (city of Detroit and surrounding suburban areas). All participants provided written, informed consent. Study protocols were approved by the Institutional Review Board at HFHS.

Definition of Antimicrobial Use

As part of a study specifically examining racial (i.e., black-white) differences in vitamin D, maternal prenatal and delivery medical records were abstracted for data including antimicrobial use. Antibiotic use was defined as systemic antibiotic use (ingestion, intravenous, intramuscular) at any time during pregnancy. Antifungal use was defined as use of a systemic (ingested) or vaginally applied antifungal medication any time during pregnancy.¹⁸ We defined use of antimicrobials by trimester as follows: 1st trimester if used between 0 and <14 weeks gestational age; 2nd trimester if used 14–<27 weeks gestational age; and 3rd trimester if used 27 weeks gestational age through, and including, delivery. Number of prenatal antibiotics used was categorized as 0, 1, 2–3, or 4+.¹⁹ Antibiotics were classified based on structure/mode of action into the following groups: aminoglycosides, cephalosporins, lincosamides, quinolones, macrolides, nitroimidazoles, nitrofurantoin, penicillins, vancomycins, and sulfonamide/ trimethoprim.^{20–22}

Covariate Measurement

Maternal date of birth, race, marital status, household income, education, number of previous births and breastfeeding at one month were self-reported. Medical records were abstracted to obtain height and weight at first prenatal care visit, prenatal antiviral use, mode of delivery, gestational age at delivery and infant birthweight. Gender- and gestational-age adjusted birthweight Z-scores were calculated using the US population as reference.²³ Child medical records were abstracted to obtain information on antibiotic use before 1 month and 6 months of age.

Child Body Size Measurement

At the study's 2-year research clinic visit, trained field staff measured child height in stocking feet with a wall stadiometer; child weight was measured with the child in light clothing using a balance beam physician scale. BMI Z-scores and percentiles were calculated according to the 2000 Centers for Disease Control and Prevention age- and gender-specific growth charts. Overweight was defined as BMI between the 85th and 95th percentile and obesity as BMI 95th percentile.

Statistical Analysis

Maternal, newborn and child characteristics were compared by prenatal antibiotic or antifungal exposure using a chi-square test of independence for discrete characteristics and a Student's t-test for continuous characteristics.

Logistic regression was used to examine the association between prenatal antibiotic or antifungal use and overweight/obesity (BMI 85th percentile); linear regression was used for BMI Z-score. Models were fit unadjusted and adjusted for infant gender, mode of delivery (cesarean section or vaginal), ever breastfed, maternal age, maternal education, maternal

race (white or black), birthweight Z-score, child age (in months) at the 2 year visit and maternal BMI at first prenatal care visit. To examine if associations varied by mode of delivery, child gender, maternal race or ever breastfed, multiplicative interaction terms were fit. Similar models were fit to determine if type of antibiotic (ever use of cephalosporin, ever use of macrolide, ever use of nitroimidazole, ever use of nitrofurantoin, ever use of penicillin, or ever use of other antibiotic (aminoglycoside, lincosamide, quinolone, vancomycin, or sulfonamide/trimethoprim) was associated with BMI at age 2 years.

To test for differences in timing of antibiotic or antifungal exposure across pregnancy, multiple informant models were used, which allowed us to test differences in an exposure-outcome relationship across time windows while maintaining the effect estimates that would be obtained fitting separate regression models for each time point.²⁴ A score test of the equality of all the trimester-specific parameter estimates was used to evaluate differences across trimesters.²⁴ A generalized estimating equation approach with linear and logistic regression was utilized to fit the multiple informant models for BMI Z-score and overweight/obesity, respectively.

Not all WHEALS children completed a 2-year clinic visit.¹⁷ To account for loss-to-follow-up, we calculated inverse probability weights (IPW) for complete follow-up.²⁵ IPW were calculated by fitting a logistic regression model for complete follow-up at age 2 years with the following baseline maternal factors: age, race, insurance type, income (including whether or not the question was answered), education, smoking status, prenatal alcohol use, urban residence, marital status, history of asthma/allergies, and mode of delivery and obtaining the predicted probability of successful follow-up. Data were reanalyzed using the IPW as model weights to adjust for bias due to incomplete follow-up. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analysis.

Results

A total of 1,258 children were originally included in WHEALS; 659 of these children completed a 2-year clinic visit with height and weight measurement. We excluded 108 children where the maternal chart was not abstracted and 24 children where maternal antimicrobial use was unknown. We compared maternal and child characteristics between the 527 included in the sample to the 731 excluded from the analytic sample; compared to those excluded, those included tended to have slightly older maternal age at delivery (30.1 vs. 29.2 years), to be black (69.3% vs. 56.5%) and to be slightly larger at birth (3349 vs 3270 g) (all $P < 0.05$).

In our study, 303 (57.5%) women had antibiotic use and 101 (19.2%) had antifungal use during pregnancy. There were 577 antibiotic courses and 131 antifungal courses in the 527 women, giving a total of 1.09 antibiotic and a total of 0.25 antifungal courses per pregnancy in our cohort. Nearly all 538/577 (93.2%) the antibiotic courses were systemic (commonly oral administration); 24 (4.2%) antibiotic courses were delivered vaginally and only 15 (2.6%) were delivered topically. Compared to women not exposed to antibiotics, those with antibiotic exposure were slightly younger, were more likely to be black, had lower household income, lower education levels, had greater prenatal antiviral exposure and were

less likely to ever breastfeed (Table 1). Black women, those with lower household income, those exposed to an antiviral prenatally and women carrying a male child were more likely to have prenatal antifungal use (Table 1). There was no association of prenatal antibiotic or antifungal use with child use of antibiotic before 1 or 6 months of age (all $P>0.14$).

Prenatal antimicrobial use and BMI at age 2 years

Mean BMI of the WHEALS children at age 2 years was 16.6 ± 1.7 kg/m² and mean BMI Z-score was 0.08 ± 1.1 ; 90 (17.1%) WHEALS children were overweight/obese at age 2 years. There was no evidence that prenatal antibiotic use was associated with overweight/obesity risk and there was no evidence prenatal antifungal medication use was associated with BMI Z-score or overweight/obesity at age 2 years (Table 2). Prenatal antibiotic use was positively associated with BMI Z-score at age 2 years ($P=0.046$); after covariate adjustment, children born to mothers who used antibiotics in the prenatal period had an estimated 0.20 ± 0.10 unit higher BMI Z-score at age 2 years compared to children born to mothers who did not use prenatal antibiotics (Table 2). There was no evidence that the association between prenatal antibiotic or antifungal medication use with child BMI varied by mode of delivery, child gender, maternal race, or breastfeeding status (all interaction $P>0.11$).

Although there was no evidence of a prenatal antibiotic-by-delivery mode interaction with childhood BMI, given our *a priori* hypothesis that the maternal microbiome may mediate associations between prenatal antibiotic use and childhood obesity, we refit our models stratified by delivery mode. In the fully-adjusted model, prenatal antibiotic use was not statistically significantly associated with BMI Z-score at age 2 years (0.17 ± 0.18 ; $P=0.35$) in offspring of women who delivered via C-section; in contrast, the association of prenatal antibiotic use with BMI Z-score at age 2 years (0.23 ± 0.13 ; $P=0.064$) approached statistical significance in women who delivered vaginally.

Trimester-specific antimicrobial use and BMI at age 2 years

Trimester of prenatal antibiotic exposure was associated with BMI Z-score and overweight/obesity at age 2 years (Table 3). In the fully adjusted model, there was evidence for a trimester-specific effect of antibiotic use with BMI Z-score (interaction $P=0.032$); 1st trimester antibiotic use was associated with a 0.21 ± 0.12 unit higher BMI Z-score ($P=0.071$), 2nd trimester antibiotic use was associated with a statistically significant 0.28 ± 0.13 unit higher BMI-score ($P=0.028$), but 3rd trimester use was not associated with BMI Z-score ($P=0.691$). Results were similar for odds of overweight/obesity; in the fully-adjusted model, there was borderline suggestive significant evidence of a trimester-specific effect of antibiotic use (interaction $P=0.098$). Children born to mothers who used antibiotics in the 1st trimester had 1.78 (95% CI OR: 1.07, 2.98) times greater odds of being overweight/obese at age 2 years ($P=0.028$); there was no association of 2nd or 3rd trimester antibiotic use and odds of overweight/obesity at age 2 years. There was no evidence for a trimester-specific effect of antifungal use on childhood BMI at age 2 years.

Dose-response relationship with antibiotic use

Most women who used antibiotics had one exposure over pregnancy ($n=157$; 51.8%) (Table 1). Figure 1 shows the relationship between number of prenatal antibiotics used and mean

BMI Z-score at age 2 years, with the highest BMI Z-score seen in children with the greatest number of prenatal exposures to antibiotics, however this was not statistically significant (P -trend=0.144). There was no association of number of antibiotics used with overweight/obesity. Only 17 women had multiple uses of antifungal medications (Table 1), thus we did not evaluate potential dose-response relationships for antifungal use.

Antibiotic Type and Body Mass Index

Antibiotic use fell into the following groupings: ever penicillin use (n=189 uses); ever nitroimidazole use (n=112 uses); ever cephalosporin use (n=87 uses); ever nitrofurantoin use (n=72 uses); ever macrolide use (n=62 uses); and ever use of other antibiotic (n=55 uses). After covariate adjustment, compared to children born to women without antibiotic exposure, children born to a mother ever exposed to macrolides had a statistically significantly higher BMI Z-score (0.37 ± 0.18 ; $P=0.039$). No other antibiotic type was associated with BMI Z-score. Antibiotic type was also not associated with overweight/obesity.

Sensitivity Analysis

Model inferences were similar after accounting for IPW. In the fully adjusted model, the association of use of prenatal antibiotics with BMI Z-score was slightly attenuated ($\beta=0.19\pm 0.11$; $P=0.069$). There remained evidence for a trimester-specific effect of prenatal antibiotic use on BMI Z-score (interaction $P=0.035$) and overweight/obesity (interaction $P=0.069$). First-trimester antibiotic use was associated with a mean increase in BMI Z-score of 0.21 ± 0.12 ($P=0.069$) and 2nd trimester antibiotic use was associated with a mean increase in BMI Z-score of 0.29 ± 0.13 ($P=0.023$). First trimester antibiotic use was also associated with a 1.85 (95% CI: 1.09, 3.16; $P=0.023$) times increased odds of overweight/obesity.

Discussion

In the current study, prenatal antibiotic, but not antifungal, exposure was associated with increased risk of offspring having a larger BMI Z-score at age 2 years. We provide new evidence suggesting that this association varies by timing of the antibiotic exposure, with antibiotic exposure in the 1st or 2nd trimester, but not the 3rd trimester, associated with greater BMI Z-score at age 2 years. Similarly, exposures to antibiotics in the 1st trimester were associated with overweight/obesity at age 2 years. Even at early ages, children who are obese are at higher risk of becoming obese adolescents and adults;²⁶ prenatal antibiotic use may be one modifiable exposure that could reduce the current rates of childhood obesity, particularly if we are able to reduce unnecessary antibiotic use.

Antibiotic use during pregnancy is associated with alterations in the vaginal microbiome at gestational week 36, with significantly increased *Staphylococcus* species in women treated with oral antibiotics.²⁷ Particularly in vaginally-born infants, the infant gut, skin and oral microbiome resembles the maternal vaginal microbiome.²⁸ Children with greater *Staphylococcus aureus* counts in fecal samples from 6 or 12 months of age are statistically significantly more likely to be overweight at age 7 years.²⁹ Thus, if prenatal antibiotic exposure increases vaginal *Staphylococcus aureus* numbers, this could explain the increased

risk of larger BMI at age 2 years detected in our study. In animal models, maternal antibiotic treatment is associated with alterations in the offspring gut microbiome.³⁰ While intra-partum maternal antibiotic use in Group B *Streptococcus* positive mothers is associated with alterations in the infant gut microbiome,^{31, 32} to our knowledge, data from humans examining if prenatal antibiotic use over various gestational ages is associated with infant gut microbiome are lacking. Antibiotic use during the last month of pregnancy was not associated with the infant gut microbiome at age 1 month,³³ which is consistent with our finding that 3rd trimester antibiotic exposure is not associated with childhood BMI at age 2 years. Given the microbial dynamics that occur normally in the maternal gut and vaginal microbiome over pregnancy,^{34–36} which are postulated to play a role in priming fetal development, it is plausible that antibiotic-associated maternal microbiome perturbation may impact post-natal infant microbiome development, and, subsequently, child health measures. Our results, which showed a stronger, albeit only near statistically significant association of maternal antibiotic use with BMI Z-score at age 2 in children delivered vaginally compared to by C-section further suggests that alterations in the microbiome may be a mechanism linking maternal antibiotic use with childhood BMI.

In addition to mechanisms linked to the microbiome, differential timing of antibiotics over gestational development could directly impact the developing endocrine system, and thus prime a fetus for future risk of obesity. Development of the human endocrine system commences at approximately gestational week 4, involving hormone production related to subsequent fetal growth in gestational weeks 4–10.³⁷ In contrast, fetal adipose tissue deposition primarily occurs throughout the latter 3rd of gestation.³⁸ Hence exposures at distinct periods of gestation may have a differential impact on fetal development. For instance, data from several studies conducted on pregnancies that occurred during famines suggest that timing of the exposure, that is, under-nutrition in early pregnancy, may be important for increased risk of offspring obesity.³⁹ Maternal antibiotic use may have a similar trimester-specific effect on the fetal endocrine system and development.

Alternative mechanisms by which prenatal antibiotic exposure may impact childhood BMI are possible. Antibiotic exposure could impact the development, implantation or function of the placenta, subsequently affecting development of the fetus and future growth. Limited data exists describing the impact of antibiotics on the placenta, however, in a recent study examining amniotic membrane samples from a single placenta, antibiotic exposure damaged the cell membrane and resulted in loss of microvillia.⁴⁰ The placenta undergoes rapid development during the first trimester of pregnancy⁴¹ and itself has a distinct microbiome that resembles the oral microbiome⁴²; antibiotic exposure early in pregnancy may similarly impact the placental microbiome at a critical stage of fetal development. Data from the Project Viva cohort demonstrated a trimester-specific effect of antibiotic exposure on leptin, a hormone involved in energy balance and appetite suppression; exposures in the 1st and 2nd trimester were associated with non-statistically significant lower levels of cord blood leptin, whereas exposures in the 3rd trimester were associated with statistically significant higher levels of cord blood leptin.⁴³ Lower cord blood leptin levels are associated with higher BMI at age 3 years.⁴⁴ Thus, although the associations were not statistically significant, the finding of lower leptin in cord blood following 1st or 2nd trimester antibiotic exposure is consistent with our finding that earlier pregnancy antibiotic exposure is associated with larger BMI at

age 2 years. Finally, prenatal exposure to antibiotics could increase risk of antibiotic use in early childhood, which is known to increase risk of obesity;⁴⁵ however, in our cohort, prenatal antibiotic use was not associated with early childhood antibiotic use, suggesting that this was not acting as a confounder in our study. However, each of these potential mechanisms requires further study.

To our knowledge, few previous studies specifically examined prenatal antibiotic use and childhood BMI and none have examined antifungal use. In the Northern Manhattan Mothers and Children study, antibiotic exposure in the 2nd or 3rd trimester was associated with risk of obesity and BMI Z-score at age 7.¹¹ In contrast to our findings at age 2 years, 1st trimester antibiotic use was not associated with childhood BMI at age 7 years. Similarly, in a study of Danish schoolchildren ages 7–16 years, prenatal antibiotic exposure was associated with overweight and obesity risk.¹² In a study conducted in Geisinger Clinic data, however, prenatal antibiotic orders were not associated with BMI Z-score at age 3 years.¹³ There are several differences in these studies which may explain some of these varying results. Antibiotic use in WHEALS was defined based on medical chart review, compared to self-report during a 3rd trimester interview in the Northern Manhattan study; women may have difficulty self-reporting medication use, particularly early in pregnancy. The prevalence of antibiotic use in WHEALS in the 2nd and 3rd trimester was 32.1% compared to 16% in the Northern Manhattan study, 33% in the Danish study, and 60.4% of women in the Geisinger study were ordered antibiotics prenatally. While WHEALS is comprised of primarily black and white women, the Northern Manhattan study is comprised primarily of black and Dominican women, the Danish study consisted of Dutch women, and the Geisinger study was nearly all white. Finally, the age at childhood BMI measurement (age 2 in WHEALS vs. age 7 years in the Northern Manhattan Study, age 7–16 years in the Danish study and age 3 years in the Geisinger study) differed. Electronic health record data was used to define child BMI at age 3 years in the Geisinger study, compared to measurements obtained by research staff in WHEALS. Overall, there is evidence to support a role for prenatal antibiotic use and childhood BMI; future studies that address BMI trajectories throughout childhood are needed.

We found evidence to suggest that macrolide antibiotic use in pregnancy was associated with higher BMI Z-score at age 2 years. One recent study of antibiotic exposure in the first year of life showed that each class of antibiotic studied (narrow spectrum, broad spectrum and macrolides) was associated with weight gain through age 8 years.⁴⁵ Saari et al (2015) found that macrolide use in infancy had the greatest impact on weight gain in children through age 24 months; these authors attributed this to pharmacokinetic properties of macrolides, which are excreted in bile and thus may have direct contact with microbiota in the colon, compared to the other classes of antibiotics which are eliminated by the kidneys.⁹ In a study of 142 Finnish children ages 2–7 years, macrolide, but not penicillin use was associated with a persistent change in the composition and function of the gut microbiome; macrolide use was also positively associated with BMI Z-score.²² Findings were similar in a mouse model; tylosin, a veterinary-medicine macrolide, given shortly after weaning, increased both total and lean mass of mice, compared to only lean mass increases in mice exposed to amoxicillin.⁴⁶ Further, tylosin was also associated with microbiota composition changes that persisted longer than changes in amoxicillin-exposed mice.⁴⁶ Together, these studies support

a potential microbiome-mediated role linking certain antibiotics with increases in BMI. Given that a number of women in our study used multiple antibiotic classes over pregnancy, however, these findings will require replication in a larger study that will permit exploration of the different combinations of antibiotics typically used over pregnancy.

We found no evidence that prenatal antifungal use was associated with offspring obesity risk. Although treatment of *Candida* infection alters the bacterial vaginal microbiome,¹⁶ there is limited existing data on the type of changes that occur in the vaginal microbiome as a result of antifungal use and how those changes are transmitted to offspring. Given the propensity for microbiota re-assembly following perturbation, topical antifungal treatment of vaginal infection, which was the most common route of exposure in our study, may only be pertinent in the period immediately prior to birth.

There are several limitations to the current investigation. We assigned antimicrobial use to a specific trimester based on pregnancy dating information; inaccurate reporting of last menstrual period for instance may have resulted in incorrect assignment of exposure time. Although information on antimicrobial use was obtained from the medical record and thus is not subject to recall bias, we do not have information on whether or not the woman took the medication as prescribed. We do not have comprehensive information on the symptoms or specific illnesses that led to the use of prenatal antibiotics, thus, we cannot rule out that the associations detected are a result of an underlying infection. The infectious agents themselves, rather than the subsequent antimicrobial use, could impact child growth.⁴⁷ A recent longitudinal birth cohort study from Kaiser Permanente Northern California suggested that childhood infection, rather than overall early-childhood antibiotic use, was associated with childhood obesity; however, consistent with our overall hypothesis, in this study, early infancy antibiotic use (first 6 months of life) was associated with childhood obesity.⁴⁸ To our knowledge, however, similar studies have not been conducted during pregnancy, and thus future work to examine prenatal infection with and without antibiotic use, may be needed.

Conclusions

We found evidence suggesting that prenatal antibiotic use, but not antifungal use, is associated with childhood BMI at age 2 years. Higher BMI Z-score and risk of overweight/obesity were greatest for children with maternal exposures during the 1st or 2nd trimester. Inappropriate antibiotic use during pregnancy is common.⁴⁹ While there are clear indications for antibiotic use during pregnancy, inappropriate maternal antibiotic use (such as for upper respiratory infection of probable viral origin⁵⁰) may contribute to the childhood obesity epidemic. Additional studies examining if changes in the gut microbiome (both maternal and offspring) mediate associations between prenatal antibiotic use and childhood BMI are warranted.

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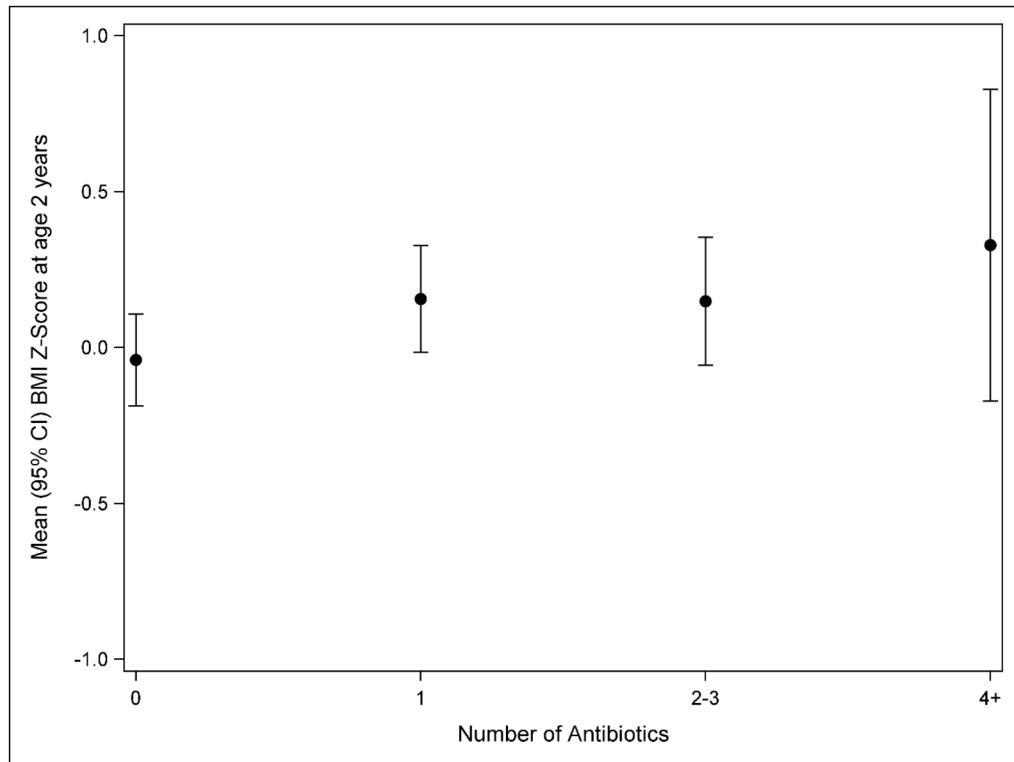


Figure 1. Relationship between number of prenatal antibiotic exposures and mean BMI Z-score at age 2 years

Table 1

Descriptive characteristics of the WHEALS participants, stratified by prenatal antibiotic use and prenatal antifungal use

	Antibiotic Use		Antifungal Use	
	Yes	No	Yes	No
N^I (%)	303 (57.5%)	224 (42.5%)	101 (19.2%)	426 (80.8%)
<i>Maternal characteristic</i>				
Age (years)	29.5 ± 5.3**	31.0 ± 4.9**	29.6 ± 5.1	30.2 ± 5.2
Race				
White	76 (25.1%)**	86 (38.4%)**	22 (21.8%)**	140 (32.9%)**
Black	227 (74.9%)	138 (61.6%)	79 (78.2%)	286 (67.1%)
BMI at first prenatal care visit (kg/m ²)	31.0 ± 8.2	29.8 ± 7.6	31.3 ± 7.3	30.3 ± 8.1
Household Income				
<\$20k	39 (15.4%)**	17 (8.5%)**	16 (19.3%)**	40 (10.8%)**
20k–<\$40k	73 (28.7%)	40 (19.9%)	15 (18.1%)	98 (26.3%)
40k–<\$80k	80 (31.5%)	60 (29.9%)	33 (39.8%)	107 (28.8%)
80k–<100k	25 (9.8%)	46 (22.9%)	13 (15.7%)	58 (15.6%)
>=100k	37 (14.6%)	38 (18.9%)	6 (7.2%)	69 (18.6%)
Highest Level Education				
< High-school Diploma	10 (3.3%)**	11 (4.9%)**	4 (4.0%)	17 (4.0%)
High-school Diploma/Equivalent	61 (20.1%)	18 (8.0%)	16 (15.8%)	63 (14.8%)
Some College	148 (48.8%)	100 (44.6%)	52 (51.5%)	196 (46.0%)
>=Bachelor's Degree	84 (27.7%)	95 (42.4%)	29 (28.7%)	150 (35.2%)
Antiviral Use				
No	281 (92.7%)**	218 (97.3%)**	410 (96.2%)**	89 (88.1%)**
Yes	22 (7.3%)	6 (2.7%)	16 (3.8%)	12 (11.9%)
<i>Neonate characteristic</i>				
Cesarean section delivery	105 (34.7%)	85 (38.0%)	43 (42.6%)	147 (34.5%)
Birth Weight (grams)	3309.1 ± 595.9	3403.1 ± 588.4	3447.3 ± 548.8	3327.5 ± 602.0
Birth Weight Z-score	-0.09 ± 1.0	0.05 ± 1.0	0.09 ± 1.0	-0.06 ± 1.0
Male gender	153 (50.5%)	120 (53.6%)	67 (66.3%)**	206 (48.4%)**
Ever breastfed	224 (76.2%)**	179 (83.6%)**	72 (73.5%)	331 (80.7%)
Ever used antibiotic before 1 month visit	6 (3.2%)	8 (6.7%)	3 (5.5%)	11 (4.4%)
Ever used antibiotic before 6 month visit	30 (19.5%)	28 (27.5%)	8 (15.4%)	50 (24.5%)
<i>Child characteristic at 2 year visit</i>				
Age (years)	2.2 ± 0.3	2.2 ± 0.2	2.2 ± 0.3	2.2 ± 0.2
BMI (kg/m ²)	16.8 ± 1.7**	16.5 ± 1.5**	16.8 ± 1.8	16.6 ± 1.6
BMI Z-score	0.17 ± 1.1**	-0.04 ± 1.1**	0.15 ± 1.1	0.06 ± 1.1
BMI category				
Underweight (BMI<5 th percentile)	20 (6.6%)	15 (6.7%)	6 (5.9%)	29 (6.8%)

	Antibiotic Use		Antifungal Use	
	Yes	No	Yes	No
Normal Weight (BMI 5 th and <85 th percentile)	231 (76.2%)	171 (76.3%)	75 (74.3%)	327 (76.8%)
Overweight (BMI 85 th and <95 th percentile)	21 (6.9%)	24 (10.7%)	14 (13.9%)	31 (7.3%)
Obese (BMI 95 th percentile)	31 (10.2%)	14 (6.3%)	6 (5.9%)	39 (9.2%)
<i>Prenatal Antimicrobial characteristics</i>				
Timing of medication exposure (trimester)				
1 st ONLY	60 (19.8%)	N/A	26 (25.7%)	N/A
2 nd ONLY	35 (11.6%)	N/A	27 (26.7%)	N/A
3 rd ONLY	100 (33.0%)	N/A	39 (38.6%)	N/A
1 st and 2 nd	21 (6.9%)	N/A	3 (3.0%)	N/A
1 st and 3 rd	36 (11.9%)	N/A	1 (1.0%)	N/A
2 nd and 3 rd	34 (11.2%)	N/A	4 (4.0%)	N/A
All 3	17 (5.6%)	N/A	1 (1.0%)	N/A
Number of medication exposures				
1	157 (51.8%)	N/A	84 (83.2%)	N/A
2–3	116 (38.2%)	N/A	14 (13.9%)	N/A
4+	30 (9.9%)	N/A	3 (3.0%)	N/A
Route of antifungal exposure				
Oral only	N/A	N/A	38 (37.6%)	N/A
Vaginal only	N/A	N/A	53 (52.5%)	N/A
Vaginal and Oral	N/A	N/A	10 (9.9%)	N/A

¹BMI at first prenatal care visit (N = 520), Household Income (N= 455), Birth Weight (N = 504), Birth Weight Z-score (N = 490), Ever breastfed (N = 508), Infant antibiotic use before age 1 month (N=307), Infant antibiotic use before age 6 months (N=256).

** $P < 0.05$ comparing women with and without the specific antimicrobial exposure

BMI, body mass index

Table 2

Association of overall prenatal antibiotic or antifungal use with body mass index (BMI) Z-score and child overweight/obese at age 2 year visit

	BMI Z-score		Overweight/Obese	
	β (se)	<i>P</i>	OR (95 % CI OR)	<i>P</i>
Any Prenatal Antibiotic Use				
Model 1	0.21 (0.10)	0.033	1.01 (0.64,1.61)	0.953
Model 2	0.20 (0.10)	0.046	1.04 (0.62, 1.74)	0.885
Any Prenatal Antifungal Use				
Model 1	0.09 (0.12)	0.464	1.26 (0.72, 2.18)	0.419
Model 2	-0.13 (0.13)	0.323	0.99 (0.53, 1.87)	0.984

Model 1: Unadjusted; Model 2: adjusted for infant gender, delivery mode, ever breastfed, maternal age, maternal race, maternal education, birthweight Z-score, child age at 2-year visit and BMI at first prenatal care visit

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Table 3

Trimester-specific association of antibiotic or antifungal use with body mass index (BMI) Z-score and child overweight/obese at age 2 year visit; evidence for a trimester-specific effect is indicated with the interaction *P* term

	BMI Z-score			Overweight/Obese		
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	$\beta \pm se$ (<i>P</i>)	$\beta \pm se$ (<i>P</i>)	OR (95 % CI OR) (<i>P</i>)	OR (95 % CI OR) (<i>P</i>)	OR (95 % CI OR) (<i>P</i>)	OR (95 % CI OR) (<i>P</i>)
Antibiotic Use						
1 st trimester	0.23±0.11 (<i>P</i> =0.043)	0.21±0.12 (<i>P</i> =0.071)	1.71 (1.05, 2.77) (<i>P</i> =0.032)	1.78 (1.07, 2.98) (<i>P</i> =0.028)		
2 nd trimester	0.24±0.12 (<i>P</i> =0.05)	0.28±0.13 (<i>P</i> =0.028)	1.44 (0.85, 2.45) (<i>P</i> =0.175)	1.34 (0.74, 2.46) (<i>P</i> =0.337)		
3 rd trimester	-0.001±0.10 (<i>P</i> =0.990)	-0.04±0.10 (<i>P</i> =0.691)	0.74 (0.45, 1.21) (<i>P</i> =0.234)	0.72 (0.42, 1.22) (<i>P</i> =0.225)		
Interaction <i>P</i>	0.070	0.032	0.094	0.098		
Antifungal Use						
1 st trimester	0.35±0.21 (<i>P</i> =0.090)	0.02±0.22 (<i>P</i> =0.915)	1.18 (0.47, 2.96) (<i>P</i> =0.729)	0.63 (0.22, 1.85) (<i>P</i> =0.403)		
2 nd trimester	-0.02±0.20 (<i>P</i> =0.907)	-0.08±0.20 (<i>P</i> =0.687)	1.23 (0.52, 2.91) (<i>P</i> =0.635)	1.18 (0.48, 2.89) (<i>P</i> =0.714)		
3 rd trimester	-0.10±0.18 (<i>P</i> =0.560)	-0.23±0.18 (<i>P</i> =0.201)	0.89 (0.38, 2.05) (<i>P</i> =0.777)	0.88 (0.40, 1.96) (<i>P</i> =0.763)		
Interaction <i>P</i>	0.221	0.578	0.943	0.787		

Model 1: Unadjusted; Model 2: adjusted for infant gender, delivery mode, ever breastfed, maternal age, maternal race, maternal education, birthweight Z-score, child age at 2-year visit and BMI at first prenatal care visit