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.

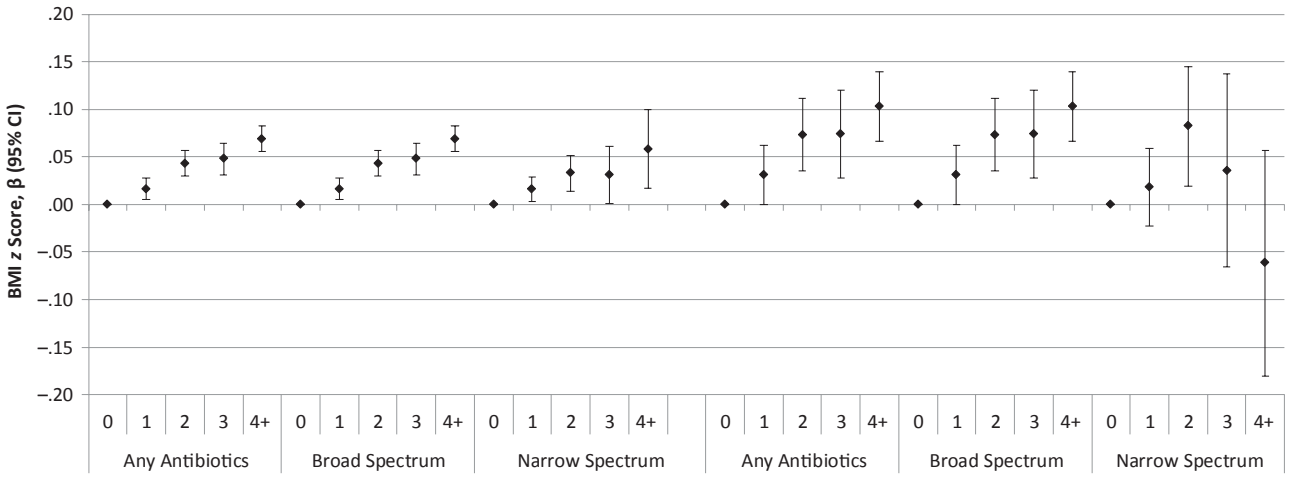

FIGURE 1

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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Supplemental Information

NOTE 1: PCORNET DESCRIPTION, CDM, AND INSTITUTIONAL REVIEW BOARD DETERMINATIONS

PCORnet currently contains health information for >128 million patients across 13 demographically and geographically diverse clinical data research networks (CDRNs). A CDM is used in the network to organize and standardize EHRs across disparate network partners and source EHR systems; additional health care data, such as data from insurance claims and pharmacy dispensings, are incorporated for some of the network partners. The PCORnet CDM version 3.0, leveraged from the Food and Drug Administration's Sentinel System, has 15 domain tables and >100 different variables, including EHR-specific data (such as prescribing records and vital measures). In having network partners convert their source system data to comply with the CDM, PCORnet fosters data consistency and result aggregation across sites. This process also allows for certain privacy protections, such as the creation of deidentified patient identifications and, for some sites, date obfuscation.

Four CDRNs, including 11 of the health care institutions participating in the study, used a central institutional review board (IRB) for review and approval. Three CDRNs with 16 health care institutions used an IRB reliance model, with 1 institution serving as the CDRN's IRB of record for the study. The 3 remaining CDRNs with 8 institutions used a combination of IRB reliance and individual site IRB review. IRB determinations differed at participating institutions: 8 institutions deemed the study to be nonhuman subjects research, foregoing IRB oversight; 9 institutions deemed it to be exempt from IRB review because the data transferred was deidentified; 18 institutions reviewed the study and determined it to be of minimal risk. The IRB of the lead site, Harvard Pilgrim Health Care Institute, also reviewed and approved the study as human subjects research with minimal risk.

NOTE 2: PROCESS FOR DEVELOPING ANTIBIOTIC CODE LOOK-UP

To capture the appropriate list of antibiotics, we used the First Databank look-up tool (http://www.fdbhealth.com/) licensed by the Sentinel Network (https://clt.sentinelsystem.org/managecondition.jsf) to manually compile a list of National Drug Code values for antibiotics. We used First Databank's functional classification, which was translated into RxNorm concept unique identifiers by using the RxNorm crosswalk available from the NLM. Similarly, we queried RxNorm directly using the Anatomical Therapeutic Chemical class J01 (antibacterials for systemic use) to extract a set of concept unique identifiers for antibiotics and merged these additional codes with those obtained above. Because not all network partners had data available from inpatient settings and because outpatient oral and intramuscular medication usage are likely more modifiable than intravenous medications, we limited the set of antibiotics to oral and common intramuscular formulations. We further curated the set to exclude some medications initially captured that were not available for distribution in the United States or were antiprotozoal medications, topical preparations, or solely available as veterinary medications. Finally, we used the RxNorm hierarchy to expand the initial set to include semantic drug form codes that had information on medication name, dose, and route of administration as well as less-specific ingredient, multi-ingredient, precise-ingredient, or brand-name codes that only had information about the ingredients in medications. For corticosteroids, we followed a similar process, limiting our selection to dose forms and ingredients available as oral formulations.

NOTE 3: PCORNET PRIVACY PROTECTIONS AND VARIABLES NEEDED TO CALCULATE ANTIBIOTIC EPISODES

A core principle of PCORnet is the use of privacy-protecting methods to the maximum extent possible. In addition to limiting data to the minimum necessary and specific code-matched records needed for the study analyses, we also masked all dates to prevent potential reidentification of records and patients. However, to calculate antibiotic exposure episodes and link antibiotic episodes with relevant infection diagnoses, we needed some measure of time intervals. In the distributed program, the date variables from the various CDM tables were used to generate 3 new, date-masked variables.

We calculated age in months for encounters and prescriptions using the birth date variable compared against the record's relevant date variable in the given table (eg, prescription order date in the prescribing table). For individual patient records that occurred in the same age month, we used age order to indicate the relative order in which various health events occurred. Record(s) that occurred earliest within the given age month were assigned a value of 1, and subsequent records were assigned a value of 2, 3, 4, etc. Records occurring on the same day were assigned the same value for the age order variable. This variable was used to assemble a timeline of relevant health events for the cohort patients. Finally, to better understand the relative distance between encounters, link antibiotics prescribed during the same treatment episode, and connect infections to antibiotics, we calculated the variable days between records. For days between records, dates were subtracted between consecutive records. Calculations were all done relative to the previous record; the first days between records value for any given cohort patient was left unpopulated.

This data structure facilitated the creation of antibiotic episodes. We joined together all antibiotics prescribed within 10 days of a previous antibiotic. We assigned the antibiotic spectrum of the episode to the higher spectrum antibiotic prescribed during the episode. For example, a prescription written on day 1 for amoxicillin (narrow), day 7 for amoxicillin, and day 10 for azithromycin (broad) became a single prescription episode for a broad-spectrum antibiotic.

To inform the distributed SAS program that built the study cohort and pulled the relevant study data, we generated technical specifications that detailed the cohort formation flowchart, required CDM variables, non-CDM variables (eg, age order, days between records, and age in months), and code-list restrictions. Programmers used the technical specifications to translate the request into a distributed SAS program, which was extensively tested both internally by using simulated data and externally by using participating network partners as β testers.

NOTE 4: CAPTURE OF COMPLEX CHRONIC CONDITIONS AND CREATING EPISODES FOR INFECTIONS

Feudtner et al[36] subclassified complex chronic diseases into 9 categories. Among cohort participants classified as having a complex chronic condition in our study, the breakdown by category was cardiovascular (31%), other congenital of genetic defect (30%), neuromuscular (15%), respiratory (14%), renal (13%), hematologic or immunodeficiency (11%), metabolic (8%), malignant neoplasms (4%), and gastrointestinal (4%). We added an additional category of growth conditions, including hypothyroidism and pituitary disorders, which was present in 6% of children. These add up to >100% because some children had >1 chronic condition.

To accommodate those institutions that recorded diagnoses in the Systematized Nomenclature of Medicine (SNOMED), we translated the ICD-9-CM codes to SNOMED Clinical Terms codes using NLM's Unified Medical Language System mappings.[44] We only accounted for diagnoses that were available through September 30, 2015, the date mandated for health care systems to switch from using ICD-9-CM codes to *International Classification of Diseases, 10th Revision* codes. We defined a child as having a complex chronic condition if the child had at least 2 diagnostic codes for any of the conditions at <72 months of age. These complex chronic condition diagnoses included diagnostic codes found after the designated exposure period of <24 months of age because of the inherent difficulty in diagnosing many chronic diseases in early childhood.

For infections, we used the Fleming-Dutra et al[35] classification system. In this system, tier 1 infections are those that almost always require antibiotics, such as pneumonia and other bacterial infections. Tier 2 infections are those for which antibiotics might be discretionary, the most prevalent of which are suppurative otitis media, sinusitis, and pharyngitis. Tier 3 infections are those that typically do not require antibiotics, such as nonsuppurative otitis media and other skin, cutaneous, and mucosal conditions. If a child had >1 same-day infection, we used a hierarchy, giving priority to lower tier infections (eg, if tier 1 and tier 2 diagnostic codes were present on the same day, we assigned the encounter as a tier 1 infection). Accounting for the likelihood that some infections would require multiple clinical encounters and multiple diagnostic codes within a brief time interval, we created infection episodes by joining together infections within 14 days; we gave priority during this interval to the lowest tier infections. We derived infections as a categorical count of infection episodes. Because of the skewed nature of this variable, we log transformed it when including in models.

NOTE 5: INCORPORATION OF MATERNAL VARIABLES IN SUBSTUDY ANALYSES

Mother-child linkages are not routinely available in EHRs. To incorporate maternal variables, we relied on 7 institutions that could

make these linkages. Five of the sites were integrated delivery systems that have available insurance identifications shared within families. One of the sites has an institutional policy that links mothers to children at the time of birth; linkages were thus available for all children born in the health care system. One site used a variety of methods to link mothers to children, including available insurance identifications, matching geocoded addresses and telephone numbers, and free-text information on emergency contacts, among other data points.

Of 214 780 children in these 7 institutions with same-day child height and weight measurements at 0 to <12 months of age and 12 to <30 months of age and at least 1 measurement after 24 months of age, 137 815 children were able to be linked to mothers. Of these children, 73 475 had same-day height and weight measurements at 48 to <72 months of age, and 53 320 of the mothers had any vitals data during pregnancy. This was the sample size for the substudy analysis.

We defined pregnancy as the period from the index child's date of birth minus 9 months (273 days). We captured several potential confounders from mothers' records, including maternal age at delivery, prepregnancy BMI captured up to 1 year before the pregnancy, diagnoses of diabetes or gestational diabetes, whether the child was delivered via vaginal birth or cesarean delivery, and maternal smoking status during pregnancy. For the prepregnancy BMI, we chose the weight closest to 9 months before the child's birth date and incorporated any height available.

We defined a mother as having diabetes if she had ≥2 of the following criteria: glycosylated hemoglobin level of ≥6.5%, ICD-9-CM code for diabetes, or receipt of any diabetes prescription during the year before pregnancy. A diagnosis of gestational diabetes required an ICD-9-CM code for gestational diabetes mellitus and no diagnosis of diabetes per the criteria above. Smoking was available in the CDM, and we restricted the capture of this data to the pregnancy period; mothers were classified as never, former, or active smokers, with active smoker designated if defined as such at any point during pregnancy. Delivery method was available in the CDM by using diagnostic codes and procedural codes available as Healthcare Common Procedure Coding System and *Current Procedural Terminology* codes.

Because of a small sample size, we excluded children with complex chronic conditions from these analyses. For the 48 908 children without a complex chronic condition, the mean age of mothers at delivery was 29.5 (SD 5.9) and the prepregnancy BMI was 27 (SD 6.3); 6.1% of mothers smoked during pregnancy (16% had an unknown smoking status), 1.3% had diabetes, 11.7% had gestational diabetes, and 19.1% had a cesarean delivery (29.3% of mothers had missing data on delivery method). The mean birth weight in grams was 3351 g (SD 529). Results are in Supplemental Tables 14 and 15.

NOTE 6: SENSITIVITY ANALYSES

We conducted several sensitivity analyses to determine if results were robust to different restrictions on the data (Supplemental Table 13). In the first sensitivity analysis, we limited the analytic sample to children with any well-child visits at <72 months of age. We conducted this analysis because we believed that these children were receiving primary care at the institution providing data and, therefore, were more likely to get most of their care there. If a child received most of their care at a specific institution, we would better capture their antibiotic prescriptions.

Second, we limited the analytic sample to sites with a ≥40% antibiotic rate at <24 months of age. Some institutions with lower antibiotic prescribing rates might have missed a large portion of antibiotic prescriptions or had a different case mix of patients (eg, tertiary care versus primary care networks); thus, it was important to determine if the prescribing rate had an impact on results.

Third, we restricted the analytic sample to children with no antibiotics linked to tier 1 infections to assess associations only for antibiotics prescribed for indications that were either discretionary (eg, tier 2 suppurative otitis media) or not indicated (eg, tier 3 nonsuppurative otitis media). This allowed for us to assess whether we found similar associations for required antibiotics versus those that were possibly not required and thus modifiable. We linked antibiotics to infectious diagnoses within 7 days of the prescription to accommodate this analysis. If >1 infectious diagnosis was linked to an antibiotic prescription, we prioritized the more serious infection (tier 2 over tier 3).

In addition to these sensitivity analyses, we assessed whether parameter estimates were sensitive to the inclusion of asthma and infections as covariates in the model. The inclusion of these covariates did slightly attenuate results but not substantively (Supplemental Tables 10 and 12). In addition, we assessed whether infections were effect modifiers of the antibiotics to weight relationship, and we found some evidence for this (Supplemental Table 11).

NOTE 7: SENSITIVITY ANALYSIS ON UNMEASURED CONFOUNDING AND A NOTE ON MEASURED TIME-VARYING CONFOUNDERS AFFECTED BY PAST EXPOSURE

We assessed the possible role of unmeasured confounding by a binary unmeasured outcome risk factor *U* using a simple approach to sensitivity analyses proposed by Vanderweele and Arah.[45] In our analysis, an important example of *U* is an indicator of socioeconomic status, breastfeeding, or diet (not available for adjustment in our study).[46,47] This sensitivity analysis approach gives a formula for bias that is due to unmeasured confounding by *U* under the assumptions that (1) the association between the mean of the outcome (child BMI *z* score at 48–<72 months of age) and *U* does not vary by level of antibiotic exposure nor by level of the measured confounders (eg, race and corticosteroids) and (2) the association between the prevalence of *U* and exposure does not vary by level of the measured confounders. As we discuss further below, the validity of this approach, along with the validity of our main analysis results, also relies on the assumption that time-varying measured confounders (eg, corticosteroids and number of encounters) are not themselves affected by past antibiotic exposure. Under these simplifying assumptions, Vanderweele and Arah[45] show that bias due to unmeasured confounding by *U* is equal to the product of the associations in (1) and (2) above.

This approach can be useful for understanding what magnitude of the associations in (1) and (2) would need to be present to eliminate our observed exposure-outcome association. Specifically, suppose that the adjusted mean difference in the BMI *z* score at 48 to <72 months of age is 0.45 for some unmeasured confounder (yes versus no); in this case, lower income versus higher income or being breastfed exclusively for 6 months versus not, adjusted for covariates. This is the association in (1).[46] As reported in Table 2, we estimated that the adjusted mean difference in the BMI *z* score at 48 to <72 months of age was higher by 0.04 (95% CI 0.03 to 0.05) among children without a complex chronic condition with any antibiotic exposure versus none at <24 months of age. As the product of $0.09 \times 0.45 = 0.05$, the association in (2) of 0.09 would lead to a bias corrected estimate of 0.0 (95% CI −0.01 to 0.01), completely eliminating the association we found. This bias corrected estimate is simply the original estimate minus the measure of bias (0.09×0.45). Similarly, the bias corrected CIs are computed by the taking the upper and lower bounds of the original CIs and subtracting 0.09×0.45. None of the variables in our model had an association of ≥0.45 with the outcome of the mean BMI *z* score; the strongest association was −0.38 for preterm birth among children with a complex chronic condition.

Another source of bias in our effect estimates may be present because of the time-varying nature of our exposure of interest and possible confounders given the potential for feedback between them. In particular, any versus no antibiotic exposure or the number of antibiotic episodes over the first 2 years of life are functions of a time-changing indicator of exposure status over the course of those 2 years. In addition, any versus no diagnosis of asthma and the number of corticosteroids, along with other covariates we included in regression models or stratified on, over that same period are also functions of time-changing indicators in that period.

We included covariates, such as asthma and the count of corticosteroids, in our regression models because we assume they were needed to control confounding. Given this assumption, ignoring these covariates would result in residual confounding. However, inclusion of these covariates in our regression models (which corresponds to a form of conditioning on them) may also result in a biased effect estimate even if all covariates needed to control confounding are included in the model and even if the model is correctly specified.

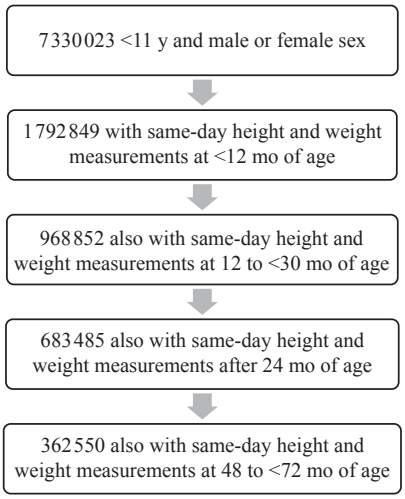
In particular, Robins[48] showed that a standard regression analysis that included (ie, conditions on) a function of a time-varying covariate L_t (with t indexing a particular time during the exposure period) would generally be biased for the causal effect of a time-varying exposure in that period if (1) L_t (eg, asthma status at t and any corticosteroid given at t) is a measured covariate needed to control confounding for the exposure effect at future times in that period and (2) L_t is itself affected by past exposure in that period. For example, this structure would hold in our study if the number of corticosteroids and/or asthma status by a time t in the first 2 years of life are needed to control confounding for the effect of future antibiotic exposure on childhood BMI and are also, themselves, affected (directly or indirectly) by previous antibiotic exposure during that first 2 years.

In this case, failure to include asthma and/or the number of corticosteroids in the model will result in residual confounding. However, including (conditioning on) these covariates may result in a particular form of selection bias if these covariates share a common cause with the outcome that is not accounted for in the analysis. Because it is particularly unreasonable to assume we have accounted for all such common causes, our conclusions in the main text rest on the additional assumption that corticosteroids and/or asthma and other time-varying covariates in our models are not affected by antibiotic exposure. We believe this to be a reasonable

assumption because we are not aware of any evidence that antibiotics are associated with the development of asthma or the subsequent use of corticosteroids; the exception would be an allergic reaction to an antibiotic requiring a corticosteroid; this would not be prevalent enough in our data to affect our results.

By the same arguments, our choice to stratify on chronic conditions is appropriate if these are unaffected by antibiotic exposure but, otherwise, may result in selection bias because of conditioning on an effect of exposure that likely shares unmeasured common causes with the outcome.[49] Again, we believe this decision is reasonable because of the nature of these chronic conditions, which are severe conditions.

Alternatives to standard regression, known collectively as "g-methods," can recover causal effects of time-varying exposures in the presence of time-varying confounders affected by previous exposure. These methods still rely on the assumptions of no unmeasured confounding and no measurement error. One relatively, computationally simple example of a g-method is an inverse probability–weighted estimation of marginal structural models. We will consider this approach in future work to ensure that we obtain similar conclusions to those reported in the main text.[50,51]



SUPPLEMENTAL FIGURE 2
Flow diagram of cohort participants.

SUPPLEMENTAL TABLE 5 PCORnet Network Partners Participating in the PCORnet Antibiotics and Childhood Growth Study

CDRN	Network Partners (Institutions Included in Network Partners if Centralized)
ADVANCE	ADVANCE (OCHIN and Health Choice Network of Florida)
CAPriCORN	NorthShore University Health System, University of Chicago Medicine, Rush University Medical Center, Lurie Children's Hospital, and Loyola Medicine
GPC	Medical College of Wisconsin, University of Iowa Health Care, Marshfield Clinic, and University of Texas Health Science Center at San Antonio
Mid-South Clinical Data Research Network	Vanderbilt University Medical Center, Greenway Health, and University of North Carolina at Chapel Hill
NYC-CDRN	New York Genome Center (Mount Sinai, Albert Einstein College of Medicine, and the Children's Hospital at Montefiore)
OneFlorida Clinical Data Research Network	OneFlorida (University of Florida Health and Tallahassee Memorial)
PEDSnet	PEDSnet centralized data mart (Children's Hospital of Philadelphia, Seattle Children's Hospital, Children's Hospital Colorado, Nemours Children's Hospital, and Nationwide Children's Hospital) and Cincinnati Children's Hospital Medical Center
Kaiser Permanente and Strategic Partners PORTAL	Kaiser Permanente Colorado, Denver Health, Kaiser Permanente Washington Health Research Institute, HealthPartners Research Foundation, Kaiser Permanente Mid-Atlantic States, and Kaiser Permanente Northwest
REACHnet	Tulane University, Ochsner Health System, and Baylor Scott and White Health North
ARCH	Boston Medical Center and Wake Forest Baptist Medical Center

ADVANCE, Accelerating Data Value Across a National Community Health Center Network; ARCH, Accessible Research Commons for Health; CAPriCORN, Chicago Area Patient Centered Outcomes Research Network; CDRN, clinical data research network; GPC, Greater Plains Collaborative; NYC-CDRN, New York City Clinical Data Research Network; PEDSnet, Pediatric Learning Health System; PORTAL, Kaiser Permanente & Strategic Partners Patient Outcomes Research To Advance Learning; REACHnet, Research Action for Health Network.

SUPPLEMENTAL TABLE 6 Demographic and Clinical Characteristics of the Study Population, Overall and Stratified by Chronic Condition Status

Characteristic	Total Study Population, *N* = 362 550	No Complex Chronic Condition, *N* = 310 947	With Complex Chronic Condition,[a] *N* = 51 603
Female sex, *n* (%)	173 908 (48)	150 549 (48)	23 359 (45)
Race, *n* (%)			
Asian American	14 513 (4)	12 972 (4)	1541 (3)
African American	97 801 (27)	85 204 (27)	12 597 (24)
White	190 812 (53)	161 814 (52)	28 998 (56)
Other	27 852 (8)	22 277 (7)	5575 (11)
Unknown	31 572 (8)	28 680 (9)	2892 (6)
Hispanic ethnicity, *n* (%)	64 019 (18)	56 255 (18)	7764 (15)
Preterm[b], *n* (%)	26 019 (7)	16 979 (5)	9040 (18)
Asthma[c], *n* (%)	47 596 (13)	38 346 (12)	9250 (18)
Systemic corticosteroid episodes[d] at <24 mo of age, *n* (%)			
0	314 395 (87)	271 298 (87)	43 097 (84)
1	32 214 (9)	27 432 (9)	4782 (9)
2	9047 (2)	7292 (2)	1755 (3)
3	3544 (1)	2689 (1)	855 (2)
4+	3350 (1)	2236 (1)	1114 (2)
Episodes for presumed infectious illnesses[e] at <24 mo of age, *n* (%)			
0	46 672 (13)	40 821 (13)	5851 (11)
1	27 986 (8)	24 351 (8)	3635 (7)
2	32 889 (9)	29 286 (9)	3603 (7)
3	34 598 (10)	30 990 (10)	3608 (7)
4+	220 405 (61)	185 499 (60)	34 906 (68)
No. encounters[f] at <24 mo of age, median (IQR)	16.0 (10.0 to 24.0)	15.0 (10.0 to 22.0)	23.0 (13.0 to 39.0)
Systemic antibiotic prescribing episodes[g] at <24 mo of age, *n* (%)			
0	153 366 (42)	130 208 (42)	23 158 (45)
1	77 250 (21)	67 285 (22)	9965 (19)
2	46 235 (13)	40 201 (13)	6034 (12)
3	29 005 (8)	25 202 (8)	3803 (7)
4+	56 694 (16)	48 051 (15)	8643 (17)
Systemic broad-spectrum antibiotic prescribing episodes[g] at <24 mo of age, *n* (%)			
0	235 024 (65)	203 728 (66)	31 296 (61)
1	62 430 (17)	53 513 (17)	8917 (17)
2	26 855 (7)	22 636 (7)	4219 (8)
3	14 582 (4)	12 115 (4)	2467 (5)
4+	23 659 (7)	18 955 (6)	4704 (9)
Systemic narrow-spectrum antibiotic prescribing episodes[g] at <24 mo of age, *n* (%)			
0	192 039 (53)	159 729 (51)	32 310 (63)
1	89 256 (25)	79 034 (25)	10 222 (20)
2	45 001 (12)	40 333 (13)	4668 (9)
3	21 152 (6)	18 903 (6)	2249 (4)
4+	15 102 (4)	12 948 (4)	2154 (4)
BMI category at 4–<6 y of age, *n* (%)			
Underweight (less than the fifth percentile)	16 310 (4)	12 860 (4)	3450 (7)
Normal wt (fifth to <85th percentile)	245 242 (68)	211 995 (68)	33 247 (64)
Overweight (85th to <95th percentile)	52 774 (15)	45 295 (15)	7479 (14)
Obese (≥95th percentile)	48 224 (13)	40 797 (13)	7427 (14)
Age, mo, mean (SD)	57.8 (5.3)	57.8 (5.4)	58.0 (4.9)
BMI *z* score, mean (SD)	0.40 (1.19)	0.41 (1.12)	0.35 (1.30)

IQR, interquartile range.

[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.

[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.

SUPPLEMENTAL TABLE 7 Multivariable Linear Regression Results for the Association of Antibiotics Episodes at <24 Months of Age With the BMI *z* Score at 48–<72 Months of Age, by Antibiotic Spectrum

Episodes[a]	No Complex Chronic Condition, *N* = 310 947		Complex Chronic Condition, *N* = 51 603	
	Model 1,[b] β (95% CI)	Model 2,[c] β (95% CI)	Model 1,[b] β (95% CI)	Model 2,[c] β (95% CI)
Any antibiotic				
0	.0 (reference)	.0 (reference)	.0 (reference)	.0 (reference)
1	.04 (0.03 to 0.05)	.02 (0.01 to 0.03)	.04 (0.01 to 0.07)	.03 (0.00 to 0.06)
2	.08 (0.07 to 0.09)	.04 (0.03 to 0.06)	.09 (0.06 to 0.13)	.07 (0.04 to 0.11)
3	.09 (0.07 to 0.11)	.05 (0.03 to 0.06)	.10 (0.06 to 0.15)	.07 (0.03 to 0.12)
4+	.12 (0.11 to 0.14)	.07 (0.06 to 0.08)	.14 (0.11 to 0.17)	.10 (0.07 to 0.14)
Broad spectrum				
0	.0 (reference)	.0 (reference)	.0 (reference)	.0 (reference)
1	.06 (0.05 to 0.07)	.03 (0.02 to 0.05)	.06 (0.03 to 0.09)	.04 (0.01 to 0.07)
2	.09 (0.07 to 0.10)	.05 (0.03 to 0.06)	.09 (0.05 to 0.13)	.07 (0.03 to 0.11)
3	.07 (0.05 to 0.10)	.03 (0.01 to 0.06)	.17 (0.12 to 0.22)	.15 (0.10 to 0.21)
4+	.12 (0.10 to 0.13)	.06 (0.05 to 0.08)	.13 (0.09 to 0.17)	.09 (0.05 to 0.14)
Narrow spectrum[d]				
0	.0 (reference)	.0 (reference)	.0 (reference)	.0 (reference)
1	.04 (0.02 to 0.05)	.02 (0.00 to 0.03)	.03 (−0.01 to 0.07)	.02 (−0.02 to 0.06)
2	.06 (0.05 to 0.08)	.03 (0.01 to 0.05)	.11 (0.05 to 0.17)	.08 (0.02 to 0.14)
3	.07 (0.04 to 0.10)	.03 (0.00 to 0.06)	.08 (−0.02 to 0.18)	.04 (−0.07 to 0.14)
4+	.11 (0.07 to 0.16)	.06 (0.02 to 0.10)	−.02 (−0.14 to 0.10)	−.06 (−0.18 to 0.06)

[a] Antibiotic episodes were defined as all antibiotics prescribed within a 10-day period of a previous antibiotic; if both narrow- and broad-spectrum antibiotics were prescribed during the episode, then the episode was a broad-spectrum antibiotic episode.
[b] Corrected for clustering by site.
[c] 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.
[d] For narrow-spectrum antibiotic exposures, analyses were limited to participants with no broad-spectrum antibiotics during the same time window as exposure or before.

SUPPLEMENTAL TABLE 8 Multivariable Linear Regression Results for the Association of Antibiotics Episodes at <24 Months of Age With the BMI *z* Score at 48–<72 Months of Age, by Broad-spectrum Antibiotic Class (Any of This Class of Antibiotics Versus None of This Class as a Reference)

	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)
Third generation cephalosporin[c]	.07 (0.05 to 0.08)	.03 (0.02 to 0.04)	.12 (0.09 to 0.16)	.09 (0.05 to 0.12)
Penicillin combination	.07 (0.06 to 0.08)	.04 (0.03 to 0.05)	.08 (0.05 to 0.11)	.04 (0.01 to 0.08)
Macrolide	.07 (0.06 to 0.08)	.02 (0.01 to 0.04)	.05 (0.02 to 0.09)	.01 (−0.02 to 0.05)
Sulfa	.11 (0.09 to 0.13)	.09 (0.07 to 0.11)	.12 (0.09 to 0.16)	.10 (0.06 to 0.14)
First or second generation cephalosporin	.06 (0.04 to 0.08)	.03 (0.01 to 0.05)	.09 (0.05 to 0.13)	.07 (0.03 to 0.11)

[a] Corrected for clustering by site, with the primary exposure defined as receiving a prescription for an antibiotic in the class versus not; these classes were not compared with one another. Results were similar when children who were prescribed other broad-spectrum antibiotics were excluded from each specific antibiotic class analysis (eg, children who were prescribed a sulfa drug were excluded from the analysis of third generation cephalosporins).
[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 mo of age, infection episodes (continuous, log transformed) at 0–<24 months of age, and age at outcome.
[c] Sample sizes for these analyses are listed In Supplemental Table 9; Numbers correspond to children coded as a "yes" for exposure to the specific antibiotic class.

SUPPLEMENTAL TABLE 9 Sample Sizes for Children Exposed to Specific Classes of Antibiotics

	No CCC, *N* with any at 0–<24 mo of age	CCC, *N* with any at 0–<24 mo of age
Third generation cephalosporin	42 968	7268
Penicillin combination	52 651	7715
Macrolide	37 673	5189
Sulfa	12 579	5623
First or second generation cephalosporin	19 166	3924

CCC, complex chronic condition.

SUPPLEMENTAL TABLE 10 Comparing Results of Models With Versus Without Including Infections as a Covariate; 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 2 Without Infections,[a] β (95% CI)	Model 2 With Infections,[b] β (95% CI)	Model 2 Without Infections,[a] β (95% CI)	Model 2 With Infections,[b] β (95% CI)
Any, mo				
0–<24	.05 (0.04 to 0.06)	.04 (0.03 to 0.05)	.07 (0.05 to 0.10)	.06 (0.04 to 0.09)
0–<6[c,d]	.06 (0.05 to 0.08)	.05 (0.04 to 0.06)	.05 (0.02 to 0.08)	.05 (0.02 to 0.08)
6–<12[c,d]	.04 (0.03 to 0.05)	.03 (0.02 to 0.04)	.04 (0.02 to 0.07)	.04 (0.01 to 0.06)
12–<24[c,d]	.04 (0.03 to 0.05)	.02 (0.01 to 0.03)	.07 (0.04 to 0.10)	.06 (0.03 to 0.08)
Broad spectrum, mo				
0–<24	.05 (0.04 to 0.06)	.04 (0.03 to 0.05)	.08 (0.06 to 0.10)	.07 (0.05 to 0.10)
0–<6[c,d]	.06 (0.04 to 0.07)	.04 (0.02 to 0.06)	.06 (0.02 to 0.09)	.05 (0.01 to 0.09)
6–<12[c,d]	.05 (0.03 to 0.06)	.03 (0.02 to 0.05)	.05 (0.02 to 0.08)	.05 (0.01 to 0.08)
12–<24[c,d]	.04 (0.03 to 0.05)	.03 (0.02 to 0.04)	.08 (0.05 to 0.11)	.07 (0.04 to 0.10)
Narrow spectrum[e], mo				
0–<24	.03 (0.02 to 0.04)	.02 (0.01 to 0.03)	.04 (0.00 to 0.07)	.03 (−0.01 to 0.06)
0–<6[c,d]	.06 (0.05 to 0.08)	.05 (0.04 to 0.07)	.04 (0.00 to 0.09)	.04 (−0.01 to 0.08)
6–<12[c,d]	.04 (0.02 to 0.05)	.02 (0.01 to 0.04)	.02 (−0.02 to 0.06)	.01 (−0.03 to 0.05)
12–<24[c,d]	.02 (0.01 to 0.04)	.01 (0.00 to 0.02)	.04 (0.00 to 0.08)	.02 (−0.02 to 0.06)

[a] 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, and age at outcome. Infection episodes are not included.

[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 (infections, 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 12–<24 months, covariates used for 12–<24 months.

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

SUPPLEMENTAL TABLE 11 Multivariable 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 Stratum of Number of Infections at <24 Months of Age

Any Antibiotics	No Complex Chronic Condition		Complex Chronic Condition	
	Model 1,[a] β (95% CI)	Model 2,[b] β (95% CI)	Model 1,[a] β (95% CI)	Model 2,[b] β (95% CI)
Stratum: 0–1 infections at <24 mo of age	.03 (0.01 to 0.05)	.02 (0.00 to 0.04)	.02 (−0.05 to 0.09)	.04 (−0.03 to 0.11)
Stratum: 2–3 infections at <24 mo of age	.02 (0.00 to 0.04)	.02 (0.00 to 0.04)	.03 (−0.04 to 0.09)	.01 (−0.06 to 0.07)
Stratum: 4+ infections at <24 mo of age	.07 (0.06 to 0.08)	.05 (0.04 to 0.07)	.11 (0.08 to 0.14)	.08 (0.04 to 0.11)
Data from Table 2 for any antibiotic at <24 mo of age without stratification	.08 (0.07 to 0.08)	.04 (0.03 to 0.05)	.09 (0.07 to 0.11)	.06 (0.04 to 0.09)

We statistically assessed whether infections were an effect modifier of the association between antibiotics and BMI *z* score. To Model 2, we added interaction terms for infections (coded as continuous and log transformed) and antibiotic use (yes versus no); interaction *P* values were <.0001 and .0009 for children without and with complex chronic conditions, respectively.

[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, tier 1 infection episodes (continuous, log transformed) at 0–<24 months of age, and age at outcome. For the final row, this estimate is slightly different from what is found in Table 2 because this model has tier 1 infections included in it.

SUPPLEMENTAL TABLE 12 Comparing Results of Models With Versus Without Including Asthma as a Covariate (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 2 Without Asthma,[a] β (95% CI)	Model 2 With Asthma,[b] β (95% CI)	Model 2 Without Asthma,[a] β (95% CI)	Model 2 With Asthma,[b] β (95% CI)
Any, mo				
0–<24	.04 (0.03 to 0.05)	.04 (0.03 to 0.05)	.07 (0.04 to 0.09)	.06 (0.04 to 0.09)
0–<6[c,d]	.06 (0.05 to 0.07)	.05 (0.04 to 0.06)	.05 (0.02 to 0.08)	.05 (0.02 to 0.08)
6–<12[c,d]	.03 (0.02 to 0.04)	.03 (0.02 to 0.04)	.04 (0.01 to 0.07)	.04 (0.01 to 0.06)
12–<24[c,d]	.02 (0.01 to 0.03)	.02 (0.01 to 0.03)	.06 (0.03 to 0.08)	.06 (0.03 to 0.08)
Broad spectrum, mo				
0–<24	.05 (0.04 to 0.05)	.04 (0.03 to 0.05)	.07 (0.05 to 0.10)	.07 (0.05 to 0.10)
0–<6[c,d]	.05 (0.03 to 0.07)	.04 (0.02 to 0.06)	.05 (0.01 to 0.09)	.05 (0.01 to 0.09)
6–<12[c,d]	.04 (0.03 to 0.05)	.03 (0.02 to 0.05)	.05 (0.02 to 0.08)	.05 (0.01 to 0.08)
12–<24[c,d]	.03 (0.02 to 0.04)	.03 (0.02 to 0.04)	.07 (0.04 to 0.10)	.07 (0.04 to 0.10)
Narrow spectrum[e], mo				
0–<24	.02 (0.01 to 0.03)	.02 (0.01 to 0.03)	.03 (0.00 to 0.07)	.03 (−0.01 to 0.06)
0–<6[c,d]	.06 (0.04 to 0.08)	.05 (0.04 to 0.07)	.04 (−0.01 to 0.09)	.04 (−0.01 to 0.08)
6–<12[c,d]	.02 (0.01 to 0.04)	.02 (0.01 to 0.04)	.02 (−0.02 to 0.06)	.01 (−0.03 to 0.05)
12–<24[c,d]	.01 (−0.01 to 0.02)	.01 (0.00 to 0.02)	.03 (−0.02 to 0.07)	.02 (−0.02 to 0.06)

[a] Corrected for clustering by site and adjusted for sex, race, ethnicity, preterm birth, 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. Asthma is not included.

[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 (infections, 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-spectrum antibiotic exposures, analyses limited to participants with no broad during the same time window as exposure or before.

SUPPLEMENTAL TABLE 13 Multivariable 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, Sensitivity Analyses

Any Antibiotics	No Complex Chronic Condition		Complex Chronic Condition	
	Model 1,[a] β (95% CI)	Model 2,[b] β (95% CI)	Model 1,[a] β (95% CI)	Model 2,[b] β (95% CI)
Limited to participants with any well-child visits at <72 mo of age, *N* = 280 590; 28 220[c]	.08 (0.07 to 0.09)	.04 (0.03 to 0.05)	.10 (0.07 to 0.13)	.05 (0.02 to 0.08)
Limited to sites with a ≥40% antibiotic prescribing rate at <24 mo of age, *N* = 284 712; 47 496[c]	.07 (0.07 to 0.08)	.04 (0.03 to 0.05)	.09 (0.07 to 0.12)	.06 (0.04 to 0.09)
Limited to participants without an antibiotic prescription linked to a tier 1 diagnosis, *N* = 285 736; 44 382[c]	.07 (0.06 to 0.08)	.04 (0.03 to 0.05)	.08 (0.05 to 0.10)	.06 (0.03 to 0.08)

[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] The 2 values represent sample sizes for children without (larger number) and with complex chronic conditions.

SUPPLEMENTAL TABLE 14 Multivariable Linear Regression Results for the Association of Antibiotics Episodes at <24 Months of Age With the BMI *z* Score at 48–<72 Months of Age, by Antibiotic Spectrum, Incorporating Maternal Covariates for 7 Health Care Institutions When Available (Data Only for Children Without Complex Chronic Conditions)

Antibiotics	Model 1,[a] β (95% CI)	Model 2,[b] β (95% CI)	Model 3,[c] β (95% CI)	Model 4,[d] β (95% CI)
	N = 48 908	*N* = 48 908	*N* = 22 310	*N* = 12 698
Any	.05 (0.03 to 0.08)	.03 (0.00 to 0.05)	.02 (−0.01 to 0.06)	.04 (−0.01 to 0.08)
Broad spectrum	.06 (0.04 to 0.08)	.03 (0.01 to 0.06)	.01 (−0.02 to 0.04)	.04 (0.00 to 0.08)
Narrow spectrum[e]	.03 (0.01 to 0.06)	.02 (0.00 to 0.05)	.04 (0.00 to 0.07)	.03 (−0.02 to 0.08)
	N = 12 698	*N* = 12 698	*N* = 12 698	*N* = 12 698
Any	.08 (0.04 to 0.12)	.05 (0.00 to 0.09)	.05 (0.01 to 0.09)	.04 (−0.01 to 0.08)
Broad spectrum	.07 (0.03 to 0.10)	.04 (0.00 to 0.09)	.04 (0.00 to 0.08)	.04 (0.00 to 0.08)
Narrow spectrum[e]	.06 (0.01 to 0.11)	.04 (−0.01 to 0.10)	.05 (0.00 to 0.10)	.03 (−0.02 to 0.08)

[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] Model 2 was additionally adjusted for maternal age, prepregnancy BMI, total gestational wt gain, pregnancy smoking status, glucose status, and mode of delivery.

[d] Model 3 was additionally adjusted for child birth wt.

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

SUPPLEMENTAL TABLE 15 Multivariable Linear Regression Results for the Association of Antibiotics Episodes at <24 Months of Age With the BMI *z* Score at 48–<72 Months of Age, by Antibiotic Spectrum and Number of Episodes, Incorporating Maternal Covariates for 7 Health Care Institutions When Available (Data Only for Children Without Complex Chronic Conditions)

Episodes	Model 1[a] (*N* = 48 908), β (95% CI)	Model 2[b] (*N* = 48 908), β (95% CI)	Model 3[c] (*N* = 22 310), β (95% CI)	Model 4[d] (*N* = 12 698), β (95% CI)
Overall				
0	.0 (reference)	.0 (reference)	.0 (reference)	.0 (reference)
1	.01 (−0.01 to 0.04)	.00 (−0.02 to 0.03)	.01 (−0.03 to 0.05)	.02 (−0.03 to 0.07)
2	.06 (0.03 to 0.09)	.03 (0.00 to 0.07)	.03 (−0.01 to 0.08)	.03 (−0.02 to 0.09)
3	.07 (0.04 to 0.11)	.05 (0.01 to 0.09)	.05 (−0.01 to 0.10)	.07 (0.00 to 0.14)
4+	.11 (0.08 to 0.14)	.07 (0.03 to 0.10)	.03 (−0.01 to 0.08)	.08 (0.01 to 0.14)
Broad spectrum				
0	.0 (reference)	.0 (reference)	.0 (reference)	.0 (reference)
1	.04 (0.02 to 0.07)	.03 (0.00 to 0.05)	.01 (−0.03 to 0.04)	.02 (−0.02 to 0.07)
2	.05 (0.01 to 0.09)	.02 (−0.02 to 0.06)	.01 (−0.04 to 0.07)	.02 (−0.05 to 0.09)
3	.10 (0.04 to 0.15)	.07 (0.01 to 0.12)	.06 (−0.02 to 0.13)	.12 (0.02 to 0.22)
4+	.11 (0.06 to 0.16)	.07 (0.02 to 0.12)	.02 (−0.05 to 0.08)	.07 (−0.01 to 0.16)
Narrow spectrum[e]				
0	.0 (reference)	.0 (reference)	.0 (reference)	.0 (reference)
1	.02 (−0.01 to 0.05)	.02 (−0.01 to 0.05)	.03 (−0.01 to 0.07)	.04 (−0.01 to 0.10)
2	.04 (0.00 to 0.09)	.03 (−0.01 to 0.08)	.04 (−0.02 to 0.10)	.01 (−0.07 to 0.08)
3	.05 (−0.02 to 0.12)	.03 (−0.04 to 0.10)	.07 (−0.02 to 0.16)	.04 (−0.08 to 0.16)
4+	.09 (−0.02 to 0.20)	.03 (−0.08 to 0.14)	.00 (−0.16 to 0.15)	−.06 (−0.26 to 0.13)

[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] Model 2 was additionally adjusted for maternal age, prepregnancy BMI, total gestational wt gain, pregnancy smoking status, glucose status, and mode of delivery.

[d] Model 3 was additionally adjusted for child birth wt.

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

SUPPLEMENTAL TABLE 16 Multivariable Logistic Regression Results for the Association of Any Exposure to Antibiotics at <24 Months of Age and Risk Obesity (≥95th Percentile) at 48–<72 Months of Age, by Timing of Antibiotic Prescription (Comparison is to BMI in the <85th Percentile)

Antibiotics	No Complex Chronic Condition, *N* = 265 652[a]		Complex Chronic Condition, *N* = 44 124[a]	
	Model 1,[b] OR (95% CI)	Model 2,[c] OR (95% CI)	Model 1,[b] OR (95% CI)	Model 2,[c] OR (95% CI)
Any, mo				
0–<24	1.10 (1.08 to 1.12)	1.04 (1.01 to 1.06)	1.09 (1.04 to 1.15)	1.00 (0.94 to 1.06)
0–<6[d,e]	1.18 (1.14 to 1.21)	1.09 (1.06 to 1.13)	1.07 (1.00 to 1.14)	1.01 (0.94 to 1.08)
6–<12[d,e]	1.10 (1.08 to 1.13)	1.02 (1.00 to 1.05)	1.05 (1.00 to 1.11)	0.96 (0.90 to 1.02)
12–<24[d,e]	1.08 (1.06 to 1.11)	1.01 (0.99 to 1.04)	1.10 (1.04 to 1.15)	1.00 (0.94 to 1.06)
Broad spectrum, mo				
0–<24	1.11 (1.08 to 1.13)	1.06 (1.04 to 1.09)	1.10 (1.05 to 1.16)	1.03 (0.97 to 1.09)
0–<6[d,e]	1.17 (1.12 to 1.23)	1.08 (1.03 to 1.14)	1.05 (0.97 to 1.14)	1.00 (0.92 to 1.09)
6–<12[d,e]	1.10 (1.07 to 1.13)	1.03 (1.00 to 1.06)	1.06 (1.00 to 1.13)	0.99 (0.92 to 1.06)
12–<24[d,e]	1.10 (1.07 to 1.12)	1.05 (1.02 to 1.07)	1.12 (1.06 to 1.18)	1.04 (0.97 to 1.11)
Narrow spectrum,[f] mo				
0–<24	1.06 (1.03 to 1.08)	1.01 (0.98 to 1.04)	1.04 (0.97 to 1.12)	0.96 (0.89 to 1.04)
0–<6[d,e]	1.17 (1.12 to 1.22)	1.09 (1.04 to 1.14)	1.09 (0.98 to 1.20)	1.01 (0.91 to 1.12)
6–<12[d,e]	1.09 (1.06 to 1.12)	1.02 (0.99 to 1.05)	1.02 (0.94 to 1.11)	0.93 (0.85 to 1.02)
12–<24[d,e]	1.04 (1.01 to 1.07)	1.00 (0.96 to 1.03)	1.04 (0.95 to 1.13)	0.97 (0.89 to 1.07)

[a] The number is smaller here than in other models because children with a BMI from the 85th to <95th percentile were excluded from this model.

[b] Corrected for clustering by site.

[c] 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.

[d] 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.

[e] For exposure time windows, covariates were used during the same time window (infections, 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.

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

SUPPLEMENTAL TABLE 17 Associations of Covariates With the BMI z Score at 48–<72 Months of Age in Models With Infections Included

Covariates	No Complex Chronic Condition (*N* = 310 947), β (95% CI)	Complex Chronic Condition (*N* = 51 603), β (95% CI)
Any antibiotics at <24 mo	.04 (0.03 to 0.05)	.06 (0.04 to 0.09)
Female sex (yes versus no)	.01 (0.01 to 0.02)	.01 (-0.02 to 0.03)
Age at outcome (mo)	.01 (0.00 to 0.01)	.00 (0.00 to 0.01)
Preterm (yes versus no)	−.22 (−0.24 to −0.20)	−.38 (−0.41 to −0.35)
Asthma (yes versus no)	.15 (0.14 to 0.17)	.14 (0.10 to 0.17)
Corticosteroid episodes at <24 mo (continuous, 0–4+)	.06 (0.05 to 0.07)	.05 (0.03 to 0.06)
No. encounters at <24 mo (log transformed)	−.02 (−0.02 to −0.01)	−.03 (−0.04 to −0.01)
Infection episodes at <24 mo (log transformed)	.02 (0.02 to 0.02)	.01 (0.00 to 0.02)
Race		
Asian American	−.21 (−0.23 to −0.19)	−.32 (−0.38 to −0.25)
African American	.06 (0.05 to 0.07)	.05 (0.02 to 0.08)
Other	.03 (0.02 to 0.05)	.03 (−0.01 to 0.07)
Unknown	.03 (0.02 to 0.05)	.11 (0.05 to 0.16)
White	.0 (ref)	.0 (ref)
Hispanic (yes versus no)	.34 (0.33 to 0.35)	.24 (0.21 to 0.28)

The model was adjusted for all covariates at the same time. We also assessed for the possibility that antibiotics were mediating the relationship between infections and wt outcomes. To do so, we ran models without including antibiotics (and only including infections). These models had parameter estimates for log-transformed infections of 0.02 (95% CI 0.01 to 0.03) for children without and 0.02 (95% CI 0.02 to 0.03) for children with complex chronic conditions, revealing minimal difference.

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