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# The Association between Early Antibiotic Exposure and Obesity Development in Childhood

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## Abstract

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Young children are frequently exposed to antibiotics, an improved understanding of the relationship between antibiotic exposure in early life and adiposity in childhood is warranted. We hypothesize early childhood antibiotic exposure is associated with overweight development. We formed a longitudinal birth cohort from 2002-2010, born in a health care system in WA. Antibiotic exposure was defined as courses of antibiotics (1 course = 1-14 days) received from 0-47 months of age. The outcome was overweight (BMI % $\geq 85^{th}$%) at 48-59 months. Multivariable logistic and linear regression models were used.72% of children were antibiotic exposed. In a multivariable logistic regression model, there was association between antibiotic exposure and overweight development (OR: 1.03, 95% CI: 1.01. 1.05). Children had a 3% higher odds of overweight development at 48-59 months for each additional course of antibiotics at 0-47 months. This association affords an opportunity to explore a physician-modifiable risk factor for overweight.

# TABLE OF CONTENTS

List of Figures ........................................ i

List of Tables ........................................ iii

1. Introduction ........................................ 1
2 Methods ........................................ 3
2.1 Setting ........................................ 3
2.2 Study population ........................................ 3
2.3 Exposure ........................................ 4
2.4 Outcome ........................................ 5
2.5 Covariates ........................................ 6
2.6 Study Procedures ........................................ 7
2.7 Analysis ........................................ 7
3 Results ........................................ 9
4 Discussion ........................................ 14
4.1 Strengths and limitations ........................................ 16
4.2 Conclusions and Implications ........................................ 18

Bibliography ........................................ 19

# LIST OF FIGURES

Figure 1. BMI category at 48 – 59 months 18

Figure 2. Dose-response of antibiotic exposure and odds of overweight development 20

# LIST OF TABLES


Table 1. Type of Antibiotic 12

Table 2. Data sources and elements 14

Table 3. Participant and maternal characteristics 17

Table 4. Logistic regression of antibiotic exposure as a continuous variable and overweight category as a dichotomous variable 19

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## 1. Introduction

Childhood obesity is a major public health problem in the US and globally.[1-3] The prevalence of childhood overweight and obesity remain at record high levels affecting an estimated 31.8% of youth in the US.[3] Pediatric conditions such as obstructive sleep apnea, nonalcoholic fatty liver disease, asthma, and mental health disorders, including attention deficit hyperactivity disorder, anxiety and depression are associated with child obesity.[4-7] Additionally, overweight in childhood is a well described risk factor for chronic diseases in adulthood such as type 2 diabetes mellitus, cardiovascular disease, depression and several types of cancers.[8] Reducing childhood obesity is a national health goal of Healthy People 2020.[9] Identifying modifiable risk factors for childhood obesity is important in order to develop appropriate interventions and policies.

Gut microbiota, defined as the commensal bacteria present normally in the gut, play a role in nutritional status of the host and are implicated in the development of obesity. The gut becomes colonized initially by microorganisms from the mother during delivery and breastfeeding, and from the surrounding environment.[10,11] Children typically establish their adult gut microbiota by 1-3 years of age. There are several lines of evidence suggesting that obese children have a different gut microbial composition than their lean peers.[12,13] One small dietary intervention study conducted in Europe found that adolescents who lost weight experienced a change in their gut microbial composition.[14]

These small gut microbiota and weight status studies in humans are supported by research in mouse models whereby conventionally raised mice have more body fat than germ-free mice. Moreover, the germ-free mice were protected from diet-induced obesity, further supporting the idea that the gut microbiota plays a role in nutritional status.[15] The gut microbial

composition affects both energy and lipid metabolism in mouse models.[16] A mouse model of early life antibiotic exposure at subtherapeutic levels found both increased adiposity and altered gut microbiota in young mice.[17]

Antibiotics cause perturbation of the gut microbiota[18], and antibiotics are prescribed in approximately 21% of outpatient pediatric visits.[19] Systemic antibiotics (e.g. amoxicillin) accounted for one quarter of all outpatient pediatric prescriptions in the US from 2002-2010.[20] The composition of the gut microbiota influences metabolism; therefore, the effect of antibiotics on the establishment of children's gut microbiota may have important implications for childhood obesity development.[13,15]

Thus, there is growing evidence of a relationship between gut microbial composition and weight status in animals and humans.[12-15,18,19] Because young children are frequently exposed to antibiotics, an improved understanding of the relationship between antibiotic exposure in early life and adiposity in childhood is warranted.[12-15,18,19] Recent studies in human children have shown a relationship between early life antibiotic exposure and obesity development in later childhood.[21-26] These studies were limited in that they did not include an assessment of the impact of maternal antibiotic receipt during pregnancy; did not employ antibiotic prescription fill data or link with different databases including birth certificate data; and failed to compare anti-anaerobic and non-anti-anaerobic antibiotics. Two studies were able to include antibiotic dispensation as the best approximation of the child's antibiotic receipt.[25,26]

To address this gap this study aimed to include 1) maternal factors – maternal antibiotic receipt during pregnancy and maternal BMI; 2) specific factors in a United States population – antibiotic prescription fill data, and linkage of electronic medical record data with birth

certificate data; and 3) antibiotic type – comparing anti-anaerobic and non-anti-anaerobic antibiotics.

Therefore, our objective was to evaluate the association between early childhood antibiotic exposure at 0-47 months old and overweight development at age 48-59 months. Secondarily, we aimed to evaluate the effects of both first antibiotic exposure timing and antibiotic type on the risk of overweight development.

# 2 Methods

## 2.1 Setting

We examined a birth cohort of children enrolled in Group Health (GH), a large nonprofit health care system that provides comprehensive health care throughout Washington State (WA) including to low-income patients whose insurance is contracted through Medicaid, WA Basic Health and the State Children's Health Insurance Program.[27] We utilized prior established linkages between the GH electronic medical records and the WA Department of Health (DOH) birth certificate database, as well as between mothers and babies with the GH electronic medical records.[28,29] The GH database has 30 years of pharmaceutical data including prescription fills, medication type, dosing and prescribed duration from pharmacies and clinics both within and external to the GH system.

## 2.2 Study population

We included children born in 2002-2010 who 1) were enrolled in GH at birth and followed continuously for at least 48 months; 2) had birthweight data available on WA DOH birth certificate records; and 3) had weight and length/height recorded at least once between 0-47 months, and again between 48–59 months in the GH database. Children with diagnoses that may

have influenced antibiotic receipt and/or weight status—specifically children with cystic fibrosis, malignancy, immunodeficiency, HIV, congenital heart disease, or Prader-Willi syndrome—were excluded.

## 2.3 Exposure

We defined each antibiotic exposure as one oral antibiotic course (equivalent to 1 prescription for 1-14 days of antibiotic therapy) from 0-47 months of age. The GH database has prescription fill information for all medications including those prescribed outside the GH system (e.g. at Urgent Care), capturing 97% of all prescriptions to GH enrollees.[30] Given that it is not feasible to conduct a study with directly observed therapy, pharmaceutical fill data serves as a reasonable objective proxy for taking the medication. The GH database includes the type of antibiotic received, dosing and duration of therapy. We did not include topical, ophthalmic, otic, or intrathecal therapy as exposures because we thought they would have limited effect on the gut microbiota. For our evaluation of the association between antibiotic type and obesity development, we classified the antibiotics based on a study examining childhood antibiotic exposure and development of Inflammatory Bowel Disease (IBD) by Kronman et al., (Table 1).[31] The antibiotics were categorized into anti-anaerobic and 'other or none' because we hypothesized that the anti-anaerobic antibiotics would have the greatest effect on the gut flora based on prior studies demonstrating that anaerobes make up the majority of the gut microbial community.[32]

**Table 1. Type of Antibiotic**

| **Anti-anaerobic** |
|---|
| Penicillin |
| Broad spectrum penicillin |
| Tetracycline |
| Metronidazole |
| Lincosamide |
| Glycopeptide (oral vancomycin) |
| Cefoxitin |
| Carbapenem |
| **Other** |
| Macrolide |
| Sulfonamide |
| Cephalosporin |
| Fluoroquinolone |
| Glycopeptide (IV vancomycin) |

## 2.4 OUTCOME

According to the Centers for Disease Control and Prevention (CDC), children are classified as overweight if they had a body mass index (BMI) or weight-for-length ≥ 85th percentile and <95th percentile; while children classified as obese have a BMI or weight-for-length ≥ 95th percentile.[2] For the purposes of this study, we combined the CDC-defined overweight and obesity criteria (i.e. BMI or weight-for-length ≥ 85th percentile) into a single outcome, which we will henceforth call overweight. BMI is calculated from the height (in centimeters) and weight (in kilograms) for

children 24 months or older; while weight-for-length is calculated for children less than 24 months old. The height, length and weight outcomes were based on values measured and recorded by GH medical staff as part of the routine clinical visit for children seen by providers at GH. We also report an outcome of BMI z-score. The BMI and BMI z-score were based on the 2000 CDC Reference values.[33] We chose being overweight at age 48-59 months as our primary outcome because being overweight at this age has been associated with being overweight in adolescence[34], most children have a well-child visit (with height and weight recorded) in anticipation of preschool enrollment at age 48-59 months, and most children have developed a stable microbiota by this age.[35]

## 2.5 Covariates

We included covariates in our analyses that we anticipated could be confounders or precision variables in the association between antibiotic exposure and obesity development. Birth weight was obtained from the WA DOH birth certificate records database. Subsequent weights, lengths (<24 months), and heights (≥24 months) were abstracted from the GH database. Maternal education level by self report and Medicaid status were considered proxies for socioeoconomic status. Other covariates and their data sources are listed in Table 2.

**Table 2. Data sources and elements**

| Data Elements | GH Database | WA DOH Birth Certificate Database |
|---|---|---|
| Antibiotic exposure | X | |
| BMI at 4 years old | X | |
| Birth weight | | X |
| Gestational age | | X |
| Sibling status (parity) | | X |
| Race/ethnicity | | X |
| Maternal BMI | X | X |
| Maternal oral antibiotics (during pregnancy) | X | |
| Type of delivery | | X |
| Maternal smoking | | X |
| Socioeconomic status | X | X |
| Asthma diagnosis[∫] | X | |
| Medicaid status | | X |
| Maternal GBS diagnosis | X | |

[∫]This includes ICD-9 codes and sub-codes of 517 and 493.

## 2.6 Study Procedures

This study was approved independently by the Institutional Review Boards of Group Health Research Institute, Seattle Children's Hospital and the Washington State Department of Health.

## 2.7 Analysis

Antibiotic exposure was evaluated both as a continuous variable  illustrating frequency of antibiotic courses "exposed" defined as all antibiotic exposure from 0-47 months, and

"unexposed" as no antibiotic exposure. The outcome was evaluated as a dichotomous variable with overweight defined as presence of BMI ≥ $85^{th}$ percentile, and as a continuous variable using BMI z-score. If a subject had multiple BMI data points during the 48-59 month range, the latest data point available was used in the analysis. BMI z-scores were not included in the analysis if they had an absolute value ≥ 5. Significant covariates ($p<0.05$;Table 1) remained in the final model for the association between antibiotic exposure and overweight.

The relationship between antibiotic exposure as a continuous variable from 0-47 months and BMI ≥ $85^{th}$ percentile at 48-59 months was evaluated using multivariable logistic regression. Multivariable linear regression was conducted to evaluate the relationship between antibiotic exposure as a continuous variable from 0-47 months and BMI z-score as a continuous variable at 48-59 months. The timing of first antibiotic exposure was categorized as < 12 months, 12-24 months and 24-47 months; then each category was compared to the no antibiotic exposure group in a logistic regression model with BMI ≥ $85^{th}$ percentile at 48-59 months as the outcome. Additionally, the type of antibiotic was considered and two categories were made: (1) anti-anaerobic or (2) non-anti-anaerobic and no antibiotics, in order to evaluate the relationship between the type of antibiotic received and the outcome of BMI ≥ $85^{th}$ percentile at 48-59 months in a logistic regression model.

We conducted a sensitivity analysis adding maternal group B streptococcus (GBS) diagnosis into the model as a proxy for the intrapartum intravenous antibiotic prophylaxis GBS positive mothers receive just before delivery.[36] Additionally, we conducted a sensitivity analysis adding maternal BMI into the model for mothers with this data available.

BMI and BMI z-scores were calculated using Stata 13.0 (College Station, TX: StataCorp LP) and the program *zanthro,* which is based on the 2000 CDC Reference values.[33,37] All descriptive statistics and regression models were conducted with Stata 13.0.

## 3 Results

Among the 4,938 children in our cohort, 3554 (72%) received antibiotics at least once from age 0-47 months. We describe the baseline characteristics of our cohort –both the children and their mothers– in Table 3. Children who were exposed to antibiotics were more often male, more often had a diagnosis of asthma, and were more often recipients of Medicaid. The mothers of antibiotic-exposed children were more often white, more often received oral antibiotics during pregnancy, and had higher BMIs. Children in the antibiotic-exposed group were nearly 1 month older than the unexposed group at the outcome (51.4 months and 50.7 months, respectively). There was no difference in prevalence of overweight (≥ 85-95$^{th}$ percentile), between the exposed and unexposed groups. However, the exposed group had a higher prevalence of obesity (BMI > 95$^{th}$ percentile) at last study visit than the unexposed group at 5% versus 3% (chi square test, p=0.036; Figure 2). The majority of children (53%) in the antibiotic-exposed group had their first antibiotic exposure at < 12 months.

**Table 3. Participant and maternal characteristics**

| Participant characteristics | Antibiotic exposed N=3533 (71.6%) | Antibiotic unexposed N=1405 (28.4%) | P value |
|---|---|---|---|
| Female, n (%) | 1655 (46.8) | 727 (51.7) | 0.002 |
| Age in months at outcome, mean ± SD | 51.4 ± 3.4 | 50.7 ± 3.1 | <0.001 |
| Gestational age in weeks, mean ± SD | 39.0 ± 2.4 | 39.1 ± 1.7 | 0.119 |
| Birth weight in grams, mean ± SD | 3442 ± 529 | 3450 ± 551 | 0.637 |
| Delivery type, n (%)<br>Vaginal<br>C-section | <br>2575 (72.9)<br>959 (27.1) | <br>1036 (73.7)<br>369 (26.3) | <br>0.532 |
| Sibling status (parity), n (%)<br>≥ 1 | <br>1927 (54.5) | <br>737 (52.5) | <br>0.188 |
| Child asthma, n (%) | 548 (15.5) | 66 (4.7) | <0.001 |
| Medicaid, n (%) | 182 (5.2) | 39 (2.8) | <0.001 |
| **Maternal characteristics** | | | |
| Race, n (%)<br>White<br>Asian/Pacific Islander<br>Other[ʃ] | <br>2701 (76.4)<br>532 (15.1)<br>301 (8.5) | <br>985 (70.1)<br>305 (21.7)<br>115 (8.2) | <br><0.001 |
| Hispanic ethnicity, n (%) | 186 (5.4) | 77 (5.6) | 0.805 |
| Maternal education, n (%)<br>Some High School<br>Completed High School<br>Some college | <br>426 (12.2)<br>676 (19.3)<br>2400 (68.5) | <br>107 (11.9)<br>221 (15.8)<br>1012 (72.3) | <br><0.001 |
| Maternal BMI, kg/m$^2$ mean ± SD[€] | 26.8 ± 6.4 | 25.9 ± 6.0 | <0.001 |
| Maternal oral antibiotics during pregnancy, n (%) | 1127 (31.9) | 332 (23.6) | <0.001 |

[ʃ]Other includes black, Native American, Latino and unknown.

[€]Due to 33% are missing this was not included in the final model; however, a sensitivity analysis was conducted.

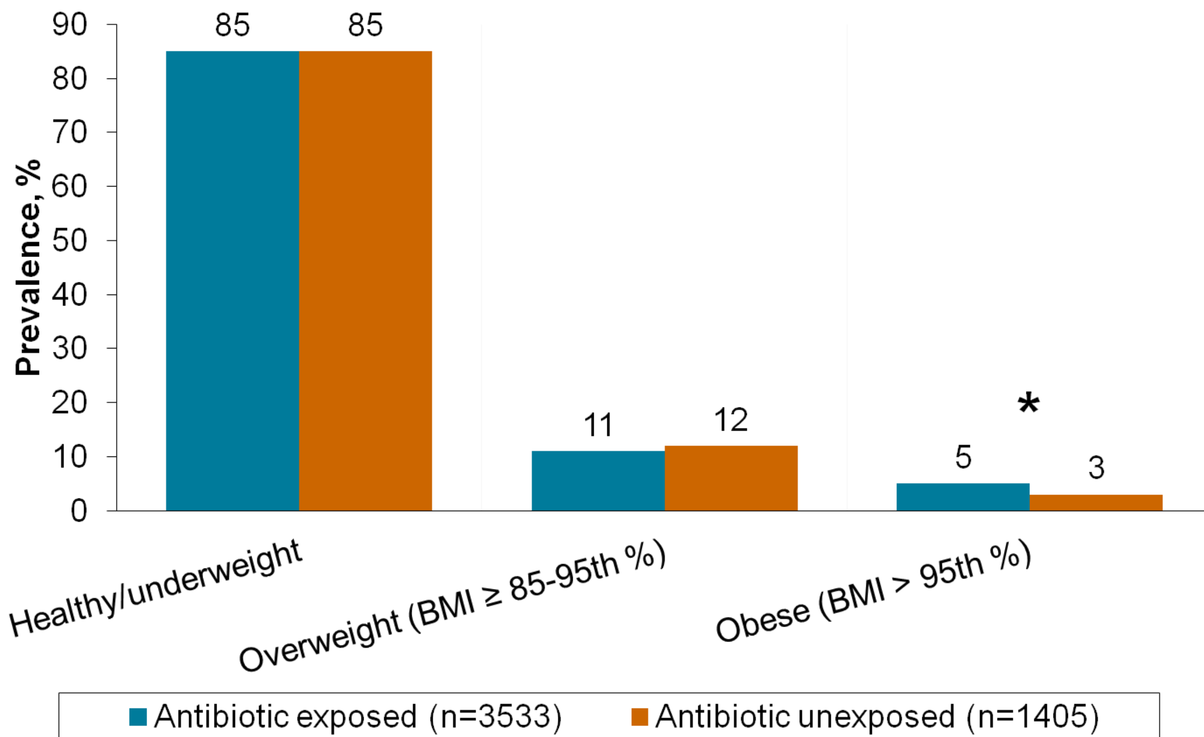


**Figure 1. BMI category at 48 – 59 months**

In a multivariable model adjusted for: sex, Medicaid status, maternal oral antibiotic exposure, asthma diagnosis, race, maternal education, birth weight and delivery type, the odds of overweight were 3% higher for each additional course of antibiotics that a child received from age 0-47 months (OR: 1.03, 95% CI: 1.01. 1.05; Table 4). This dose-response relationship is shown in Figure 3. Children who received the mean number of antibiotic courses (3.5 courses) had an 11% higher odds of overweight development (OR: 1.11, 95% CI: 1.01, 1.19). We conducted a sensitivity analysis adding maternal diagnosis of Group B Strep diagnosis during pregnancy (a proxy for maternal intravenous antibiotic exposure at delivery) and the significant association between antibiotic exposure and overweight development remained [OR: 1.03 (95% CI: 1.01, 1.05)]. An additional sensitivity analysis was conducted with the 67% of Moms who had BMI data available, similarly the association between antibiotic exposure and overweight

development remained, however, the lower end of the CI was at 1.00 [OR: 1.03 (95% CI: 1.00, 1.06)].

**Table 4. Logistic regression of antibiotic exposure as a continuous variable and overweight category as a dichotomous variable**

| Variable | Odds Ratio | 95% Confidence Interval | P value |
|---|---|---|---|
| Antibiotic exposure[€] | 1.03 | 1.01, 1.05 | 0.006 |
| Sex | | | |
| Female (n=2382) | 1.00 | Reference | |
| Male (n=2557) | 0.77 | 0.67, 0.88 | <0.001 |
| Medicaid recipient | | | |
| No (n=4717) | 1.00 | Reference | |
| Yes (n= 221) | 1.31 | 0.96, 1.79 | 0.093 |
| Maternal antibiotic exposure[€] | 1.08 | 1.02, 1.15 | 0.014 |
| Asthma | | | |
| No (n = 4324) | 1.00 | Reference | |
| Yes (n=614) | 1.34 | 1.11, 1.61 | 0.003 |
| Race | | | |
| White (n=3686) | 1.00 | Reference | |
| Asian/Pacific Islander (n=837) | 1.00 | 0.82, 1.21 | 0.987 |
| Other[∫] (n=416) | 1.10 | 0.87, 1.38 | 0.435 |
| Maternal education | | | |
| Some High School (n=593) | 1.00 | Reference | |
| Completed High School (n=897) | 1.23 | 0.97, 1.56 | 0.080 |
| Some College (n=3412) | 0.84 | 0.68, 1.04 | 0.114 |
| Birth weight in grams[€] | 1.0005 | 1.0003, 1.0007 | <0.001 |
| Delivery type | | | |
| Vaginal delivery (n=3611) | 1.00 | Reference | |
| Cesarean section (n=1328) | 1.13 | 0.98, 1.31 | 0.102 |

[€] Denotes continuous variable.
[∫]Other includes black, Native American, Latino and unknown.

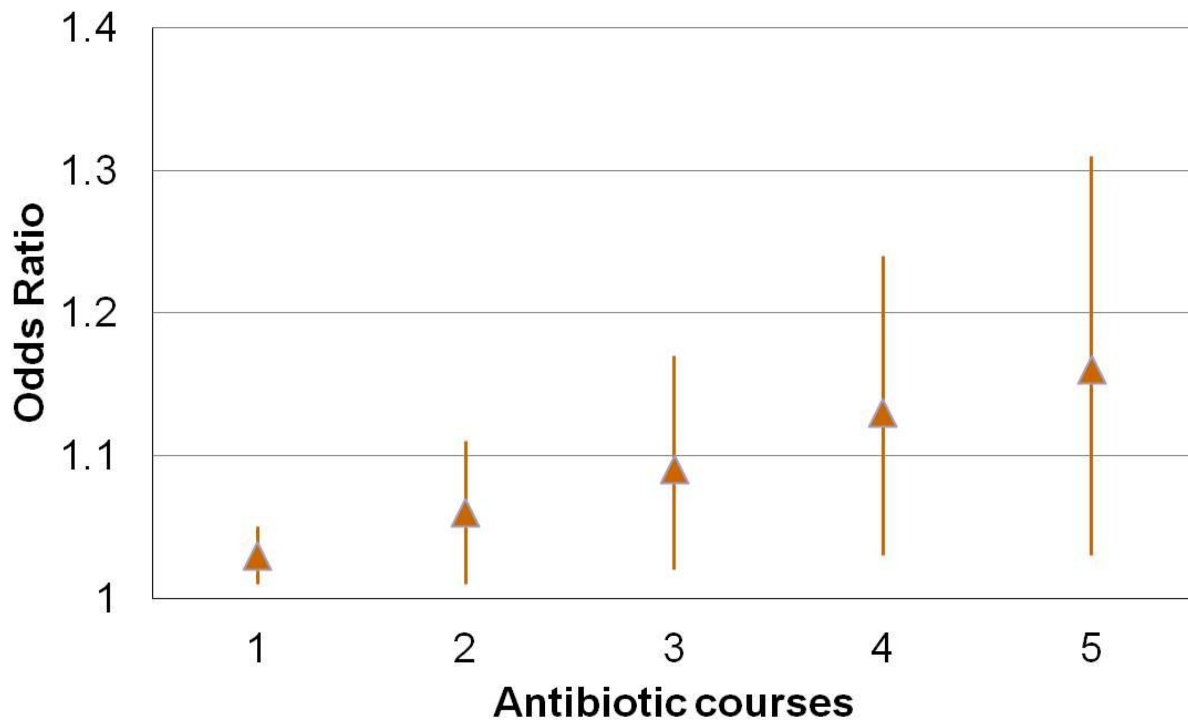


**Figure 2. Dose-response of antibiotic exposure and odds of overweight development**
*The range of antibiotic exposures on the x-axis represents the of antibiotic exposure.

In a multivariable logistic regression model, when antibiotic exposure was categorized into anti-anaerobic antibiotic exposure compared to a combined category of non-anti-anaerobic antibiotics and no exposure (Table 1), there was an association between type of antibiotic exposure and overweight development. The odds of developing overweight was 4% higher for each additional course of anti-anaerobic antibiotics a child received (OR: 1.04, 95% CI: 1.01, 1.08); this model was adjusted for: sex, Medicaid status, maternal oral antibiotic exposure, asthma diagnosis, race, maternal education, birth weight and delivery type. Among children who received the mean number of anti-anaerobic courses (2.4 courses), their odds of overweight development was 10% higher (OR: 1.10, 95% CI: 1.01, 1.20).

When the age of the child's first antibiotic exposure was categorized into four categories (none, <12 months, 12-23.99 months, and 24-47 months). In a multivariable logistic regression model children who received antibiotics at <12 months compared to the reference group of none had an 18% higher odds of being overweight (OR: 1.18, 95% CI: 1.14, 1.21). This model was adjusted for: sex, medicaid recipient, maternal oral antibiotic exposure, asthma diagnosis, race, maternal education, birth weight and delivery type. Children who received their first dose of antibiotics at 12-23.99 months or at 24-47 months compared to the reference had lower odds of overweight development (OR: 0.94, 95% CI: 0.91, 0.98; OR: 0.85, 95% CI: 0.81, 0.89, respectively).

In a multivariable linear regression model when both antibiotic exposure and BMI z-score were continuous variables we found an association between antibiotic exposure and higher BMI z-score. For each additional antibiotic course children received, there was a 0.012 higher BMI z-score (95% CI: 0.003, 0.021); this model was adjusted for: sex, Medicaid status, maternal oral antibiotic exposure, asthma diagnosis, race, maternal education, birth weight and delivery type. Children with the mean number of antibiotic exposures (3.5 courses) would have a 0.042 higher BMI z-score.

# 4 DISCUSSION

In our longitudinal birth cohort study combining data from the WA state birth certificate database and GH, we found that for each additional course of antibiotics children were exposed to between 0-47 months, they had a 3% higher odds of overweight development at 48-59 months. This relationship was higher for children who were exposed to anti-anaerobic antibiotics. Children who were exposed to their first antibiotics at less than 12 months of age

had the highest odds of later overweight development. Additionally, we found that children's BMI z-score increased for each additional antibiotic exposure.

Our findings overall align with those of prior longitudinal studies that found a relationship between antibiotic exposure in infancy and weight status in later childhood[21-23,25,26]. In a prior study of children receiving primary care in Philadelphia, they found an association between broad spectrum antibiotic exposure at 0-5 months and/or 6-11 months and obesity (BMI >95$^{th}$ percentile) development at ages 24-59 months (RR = 1.11, and 1.09, respectively); they did not find an association for a child's first exposure to broad spectrum antibiotics at 12-17 months or 18-24 months.[23] These results are in some contrast to our findings wherein first exposure to antibiotics of any type at < 12 months was associated with greater odds of overweight development in later childhood, i.e. at 48-59 months.

While prior research in this area has classified antibiotics as 'narrow spectrum' (i.e. amoxicillin and penicillin) vs. 'broad spectrum',[23] we classified antibiotic exposure as anti-anaerobic vs. other antibiotics[31] because the gut microbiota are predominantly anaerobic and have been shown to be affected by anti-anaerobic antibiotic exposure.[10,32] The antibiotics classified as narrow spectrum in others studies were classified as anti-anaerobic in our study, which suggests that our findings were different as it relates to amoxicillin and penicillin exposure. This difference may be due to difference in regional and global prescribing patterns wherein the broad spectrum category may have included other anti-anaerobic antibiotics (i.e. amoxicillin-clavulanic acid). Another reason for the difference in findings of our study compared to other studies may be the difference in study populations -- our study was a primarily white high-income population while the prior US study had a higher proportion of low-income minority children and the other cohorts were based in Europe, the inclusion of maternal factors

(antibiotics and BMI) and birthweight, and the use of antibiotic dispensing rather than prescribing data.

A recent study from a Finnish cohort found an association between antibiotic exposure at <6 months of age, as well as with repeated antibiotic exposures up until 23 months of age, with an outcome of higher BMI z-score at 24 months old.[26] This study's exposure was based on antibiotic dispensing data from the Finnish Drug Prescription register, and linked medical record data and birth certificate data. However, they did not include maternal factors such as BMI and antibiotic receipt during pregnancy, and their outcome was ascertained earlier than ours. They found a greater association between antibiotic exposure to repeated courses of macrolides and higher BMI z-score than amoxicillin or cephalosporin. This finding differs from ours because in our study macrolides would have been grouped in the 'other' category, rather than the anti-anaerobic category.

Further, a study in a Manhattan mother-baby dyad cohort found that maternal antibiotic exposure in pregnancy has been associated with childhood overweight at age 7 years.[38] They postulate that this finding is due to the important role that the mother's gut microbiota plays in the development of her child's microbiota and an alteration in the mother's microbiota may affect that of the child. [38] We found maternal antibiotics to be associated with childhood overweight in our multivariable model, therefore, this may also be an important area for further evaluation in the life course study of childhood overweight.

## 4.1 STRENGTHS AND LIMITATIONS

Our study has several strengths one was our ability to include data from the WA state birth certificate database due to the prior established linkage between GH electronic health records and the birth certificate records is a strength of our study.[29] Further, the GH electronic

health records can be linked between the mother and baby in order to incorporate important elements during pregnancy, such as maternal BMI, maternal diagnoses, and maternal antibiotic receipt.[28] The ability to account for these variables is unique to US cohort studies that are frequently limited by the inability to link across generations or with birth certificate records. Our study contributes to the current landscape of longitudinal observational studies on this topic because we were able to include maternal factors in our analyses. Maternal BMI has been demonstrated to be an important factor in long term childhood weight status and was included as a sensitivity analysis for those Mom-baby dyads with this data available.[39]

This study was also able to utilize pharmaceutical fill data, which has been shown to be superior to prescribing data and does not rely on parental recall of antibiotic receipt.[40] The pharmaceutical fill database includes all antibiotics that were prescribed including those outside of the GH system.[40] Our study inclusion criteria required that children were continuously enrolled in our study throughout the exposure period (0-47 months), therefore it is unlikely that they had antibiotic exposures that were missing due to change in health care provider or moving out of the GH system.

Our study was limited by the fact that it was conducted in a primarily white and high income cohort in Washington State that may not be generalizable nationally. An additional limitation of our study is that we were unable to include a variable about breastfeeding status in our models because it was inconsistently and incompletely ascertained in the GH electronic health record data. Future studies exploring the nature of this association should endeavor to explore the potential confounding or mediating impact of breastfeeding on antibiotic exposure in early life and weight status in later childhood. Additionally, we were unable to include intravenous antibiotic exposure in our study because we did not have complete ascertainment of

this variable in the GH data. The majority of children who are exposed to antibiotics in the hospital will be discharged on antibiotics so it is less likely that we will miss a child's entire antibiotic course. This does, however, limit our ability to determine whether the association between antibiotics and weight status differs based on type of antibiotic delivery.

## 4.2 CONCLUSIONS AND IMPLICATIONS

Antibiotic exposure has a dose-response relationship with weight status during childhood. In particular, when children receive antibiotics at less than 12 months old and if they receive anti-anaerobic antibiotics they have a higher risk of overweight development. Additionally, maternal antibiotic exposure is associated with child overweight and may provide an opportunity to further evaluate antibiotic exposure as a factor in the life course approach to overweight.

Child overweight remains a significant concern during childhood and throughout the life course. The association between antibiotic exposure and overweight development affords an opportunity to explore a physician-modifiable risk factor for overweight as an avenue for overweight prevention in children. Children continue to receive antibiotics almost twice as often as they are indicated for the treatment of common bacterial infections based on prevalence of bacterial infections[41], and decreasing unnecessary prescribing could play a role in overweight prevention.

Experimental studies into the mechanism of the association between antibiotic exposure and overweight development in childhood would be a natural future direction. One particular area of great interest is in the gut microbiota, which is one postulated mechanism for this relationship. Additionally, given that antibiotics are indicated for bacterial infections, another area of inquiry may evaluate the duration of an antibiotic course and its potential impact on weight status, or the potential mediating role of probiotic use when antibiotics are necessary.

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