Early Antibiotic Exposure and Weight Outcomes in Young Children

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abstract

OBJECTIVES: To determine the association of antibiotic use with weight outcomes in a large cohort of children.

METHODS: Health care data were available from 2009 to 2016 for 35 institutions participating in the National Patient-Centered Clinical Research Network. Participant inclusion required same-day height and weight measurements at 0 to <12, 12 to <30, and 48 to <72 months of age. We assessed the association between any antibiotic use at <24 months of age with BMI *z* score and overweight or obesity prevalence at 48 to <72 months (5 years) of age, with secondary assessments of antibiotic spectrum and age-period exposures. We included children with and without complex chronic conditions.

RESULTS: Among 1 792 849 children with a same-day height and weight measurement at <12 months of age, 362 550 were eligible for the cohort. One-half of children (52%) were boys, 27% were African American, 18% were Hispanic, and 58% received ≥1 antibiotic prescription at <24 months of age. At 5 years, the mean BMI *z* score was 0.40 (SD 1.19), and 28% of children had overweight or obesity. In adjusted models for children without a complex chronic condition at 5 years, we estimated a higher mean BMI *z* score by 0.04 (95% confidence interval [CI] 0.03 to 0.05) and higher odds of overweight or obesity (odds ratio 1.05; 95% CI 1.03 to 1.07) associated with obtaining any (versus no) antibiotics at <24 months.

CONCLUSIONS: Antibiotic use at <24 months of age was associated with a slightly higher body weight at 5 years of age.

WHAT'S KNOWN ON THIS SUBJECT: Antibiotics may promote weight gain among children through direct effects on growth and metabolic consequences associated with changing the microbiome. Research in humans is mixed, with diverging results in studies in which early childhood antibiotic exposure and growth is assessed.

WHAT THIS STUDY ADDS: Among 362 550 children in 35 health care institutions, there was a small association between antibiotic use at <24 months of age and higher BMI *z* scores and overweight or obesity prevalence at 48 to <72 months of age, with modest dose response.

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Overuse of antibiotics is common and associated with side effects and the development of antibiotic resistance.[1] Antibiotics also modify the gut microbiome in ways that could lead to weight gain and obesity.[2–8] Antibiotics promote weight gain in animals,[9] but the relationship in humans is less clear. Authors of a recent meta-analysis found that antibiotic exposure at <24 months of age (versus no exposure) was associated with a higher risk of overweight and obesity in later childhood, with a higher mean BMI *z* score of 0.07 (95% confidence interval [CI] 0.05 to 0.09).[10] Studies have not been consistent, however, and variation may result from heterogeneity of study populations and different strategies for defining exposures and outcomes.[11–13]

Authors of several studies have examined antibiotics and weight outcomes,[14–17] but it is unclear if and how the age of exposure contributes to this association. The microbiome is established in early childhood and has some stability after the first 6 months of life.[18,19] Abrupt alterations by antibiotics during this formative period could potentially have long-lasting effects. The type of antibiotics (narrow- versus broad-spectrum) and the number of exposures also may lead to differential effects on the microbiota and weight.[3] Another area of recent investigation has been the possible role of infections as a risk factor for obesity. Several infections, especially adenoviruses, have been linked to obesity and weight gain in animal models.[20] In one large longitudinal study, Li et al[13] found that infections were associated with obesity in children and that controlling for infections attenuated the relationship between antibiotics and obesity.[21]

Data from electronic health records (EHRs) and other health care data provide a foundation for large studies of the comparative effectiveness and safety of treatments.[22] Given the mixed evidence for the relationship between antibiotics and obesity, the reliance of previous studies on data from single institutions, the need for large samples to investigate heterogeneity of treatment effects, and the importance of this potential association to parents, our objective for this study was to examine more precisely than in previous studies the association of early-life antibiotic use on children's weight using data from a diverse multi-institutional national research network. We studied the association of spectrum, dose response, and the timing of antibiotics on body weight and overweight or obesity.

METHODS

The National Patient-Centered Clinical Research Network (PCORnet) (pcornet.org) is a distributed research network that facilitates multi-institutional observational research and pragmatic clinical trials. The network standardizes EHR and other health care data to a common data model (CDM) (Note 1 of the Supplemental Information).[23–26] For this study (discussed in detail elsewhere), there were 35 contributing institutions (Supplemental Table 5).[26] The institutional review boards responsible for each institution approved the study (Note 1 of the Supplemental Information), allowing for the transfer of deidentified patient-level data to Harvard Pilgrim Health Care Institute, where statistical analyses were conducted. Code lists and statistical programs used for this study are available at https://github.com/pcornet-analytics/antibiotics.

Cohort Formation

We required children to have a valid birth date, a patient identifier, and a same-day height and weight measurement at each of the following ages: 0 to <12 months (N = 1 792 849), 12 to <30 months (N = 968 852), and 48 to <72 months of age (N = 362 550) (Supplemental Fig 2). Requiring multiple measurements during the exposure period created a cohort of children with established connections to the health care institution, increasing the probability of having more complete antibiotic prescribing data.

Development of Study Specifications and Variables

Exposure

PCORnet requires institutions to convert their institutional medication codes to the National Library of Medicine's (NLM's) RxNorm terminology.[27] We constructed a set of terms for systemic antibiotics using NLM resources and other systematic look-up tools (Note 2 of the Supplemental Information).[28,29] Because oral and intramuscular medication usage are more modifiable than intravenous medications, we included only oral and common intramuscular formulations (eg, ceftriaxone). Further, some institutions did not have ready availability of intravenous medication administrations.

Because records commonly omitted days supply, we could not determine the exact length of each prescription. We also wanted to account for multiple antibiotic prescriptions given during the same treatment episode. Therefore, we deduplicated same-day prescriptions and created antibiotic treatment episodes by joining antibiotic prescriptions within 10 days, giving priority to the broadest-spectrum antibiotic prescribed (Note 3 of the Supplemental Information). Of antibiotic episodes, 91.6% had only 1 prescription; 99.6% of episodes spanned ≤30 days. We created age period (0–<6 months, 6–<12 months, and 12–<24 months) exposure variables to examine for

the possibility of sensitive periods of antibiotic exposure.

Our main independent variable was antibiotic use at <24 months of age, defined as any versus no antibiotic prescriptions. To assess dose response, we developed a categorical count of antibiotic treatment episodes (0–≥4). We also separately examined the use of narrow- (penicillin, amoxicillin, and dicloxacillin) and broad-spectrum antibiotics. Broad-spectrum antibiotics included penicillin combinations (eg, amoxicillin and clavulanic acid).

Outcomes

The primary outcome was a single age- and sex-specific BMI *z* score measured closest to 60 months of age, falling within the range of 48 to <72 months (5 years) of age. This was an appropriate age for follow-up because most childhood obesity is incident by 5 years of age, and adiposity rebound typically occurs in that age range.[30,31] From same-day height and weight measurements, we calculated BMI as kilograms per meter squared and used the Centers for Disease Control and Prevention 2000 growth curves to assign age- and sex-specific BMI *z* scores, excluding biologically implausible values.[32] Secondary outcomes (also assessed at age 5 years) were overweight or obesity, which was defined as an age- and sex-specific BMI ≥85th percentile, and obesity, which was defined as an age- and sex-specific BMI ≥95th percentile; a BMI <85th percentile was the comparison.

Confounders and Effect Modifiers

We selected confounders a priori. We defined asthma as ≥2 asthma diagnosis codes at <72 months of age, and we defined preterm status as any preterm diagnosis code at <24 months of age. We included these diagnoses because of strong associations with weight outcomes, infections, and antibiotic use in children.[33,34] For corticosteroids (also associated with weight and an increased risk for infections), we included only oral formulations and defined use at <24 months of age as a categorical count of episodes (0–≥4).

Health care use could be associated with antibiotic prescriptions and child weight if use reflects underlying illnesses or parenting behaviors. We counted all clinical encounters, including inpatient, emergency, or ambulatory visits at <24 months of age. For some institutions, counts may have included some nonvisits, such as telephone encounters. We categorized race as Asian American, African American, white, other, or unknown and Hispanic ethnicity using yes or no.

To evaluate the role of infections, we did several analyses. Infections could introduce confounding by indication (eg, antibiotics are nearly always prescribed for infections); therefore, we included infections in most models. Because the count of infections was skewed, we log transformed the count and included it as a continuous variable in models. We also examined effect modification in models in which we stratified by the number of infections (0–1, 2–3, and ≥4). To account for the possibility of residual confounding from severe infections, which nearly always required antibiotics and lead to the most robust immune responses, we controlled for tier 1 infections in these stratified models. We classified infections coded in encounters as tier 1, 2, or 3 using the approach of Fleming-Dutra et al[35] (Note 4 of the Supplemental Information). Tier 1 infections nearly always require antibiotics (eg, pneumonia), and tier 3 typically do not (eg, nonsuppurative otitis media).[35] Antibiotics also could mediate a relationship between infections and weight outcomes; however, because our primary objective for this study was to investigate antibiotics and weight outcomes, we focused on how infections could alter that relationship.

For sensitivity analyses, we defined well-child visits using diagnostic codes, the Healthcare Common Procedure Coding System, and *Current Procedural Terminology* codes. We stratified all models by complex chronic conditions because we considered them to be effect modifiers. Children with these conditions were likely to have substantially different patterns of growth and interactions with the health care system from those of counterparts. We used the list of conditions and corresponding *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes reported by Feudtner et al[36] to identify these children; we excluded asthma and added hypothyroidism and pituitary disorders. We expanded the code list by searching for these diseases using an Optum ICD-9-CM dictionary (Note 4 of the Supplemental Information).[36,37] We required >1 diagnostic code at <72 months of age.

Secondary Analysis Incorporating Maternal Variables

Seven institutions could link maternal EHR data with child EHR data using different methods: links made at the child's delivery, insurance identifiers (most common), and home address, phone numbers, and emergency contacts. We extracted maternal age at delivery, prepregnancy BMI, diabetes or gestational diabetes status, birth weight, pregnancy smoking status, and delivery mode and ran models, controlling for all these variables at once (Note 5 of the Supplemental Information).

Statistical Analyses

We fit linear mixed-effects regression models stratified by complex chronic condition status to examine associations of any antibiotic use at <24 months of age with the BMI *z* score at 5 years of age, and we fit similar logistic models for the outcome of overweight or obesity (BMI ≥85th vs <85th percentile) and obesity (BMI ≥95th vs <85th percentile). We accounted for clustering by network partner and controlled for sex, race, ethnicity, preterm birth, asthma, infections, corticosteroid episodes, encounters at <24 months of age, and age at outcome. We also examined dose response as the number of antibiotic episodes at <24 months of age associated with weight outcomes.

We fit models using age period–specific exposures (0–<6 months, 6–<12 months, and 12–<24 months) in which we adjusted for antibiotic exposures during previous age periods and covariates contemporaneous with the exposure (corticosteroids and encounters). We further assessed narrow- and broad-spectrum antibiotic use at <24 months of age and by age periods, and we examined the 5 most common classes of broad-spectrum antibiotics. For narrow-spectrum exposures, we limited analyses to children with no broad-spectrum exposures during the same exposure time window or before. To account for effect modification by infections, we stratified by the number of infections (0–1, 2–3, and ≥4) and included a count of severe infections in these strata-specific models.

We used the same approach for analyses incorporating maternal variables, which we controlled for simultaneously in 1 model. For these analyses, we only examined overall and dose-response associations with the BMI *z* score for children without complex chronic conditions because of sample size limitations. We performed all analyses using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Sensitivity Analyses

First, to capture children most closely tied to health care systems, we limited the cohort to children with any well-child visits at <72 months of age as a proxy for receiving primary care at the institution (Note 6 of the Supplemental Information). Second, we limited the analysis to sites with >40% antibiotic prescribing rates at <24 months of age. We anticipated that rates below 40% might result from missing data on prescriptions. Third, we excluded children with antibiotics given for tier 1 infections to determine if associations were similar when antibiotics were prescribed only for infections that might not require them, such as in tier 2 and 3 infections. We linked antibiotic prescriptions to the most recent infectious diagnostic code within 7 days.

RESULTS

Characteristics of Study Population

In the 35 institutions, 362 550 children met eligibility criteria (Supplemental Fig 2); 52% were boys, 53% were white, 27% were African American, and 18% were Hispanic (Supplemental Table 6). Of all children in the cohort, 14% (n = 51 603) were diagnosed with ≥1 complex chronic condition at <72 months of age. More than half of the children (58%) received at least 1 antibiotic at <24 months of age; 16% had ≥4 prescribing episodes, and 35% had at least 1 broad-spectrum antibiotic episode. Overall, 28% of the study population had overweight or obesity at 5 years of age. Children who received antibiotics were more likely to have an asthma diagnosis and had more health care encounters and infections than children who had not received antibiotics (Table 1).

Multivariable Linear Regression: BMI *z* Scores at 5 Years of Age

In models examining any antibiotic use at <24 months of age and the BMI *z* score at 5 years, we estimated a small association for children with and without complex chronic conditions (Table 2). Among children without complex chronic conditions, receiving any antibiotic at <24 months of age was associated with a higher BMI *z* score by 0.04 (95% CI 0.03 to 0.05). Results were slightly higher in magnitude (BMI *z* score 0.06 [95% CI 0.04 to 0.09]) for children with complex chronic conditions. Results for age period–specific exposures were similar (Table 2). When separately analyzing broad- and narrow-spectrum antibiotics, results revealed slightly higher BMI *z* scores for broad-spectrum antibiotics, especially for children with complex chronic conditions.

Among children without complex chronic conditions, we estimated an increasing dose response with the BMI *z* score higher by 0.02, 0.04, 0.05, and 0.07 for 1, 2, 3 and ≥4 antibiotic episodes versus none, respectively (Fig 1, Supplemental Table 7). Results of dose-response analyses separated by broad- and narrow-spectrum exposure were similar. For children with complex chronic conditions, broad-spectrum antibiotic exposure appeared nonmonotonic, with a higher estimated BMI *z* score by 0.04, 0.07, 0.15, and 0.09 for 1, 2, 3, and ≥4 episodes versus none, respectively, but less so for narrow-spectrum antibiotics, with BMI *z* score differences of 0.02, 0.08, 0.04, and −0.06. Among the most commonly-prescribed classes of broad-spectrum antibiotics, the use

TABLE 1 Demographic and Clinical Characteristics of the Study Population, Overall and Stratified by Chronic Condition Status and Antibiotic Use

Characteristic	No Antibiotics at 0–<24 mo		Yes Antibiotics at 0–<24 mo	
	No Complex Chronic Condition, *N* = 130 208	With Complex Chronic Condition[a], *N* = 23 158	No Complex Chronic Condition, *N* = 180 739	With Complex Chronic Condition[a], *N* = 28 445
Female sex, *n* (%)	65 260 (50)	10 693 (46)	85 289 (47)	12 666 (45)
Race, *n* (%)				
Asian American	5978 (5)	750 (3)	6994 (4)	791 (3)
African American	36 268 (28)	4682 (20)	48 936 (27)	7915 (28)
White	65 597 (50)	13 609 (59)	96 217 (53)	15 389 (54)
Other	9778 (8)	2808 (12)	12 499 (7)	2767 (10)
Unknown	12 587 (10)	1309 (6)	16 093 (9)	1583 (6)
Hispanic ethnicity, *n* (%)	26 757 (21)	3577 (15)	29 498 (16)	4187 (15)
Preterm[b], *n* (%)	6977 (5)	3513 (15)	10 002 (6)	5527 (19)
Asthma[c], *n* (%)	10 596 (8)	2577 (11)	27 750 (15)	6673 (23)
Systemic corticosteroid episodes[d] at <24 mo of age, *n* (%)				
0	123 892 (95)	21 663 (94)	147 406 (82)	21 434 (75)
1	5024 (4)	1006 (4)	22 408 (12)	3776 (13)
2	845 (1)	264 (1)	6447 (4)	1491 (5)
3	259 (0)	114 (0)	2430 (1)	741 (3)
4+	188 (0)	111 (0)	2048 (1)	1003 (4)
Episodes for presumed infectious illnesses[e] at <24 mo of age, *n* (%)				
0	29 480 (23)	5005 (22)	11 341 (6)	846 (3)
1	18 363 (14)	2830 (12)	5989 (3)	805 (3)
2	18 571 (14)	2486 (11)	10 715 (6)	1117 (4)
3	16 273 (12)	2132 (9)	14 723 (8)	1477 (5)
4+	47 521 (36)	10 705 (46)	137 971 (76)	24 200 (85)
No. encounters[f] at <24 mo of age, median (IQR)	12.0 (7.0 to 16.0)	17.0 (9.0 to 28.0)	19.0 (13.0 to 26.0)	29.0 (18.0 to 47.0)
Systemic antibiotic prescribing episodes[g] at <24 mo of age, *n* (%)				
0	130 208 (100)	23 158 (100)	—	—
1	—	—	67 287 (37)	9965 (35)
2	—	—	40 199 (22)	6034 (21)
3	—	—	25 202 (14)	3804 (13)
4+	—	—	48 051 (27)	8642 (30)
Systemic broad-spectrum antibiotic prescribing episodes[g] at <24 mo of age, *n* (%)				
0	130 208 (100)	23 158 (100)	73 520 (41)	8138 (29)
1	—	—	53 513 (30)	8917 (31)
2	—	—	22 637 (13)	4219 (15)
3	—	—	12 114 (7)	2468 (9)
4+	—	—	18 955 (10)	4703 (17)
Systemic narrow- spectrum antibiotic prescribing episodes[g] at <24 mo of age, *n* (%)				
0	130 208 (100)	23 158 (100)	29 521 (16)	9152 (32)
1	—	—	79 035 (44)	10 222 (36)
2	—	—	40 332 (22)	4668 (16)
3	—	—	18 903 (10)	2249 (8)
4+	—	—	12 948 (7)	2154 (8)
BMI category at 48–<72 mo of age, *n* (%)				
Underweight (less than the fifth percentile)	6062 (5)	1770 (8)	6798 (4)	1680 (6)
Normal wt (fifth to <85th percentile)	89 441 (69)	14 926 (64)	122 554 (68)	18 321 (64)
Overweight (85th to <95th percentile)	18 070 (14)	3247 (14)	27 225 (15)	4232 (15)
Obese (≥95th percentile)	16 635 (13)	3215 (14)	24 162 (13)	4212 (15)
Age, mo (SD)	57.8 (5.5)	57.9 (5.0)	57.8 (5.3)	58.1 (4.7)
BMI *z* score (SD)	0.36 (1.19)	0.30 (1.32)	0.44 (1.15)	0.39 (1.27)

IQR, interquartile range; —, not applicable.

[a] Defined as ≥2 ICD-9-CM codes for a complex chronic condition at <72 months of age on the basis of a previously published code set.

[b] One or more ICD-9-CM codes for prematurity at <24 months of age.

TABLE 1 Continued

[c] Two or more ICD-9-CM codes for asthma at <72 months of age.

[d] Multiple corticosteroids given on the same day or within 10 days of each other were considered a single prescribing episode.

[e] Defined by ICD-9-CM codes on the basis of Fleming-Dutra et al.[35]

[f] Included all encounters in the inpatient, emergency department, urgent care, and outpatient settings.

[g] Multiple antibiotics given on the same day or within 10 days of each other were considered a single prescribing episode; 91.6% of episodes included a prescription written on a single day, with 99.6% of episodes spanning ≤30 days.

of sulfa drugs was associated with a higher BMI *z* score difference at 48 to <72 months compared with that of other classes for children without complex chronic conditions (BMI *z* score difference 0.09; 95% CI 0.07 to 0.11) (Supplemental Tables 8 and 9).

Effect Modification and Sensitivity Analyses

Models that ignored infections (Supplemental Table 10) revealed slightly larger parameter estimates than those controlling for infections, suggesting some confounding by infections; for any versus no antibiotic use at <24 months of age, BMI *z* score differences were 0.05 (95% CI 0.04 to 0.06) without infections and 0.04 (95% CI 0.03 to 0.05) with infections for children without complex chronic conditions. These results were similarly attenuated for children with complex chronic conditions. When we stratified on the number of infections, allowing for effect modification, and further controlled by the number of tier 1 infections, we observed differences in the association by stratum (Supplemental Table 11). BMI *z* score differences were largest for the ≥4 infections stratum (BMI *z* score difference 0.05 [95% CI 0.04 to 0.07] for children without complex chronic conditions; BMI *z* score difference 0.08 [95% CI 0.04 to 0.11] for children with complex chronic conditions). These differences were lower by ∼50% in strata of fewer infections; for 0 to 1 infection, these differences were 0.02 (95% CI 0.00 to 0.04) for children without complex chronic conditions and 0.04 (95% CI −0.03 to 0.11) for children with chronic conditions.

Because of the complex causal relationships between asthma and weight outcomes, with asthma causing weight gain and vice versa,[33] we ran models ignoring asthma; differences in the association of antibiotics with weight outcomes were minimal only for children with complex chronic conditions (Supplemental Table 12). Sensitivity analyses that included only participants with any well-child visit at <72 months of age, that were limited to sites with a ≥40% antibiotic prescribing rate at <24 months of age, or that excluded participants with prescriptions for tier 1 infections had consistent results (Supplemental Table 13). The incorporation of maternal

TABLE 2 Multivariable Linear Regression Results for the Association of Any Exposure to Antibiotics at <24 Months of Age With the BMI *z* Score at 48–<72 Months of Age, by Timing of Antibiotic Prescription

Antibiotics	No Complex Chronic Condition, *N* = 310 947		Complex Chronic Condition, *N* = 51 603	
	Model 1,[a] β (95% CI)	Model 2,[b] β (95% CI)	Model 1,[a] β (95% CI)	Model 2,[b] β (95% CI)
Any, mo				
0–<24	.08 (0.07 to 0.08)	.04 (0.03 to 0.05)	.09 (0.07 to 0.11)	.06 (0.04 to 0.09)
0–<6[c,d]	.10 (0.09 to 0.11)	.05 (0.04 to 0.06)	.09 (0.06 to 0.12)	.05 (0.02 to 0.08)
6–<12[c,d]	.07 (0.07 to 0.08)	.03 (0.02 to 0.04)	.08 (0.05 to 0.10)	.04 (0.01 to 0.06)
12–<24[c,d]	.06 (0.06 to 0.07)	.02 (0.01 to 0.03)	.09 (0.07 to 0.12)	.06 (0.03 to 0.08)
Broad spectrum, mo				
0–<24	.08 (0.07 to 0.09)	.04 (0.03 to 0.05)	.09 (0.07 to 0.12)	.07 (0.05 to 0.10)
0–<6[c,d]	.09 (0.07 to 0.11)	.04 (0.02 to 0.06)	.09 (0.05 to 0.12)	.05 (0.01 to 0.09)
6–<12 mo[c,d]	.08 (0.07 to 0.09)	.03 (0.02 to 0.05)	.08 (0.05 to 0.11)	.05 (0.01 to 0.08)
12–<24[c,d]	.07 (0.06 to 0.08)	.03 (0.02 to 0.04)	.10 (0.08 to 0.13)	.07 (0.04 to 0.10)
Narrow spectrum,[e] mo				
0–<24	.05 (0.04 to 0.06)	.02 (0.01 to 0.03)	.05 (0.02 to 0.08)	.03 (−0.01 to 0.06)
0–<6[c,d]	.10 (0.08 to 0.11)	.05 (0.04 to 0.07)	.09 (0.04 to 0.13)	.04 (−0.01 to 0.08)
6–<12[c,d]	.06 (0.05 to 0.07)	.02 (0.01 to 0.04)	.05 (0.01 to 0.09)	.01 (−0.03 to 0.05)
12–<24[c,d]	.04 (0.03 to 0.05)	.01 (0.00 to 0.02)	.05 (0.01 to 0.08)	.02 (−0.02 to 0.06)

[a] Corrected for clustering by site.

[b] Corrected for clustering by site and adjusted for sex, race, ethnicity, preterm birth, asthma, corticosteroid episodes (continuous, 0–4+) at 0–<24 months of age, number of encounters (continuous, log transformed) at 0–<24 months of age, infection episodes (continuous, log transformed) at 0–<24 months of age, and age at outcome.

[c] For exposure time windows, Model 2 was additionally adjusted for previous antibiotics: (1) antibiotics at 6–<12 months, adjusted for 0–<6 months antibiotics and (2) antibiotics at 12–<24 months, adjusted for 0–<12 months antibiotics.

[d] For exposure time windows, covariates were used during the same time window (corticosteroids and encounters): (1) antibiotics at 0–<6 months, covariates used for 0–<6 months; (2) antibiotics at 6–<12 months, covariates used for 6–<12 months; and (3) antibiotics at 12–<24 months, covariates used for 12–<24 months.

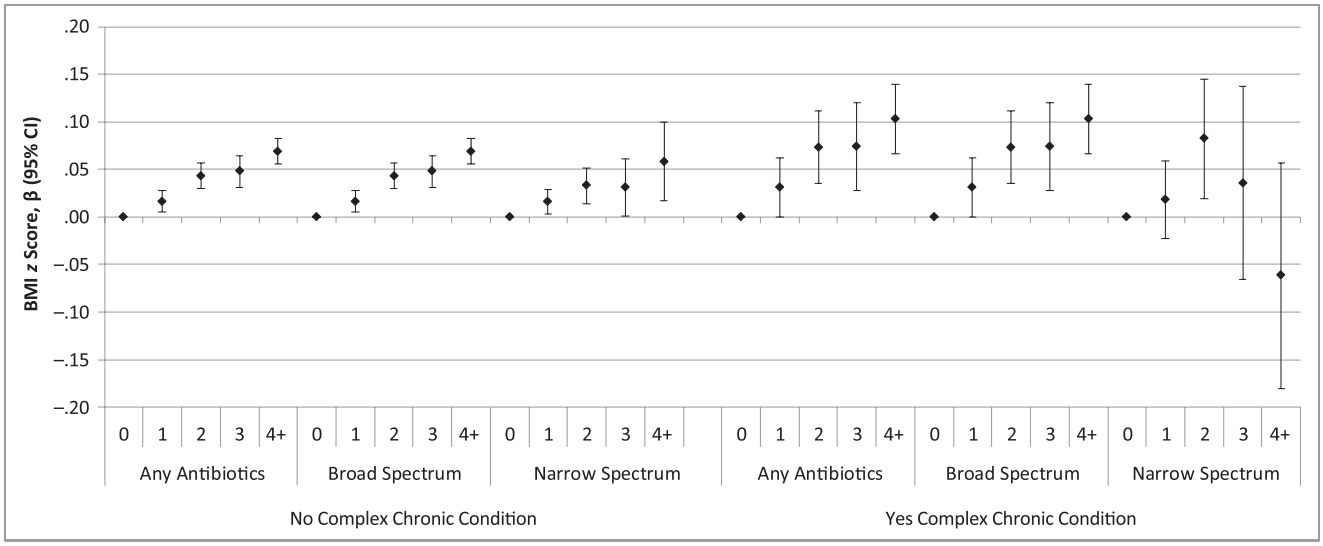

FIGURE 1

Dose-response relationship for association of antibiotic episodes at <24 months of age with BMI *z* scores at ages 48 to <72 months. This figure shows the difference in BMI *z* score at 48 to <72 months of age (5 years) according to the number of antibiotic episodes a child received at <24 months of age. Results reveal BMI *z* score differences and 95% CIs for 1, 2, 3, and ≥4 antibiotic episodes overall and for narrow- and broad-spectrum antibiotics compared with the reference of 0 antibiotic episodes. Results are stratified by whether a child had a complex chronic condition. The model was corrected for clustering by site and adjusted for sex, race, ethnicity, preterm birth, asthma, corticosteroid episodes (continuous, 0–≥4) at 0 to <24 months of age, number of encounters (continuous, log transformed) at 0 to <24 months of age, infection episodes (continuous, log transformed) at 0 to <24 months of age, and age at outcome.

confounders did not attenuate BMI *z* score differences; however, some results were no longer statistically significant. Among the 12 698 children with all available variables, fully adjusted BMI *z* score differences were 0.04 (95% CI −0.01 to 0.08) for overall, 0.04 (95% CI 0.00 to 0.08) for broad-spectrum, and 0.03 (95% CI −0.02 to 0.08) for narrow-spectrum antibiotics versus none (Supplemental Table 14).

Multivariable Logistic Regression: Overweight or Obesity at 5 Years of Age

Among children without a complex chronic condition, the odds ratio for overweight or obesity at age 5 years was 1.05 (95% CI 1.03 to 1.07) for children receiving any antibiotics at <24 months of age versus children receiving none (Table 3). Odds ratios were somewhat larger for broad-spectrum antibiotics at 1.07 (95% CI 1.05 to 1.09) than for narrow-spectrum antibiotics at 1.02 (95% CI 1.00 to 1.04). We also estimated an increasing dose response, with odds ratios of 1.01, 1.06, 1.07, and 1.10 for 1, 2, 3, and ≥4 antibiotics, respectively, compared with no antibiotics (Table 4). Odds ratios were smaller for children with complex chronic conditions and for age period–specific exposures. When examining odds for obesity as the outcome, results were similar (Supplemental Table 16).

Association of Covariates With Outcomes

Several covariates were significant predictors of the BMI *z* score at 5 years of age (Supplemental Table 17). Among children without complex chronic conditions, those who were preterm versus not preterm had BMI *z* scores that were 0.22 lower (95% CI −0.24 to −0.20). Children with an asthma diagnosis had a higher BMI *z* score of 0.15 (95% CI 0.14 to 0.17) compared with children without an asthma diagnosis. Infection episodes (included as a log-transformed variable) were associated with a higher BMI *z* score of 0.02 (0.02 to 0.02) per log-transformed episode.

DISCUSSION

This large multi-institutional national cohort of 362 550 children is the largest study to examine the association between early childhood antibiotic exposure and subsequent body weight and weight status. The analytic approach controlled for potential confounders, such as steroid use, accounted for effect modification by complex chronic conditions and infections, and included an assessment of dose response and timing of antibiotic exposure at <24 months of age. We found a small association between early childhood antibiotic exposure and BMI *z* score and odds of overweight and obesity at 5 years of age, with evidence for a dose response. Broad-spectrum antibiotic exposures were more consistently associated with a higher BMI *z* score and risk for overweight and obesity than narrow-spectrum antibiotic exposures. The timing of exposure did not substantively affect the magnitude of associations. Results were similar for children with and without complex chronic conditions, with slightly higher BMI *z* score

TABLE 3 Multivariable Logistic Regression Results for the Association of Any Exposure to Antibiotics at <24 Months of Age and Risk of Overweight and/or Obesity at 48–<72 Months of Age, by Timing of Antibiotic Prescription

Antibiotics	No Complex Chronic Condition, *N* = 310 947		Complex Chronic Condition, *N* = 51 603	
	Model 1,[a] OR (95% CI)	Model 2,[b] OR (95% CI)	Model 1,[a] OR (95% CI)	Model 2,[b] OR (95% CI)
Any, mo				
0–<24	1.10 (1.08 to 1.12)	1.05 (1.03 to 1.07)	1.09 (1.05 to 1.13)	1.01 (0.97 to 1.06)
0–<6[c,d]	1.13 (1.11 to 1.16)	1.07 (1.04 to 1.09)	1.09 (1.04 to 1.14)	1.04 (0.99 to 1.10)
6–<12[c,d]	1.10 (1.08 to 1.12)	1.03 (1.01 to 1.05)	1.05 (1.01 to 1.10)	0.98 (0.93 to 1.03)
12–<24[c,d]	1.09 (1.07 to 1.11)	1.03 (1.01 to 1.05)	1.11 (1.06 to 1.15)	1.03 (0.98 to 1.08)
Broad spectrum, mo				
0–<24	1.11 (1.09 to 1.13)	1.07 (1.05 to 1.09)	1.12 (1.07 to 1.16)	1.06 (1.01 to 1.11)
0–<6[c,d]	1.14 (1.10 to 1.18)	1.07 (1.03 to 1.11)	1.07 (1.01 to 1.14)	1.03 (0.97 to 1.10)
6–<12[c,d]	1.10 (1.08 to 1.12)	1.04 (1.01 to 1.06)	1.08 (1.03 to 1.13)	1.02 (0.97 to 1.07)
12–<24[c,d]	1.10 (1.08 to 1.12)	1.05 (1.03 to 1.07)	1.15 (1.10 to 1.20)	1.08 (1.03 to 1.13)
Narrow spectrum,[e] mo				
0–<24 mo	1.06 (1.04 to 1.08)	1.02 (1.00 to 1.04)	1.01 (0.96 to 1.07)	0.96 (0.91 to 1.02)
0–<6[c,d]	1.13 (1.09 to 1.16)	1.06 (1.03 to 1.09)	1.10 (1.02 to 1.19)	1.04 (0.96 to 1.13)
6–<12[c,d]	1.08 (1.06 to 1.11)	1.02 (1.00 to 1.05)	1.00 (0.93 to 1.07)	0.93 (0.87 to 1.00)
12–<24[c,d]	1.06 (1.03 to 1.08)	1.01 (0.99 to 1.04)	1.01 (0.95 to 1.08)	0.97 (0.90 to 1.04)

OR, odds ratio.

[a] Corrected for clustering by site.

[b] Corrected for clustering by site and adjusted for sex, race, ethnicity, preterm birth, asthma, corticosteroid episodes (continuous, 0–4+) at 0–<24 months of age, number of encounters (continuous, log transformed) at 0–<24 months of age, infection episodes (continuous, log transformed) at 0–<24 months of age, and age at outcome.

[c] For exposure time windows, Model 2 was additionally adjusted for previous antibiotics: (1) antibiotics at 6–<12 months, adjusted for 0–<6 months antibiotics and (2) antibiotics at 12–<24 months, adjusted for 0–<12 months antibiotics.

[d] For exposure time windows, covariates were used during the same time window (corticosteroids and encounters): (1) antibiotics at 0–<6 months, covariates used for 0–<6 months; (2) antibiotics at 6–<12 months, covariates used for 6–<12 months; and (3) antibiotics at 12–<24 months, covariates used for 12–<24 months.

[e] For narrow antibiotic exposures, analyses were limited to participants with no broad-spectrum antibiotics during the same time window as exposure or before.

TABLE 4 Multivariable Logistic Regression Results for the Association of Antibiotic Episodes at <24 Months of Age and Risk for Overweight and/or Obesity at 48–<72 Months of Age, by Courses of Antibiotics

Episodes	No Complex Chronic Condition, *N* = 310 947		Complex Chronic Condition, *N* = 51 603	
	Model 1,[a] OR (95% CI)	Model 2,[b] OR (95% CI)	Model 1,[a] OR (95% CI)	Model 2,[b] OR (95% CI)
Any antibiotic				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1	1.04 (1.02 to 1.06)	1.01 (0.99 to 1.03)	1.05 (1.00 to 1.11)	1.01 (0.96 to 1.07)
2	1.11 (1.09 to 1.14)	1.06 (1.03 to 1.09)	1.10 (1.03 to 1.17)	1.03 (0.96 to 1.10)
3	1.14 (1.10 to 1.17)	1.07 (1.04 to 1.11)	1.06 (0.98 to 1.14)	0.98 (0.91 to 1.06)
4+	1.17 (1.14 to 1.20)	1.10 (1.07 to 1.13)	1.14 (1.08 to 1.20)	1.03 (0.97 to 1.10)
Broad spectrum				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1	1.10 (1.08 to 1.12)	1.06 (1.04 to 1.09)	1.08 (1.03 to 1.14)	1.04 (0.99 to 1.10)
2	1.12 (1.09 to 1.16)	1.07 (1.04 to 1.10)	1.14 (1.07 to 1.23)	1.09 (1.01 to 1.17)
3	1.11 (1.07 to 1.16)	1.06 (1.02 to 1.11)	1.17 (1.07 to 1.28)	1.12 (1.02 to 1.22)
4+	1.14 (1.10 to 1.18)	1.09 (1.05 to 1.12)	1.13 (1.06 to 1.21)	1.05 (0.97 to 1.13)
Narrow spectrum[c]				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1	1.03 (1.01 to 1.06)	1.00 (0.98 to 1.03)	1.02 (0.95 to 1.09)	0.98 (0.91 to 1.05)
2	1.09 (1.05 to 1.12)	1.04 (1.00 to 1.08)	1.04 (0.93 to 1.15)	0.98 (0.88 to 1.09)
3	1.12 (1.05 to 1.18)	1.06 (1.00 to 1.12)	1.03 (0.87 to 1.22)	0.94 (0.79 to 1.12)
4+	1.15 (1.07 to 1.25)	1.07 (0.99 to 1.16)	0.84 (0.68 to 1.04)	0.78 (0.63 to 0.96)

OR, odds ratio.

[a] Corrected for clustering by site.

[b] Corrected for clustering by site and adjusted for sex, race, ethnicity, preterm birth, asthma, corticosteroid episodes (continuous, 0–4+) at 0–<24 months of age, number of encounters (continuous, log transformed) at 0–<24 months of age, infection episodes (continuous, log transformed) at 0–<24 months of age, and age at outcome.

[c] For narrow antibiotic exposures, analyses were limited to participants with no broad-spectrum antibiotics during the same time window as exposure or before.

differences for children with complex conditions compared with those for other children but slightly lower odds ratios for overweight and obesity.

Complex interplay between antibiotics and infections may exist because infections may be a confounder or modifier of the effect of future antibiotic use on weight; antibiotics also could mediate the effect of infections on weight. Time-varying confounding introduces

further challenges (Note 7 of the Supplemental Information). Inclusion of infections as a covariate in regression models slightly attenuated BMI *z* score differences among those exposed to antibiotics. When we stratified analyses by the number of infections diagnosed in children at 0 to <24 months, we found an even weaker association of antibiotics with BMI *z* score among children with fewer infections, suggesting that infections may explain some of the relationship between antibiotics and weight outcomes. We still found consistent, though small, associations for antibiotics and weight, especially for children receiving ≥4 antibiotic courses. In contrast to the Li et al[13] study, we found independent relationships between both antibiotics and infections and weight outcomes. Our study differed in some ways from that study, which had a larger age range for measuring weight outcomes (up to 18 years of age), was focused on obesity risk only, and excluded patients who had antibiotics without a linked infection.

Effect sizes in our study align closely with those of previous cohort studies and meta-analyses investigating early antibiotic exposure and subsequent childhood weight.[10,13,16,38] Among 38 522 children from a single institution, Gerber et al[12] reported children with a higher weight of 0.05 kg (95% CI −0.004 to 0.11) from 2 to 5 years of age if exposed to antibiotics in the first 6 months of life; antibiotic use at <24 months of age was associated with a weight difference of 0.15 kg. Among 8793 children in Pennsylvania, Poulsen et al,[39] reported a higher BMI *z* score of 0.09 at age 3 for children with 4 to 5 orders of antibiotics at <3 years of age. In 64 580 children from the Philadelphia area, Bailey et al[40] reported a risk ratio of 1.11 for obesity after 2 years of age for children receiving ≥4 antibiotic prescriptions at <24 months of age. The similarity and consistency of effect sizes across multiple studies and populations add credibility to our findings. Several previous studies also revealed a dose response (with larger BMI *z* score increases or risk of overweight or obesity) with repeated exposure to antibiotics.[14,15,39–41] These results reveal that perhaps cumulative exposure at the highest levels could become a concern for excess weight gain. If these results reflect a common unmeasured or poorly measured confounder, it would have to be present in many different study populations.

Although early changes in weight trajectory can have lasting impact on subsequent health outcomes, the clinical significance of a 0.02 to 0.07 increase in the BMI *z* score at age 5 years is likely negligible. For example, on the basis of our results, among 5-year-old boys and girls of average height, their weights were ∼0.11 kg (or 0.24 pounds) higher if exposed to ≥4 antibiotic courses (vs 0) at <24 months. This small risk of weight gain is unlikely to be a key factor in any individual prescribing decision for children. The population impact of a slightly higher BMI *z* score with antibiotic exposure is small as well. Among children without complex chronic conditions, we estimate the population attributable fraction of overweight and/or obesity to be ∼1.1% for those exposed to ≥4 antibiotic episodes and 2.0% for those exposed to any antibiotics.[42] Decreasing the prevalence of childhood obesity by even 1% could have important population health effects.[43] Any alteration to obesity prevalence related to antibiotics would require substantial investment in decreasing use; this reason is far outweighed by the population health benefit related to declining antibiotic resistance, which would result from decreasing antibiotics use.

This study has several limitations. Antibiotic prescribing was captured electronically and not on the basis of pharmacy dispensing or claims; therefore, misclassification of the exposure was possible, especially for antibiotics prescribed outside of the participating health care systems (eg, retail clinics). This misclassification would likely have biased results to the null. Also, we accounted for mostly oral antibiotic prescriptions, although we did capture intramuscular ceftriaxone and penicillin use. The lack of additional parenteral antibiotics may have biased the results to the null. In addition, as with any multiyear retrospective study, there was loss to follow-up, such as naturally occurred if subjects lost or changed insurance or moved. If these children were different in some way from children in the cohort, our results could have been biased. In this study, we did not collect any dates for privacy reasons; therefore, we could not estimate reasons for loss to follow-up. We estimated this in the largest network partner accounting for ∼50% of participants. One-quarter of the children with measurements available at <30 months of age had not yet reached 48 months of age and so were not eligible for inclusion in the analysis. An additional one-quarter of children were lost to follow-up by age 48 months and also did not contribute to the analysis. Lastly, the incorporation of information on infections was important to control for confounding by indication. However, EHR documentation of infections is likely highly incomplete considering that children often do not present to their health care provider for infections.

Several potential confounders were not available for this study, including socioeconomic status, diet, and breastfeeding status. EHRs rarely contain structured data for these variables, which could potentially be associated with antibiotic

exposure and weight outcomes. We conducted sensitivity analyses to determine how easily small associations could be explained by unmeasured confounding (Note 7 of the Supplemental Information).

Finally, although this sample is from multiple US health care systems, there was overrepresentation of urban environments with large health care systems, which may limit the generalizability, and of tertiary care centers, where antibiotics prescribed by pediatric primary care doctors may be missed. In sensitivity analyses limiting the sample to patients with well-child visits and institutions with a >40% antibiotic prescribing rate, our results were unchanged.

CONCLUSIONS

In this large national sample, we report a small association between antibiotic exposure at <24 months of age and overweight and obesity at 5 years of age (with evidence for a dose-response relationship), accounting for infections, chronic health conditions, and steroid use. The small associations between early antibiotic exposure and later childhood obesity are consistent with previous studies. Although these small associations may have population-level effects on obesity, the clinical significance for individual patients is negligible. This weight gain effect will likely not be an influential factor when health care providers discuss the risks and benefits of antibiotics with parents and children.

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ABBREVIATIONS

CDM: common data model
CI: confidence interval
EHR: electronic health record
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
NLM: National Library of Medicine
PCORnet: National Patient-Centered Clinical Research Network

intellectual content; Mr Lunsford and Drs Gillman, Finkelstein, Toh, and Trasande were involved in the conception and design of the study, the interpretation of data, and the acquisition of data and critically revised the article for important intellectual content; Ms Rifas-Shiman was involved in the design of the study, the analysis and interpretation of data, and the acquisition of data and drafted and critically revised the article for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Early Antibiotic Exposure and Weight Outcomes in Young Children

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