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Original Investigation

Antibiotic Exposure During the First 6 Months of Life and Weight Gain During Childhood

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IMPORTANCE Early-life antibiotic exposure has been associated with increased adiposity in animal models, mediated through the gut microbiome. Infant antibiotic exposure is common and often inappropriate. Studies of the association between infant antibiotics and childhood weight gain have reported inconsistent results.

OBJECTIVE To assess the association between early-life antibiotic exposure and childhood weight gain.

DESIGN AND SETTING Retrospective, longitudinal study of singleton births and matched longitudinal study of twin pairs conducted in a network of 30 pediatric primary care practices serving more than 200 000 children of diverse racial and socioeconomic backgrounds across Pennsylvania, New Jersey, and Delaware.

PARTICIPANTS Children born between November 1, 2001, and December 31, 2011, at 35 weeks' gestational age or older, with birth weight of 2000 g or more and in the fifth percentile or higher for gestational age, and who had a preventive health visit within 14 days of life and at least 2 additional visits in the first year of life. Children with complex chronic conditions and those who received long-term antibiotics or multiple systemic corticosteroid prescriptions were excluded. We included 38 522 singleton children and 92 twins (46 matched pairs) discordant in antibiotic exposure. Final date of follow-up was December 31, 2012.

EXPOSURE Systemic antibiotic use in the first 6 months of life.

MAIN OUTCOMES AND MEASURES Weight, measured at preventive health visits from age 6 months through 7 years.

RESULTS Of 38 522 singleton children (50% female; mean birth weight, 3.4 kg), 5287 (14%) were exposed to antibiotics during the first 6 months of life (at a mean age of 4.3 months). Antibiotic exposure was not significantly associated with rate of weight change (0.7%; 95% CI, -0.1% to 1.5%; $P = .07$, equivalent to approximately 0.05 kg; 95% CI, -0.004 to 0.11 kg of added weight gain between age 2 years and 5 years). Among 92 twins (38% female; mean birth weight, 2.8 kg), the 46 twins who were exposed to antibiotics during the first 6 months of life received them at a mean age of 4.5 months. Antibiotic exposure was not significantly associated with a weight difference (-0.09 kg; 95% CI, -0.26 to 0.08 kg; $P = .30$).

CONCLUSIONS AND RELEVANCE Exposure to antibiotics within the first 6 months of life compared with no exposure was not associated with a statistically significant difference in weight gain through age 7 years. There are many reasons to limit antibiotic exposure in young, healthy children, but weight gain is likely not one of them.

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Antibiotics are the most commonly prescribed medications for children,¹ and many of these prescriptions are inappropriate.² The costs of antibiotic overuse, including antibiotic resistance³ and adverse drug effects,⁴ are well documented. The long-term health effects of antibiotic exposure, however, are relatively unknown.

Antibiotics promote growth in livestock, and it has been hypothesized that this occurs because of structural and functional alterations of the gut microbiome.⁵ Short-term antibiotic use can result in persistent changes in the human gut microbiome.⁶ Mice given antibiotics had altered gut microbiome composition, changed carbohydrate and lipid metabolism, and increased adiposity compared with control animals.⁷ Fecal transplants in mice using stool from humans transferred the donor obesity phenotype (obese/lean) to recipient mice.⁸

Observational studies have reported associations between antibiotic exposure and body mass in children.⁹⁻¹² These associations, however, have been inconsistent both within and across studies, potentially because of differences in the setting, population, and indication for antibiotics or because of the use of different outcome and exposure definitions, analytic approaches, and observation windows.¹³ Because the public health implications of this proposed association are profound, we evaluated the association between early-life antibiotic exposure and weight gain by means of growth trajectory modeling using a singleton birth cohort of nearly 40 000 children and an analysis of twin pairs who were discordant in early-life antibiotic exposure.

Methods

Study Design and Setting

The Children's Hospital of Philadelphia Committee for the Protection of Human Subjects approved the study and granted a waiver of consent.

A retrospective, longitudinal cohort study assessed the association of early-life antibiotic exposures with childhood weight using 2 separate cohorts within the same population: (1) a retrospective, longitudinal study of singleton births and (2) a matched longitudinal study of twin pairs discordant in early-life antibiotic exposure. Data came from a network of 30 pediatric primary care practices with a common electronic health record (Epic Systems) serving children of diverse racial and socioeconomic backgrounds across southeastern Pennsylvania, southern New Jersey, and northern Delaware.

Study Population

Children were included if they were born between 2001 and 2011 at 35 weeks' gestational age or older with a birth weight of 2000 g or more and in the fifth percentile for gestational age¹⁴ and who had a preventive health visit within 14 days of life and at least 2 additional visits in the first year (to include only children likely to have received the majority of their care within the network). The observation period started at the first visit and ended with the last visit before their eighth birthday or December 31, 2012, whichever occurred first.

Children with complex chronic conditions (derived from a published algorithm¹⁵) that might affect antibiotic use or growth, who were prescribed long-term antibiotics (≥ 30 days or ≥ 2 refills), or who received more than 2 systemic corticosteroid prescriptions during any 365-day period up to age 8 years were excluded. Identification of a complex chronic condition was not limited to the primary exposure window because even though a diagnosis might have been identified and recorded after the exposure period, the condition was likely already present. Although exclusion of chronic steroid use throughout the study period would prevent identification of an association between antibiotic exposure and growth mediated by steroid use (eg, early-life antibiotics cause atopy, which is treated with steroids, which affect weight), the relationship between steroid exposure and growth has been previously established and is not the broadly hypothesized (and animal model-supported) microbiome-mediated mechanism by which antibiotics might affect growth. Data were obtained from a comprehensive electronic health record used exclusively by all practices for all office and telephone encounters since 2001.

Exposure

The primary exposure was antibiotic use in the first 6 months of life, chosen to mimic the time window when microbiome perturbation has been shown to be most influential in animal models.¹⁶ Antibiotic use in the first 24 months was examined as a secondary exposure. Antibiotic use was identified by prescriptions for systemic (oral, intramuscular, or intravenous) antibacterial agents. Any duration of therapy was included except oral therapy for less than 3 days (manual chart review revealed that these short-term prescriptions were typically canceled or changed); 95% of prescriptions were between 5 and 10 days in duration. New antibiotic prescriptions initiated more than 14 days after prior antibiotic prescriptions were considered separate courses. Exposure was classified by drug category to differentiate narrow-spectrum, broad-spectrum, and macrolide exposure (eTable 1 in the Supplement). Exposure status was analyzed as binary (≥ 1 course vs none) and multilevel (0, 1, 2, and ≥ 3 courses) categorical variables.

Outcome

The primary outcome was longitudinally measured weight in the first 8 years of life, used to model growth trajectory via changes in weight. For the primary exposure, only growth measurements obtained beyond 6 months were used for modeling growth trajectories (and beyond 24 months for the secondary exposure). Weight was selected as the primary outcome over body mass index (BMI) because BMI (as a ratio measure) can introduce bias and spurious correlations in regression settings.¹⁷ Furthermore, in the first 24 months of life, BMI is not calculated because length is measured as opposed to height. Only weight measurements from preventive health encounters were included because of concern about less reliable measurements at acute care encounters. Weight measurements identified as likely errors using an automated method (eAppendix 1 in the Supplement) were excluded.¹⁸

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Covariates

Patient demographic variables included sex, Medicaid insurance status, race (black vs nonblack, self-reported using options defined by all practices across the health care network; race has previously been shown to be associated with both antibiotic prescribing and growth trajectory¹⁹), household density (number of older siblings aged <21 years in household at birth, categorized as none, 1-2, 3-4, or ≥5), and birth year. Baseline anthropometric measures included weight at birth and length at first visit. Primary care practice was assigned using the practice visited most frequently.

Statistical Analysis

The primary analysis for the singleton cohort evaluated the relationship between early antibiotic exposure and weight trajectory using longitudinal rate regression models, a nonlinear method well suited for examining growth trajectories.²⁰ This model uses a proportional rate assumption and a general time trajectory function to estimate the difference in rate of change for an outcome (weight) associated with an exposure (antibiotics). The rate parameter for early antibiotic exposure represents the percent difference in rate of weight gain for a typical child exposed to antibiotics compared with the rate in an unexposed child. As an alternative interpretation, models can estimate the difference in accumulated weight between ages 2 and 5 years for exposed relative to unexposed. These differences can be interpreted as the added weight change associated with the rate difference between exposure groups, referred to as the attributable weight difference.

Growth trajectories were modeled using a natural cubic regression spline with knots at 500 and 1100 days²¹⁻²⁴ for the 6-month exposure models; a single knot at 1100 days was used for the 24-month model. Unlike conventional longitudinal regressions, the longitudinal rate regression model allows for covariate adjustment at both rate and mean levels. Mean-level covariates (sex, birth weight, race, Medicaid insurance status, number of siblings, birth year, baseline length, and primary care site) account for overall differences in weight associated with a covariate, which is characterized by the estimated difference in weight at baseline (ie, groups that are bigger or smaller at birth). Rate-level covariates (same as above except for primary care site, which was replaced by urban/faculty vs nonurban/nonfaculty setting) account for differences in growth trajectories associated with a covariate (ie, groups that grow at faster or slower rates). All covariates were centered on their respective sample means at the rate level to allow for interpretation of the parameter of interest relative to an average individual. Because of missingness for race (13% missing data), a multiple imputation approach with 5 replicates was used for the primary model (eAppendix 1 in the Supplement).²⁵ Predictors used in this imputation were sex, insurance type, gestational age, primary care site, number of siblings, birth weight, and standardized weight z score at last measurement. Assessment of variability due to imputation showed that the added component of variance due to variability in the parameter of interest across replicates was sufficiently small that only single imputation was used for

all secondary models (eTable 2 in the Supplement). Correlation between repeated measures within individual was adjusted for using random effects for both intercept and rate of change. This longitudinal model was replicated for each definition of early antibiotic exposure previously described. Sensitivity analyses evaluated whether exposure misclassification attenuated associations that would be clinically meaningful (eAppendix 1 in the Supplement).

For a complementary, prespecified analysis designed to control for unmeasured environmental (eg, household smoking, diet, hygiene) or genetic factors that might confound the relationship between antibiotic use and weight gain, twin sets discordant in early-life antibiotic use were identified. Differences over time were modeled in all paired weight measurements of twins (weight of exposed twin minus weight of unexposed twin) at each measurement time using linear mixed-effects regression controlling for sex, birth weight, and baseline length. Thus, the coefficient for time represents the association of early antibiotic exposure with weight difference between twins.

Hypothesis tests were 2-sided and a significance threshold of $P < .05$ was used. Analyses were performed using Stata version 13.1 (Stata Corp) and R version 3.0.1.

Calculations performed during project planning for the singleton cohort, based on preliminary data and a projected sample size of 40 100, estimated 80% power to detect a difference in growth trajectories of 4% of a standard deviation and 90% power to detect a difference of 5% of a standard deviation, both extremely small effects. A projected sample of 50 sets of twins with discordant antibiotic exposures was estimated to have 80% to 90% power to demonstrate 4% to 5% of a standard deviation of the differences in means using paired contrasts. Reported confidence intervals reflect postanalysis power on final data.²⁶

Results

Study Cohort

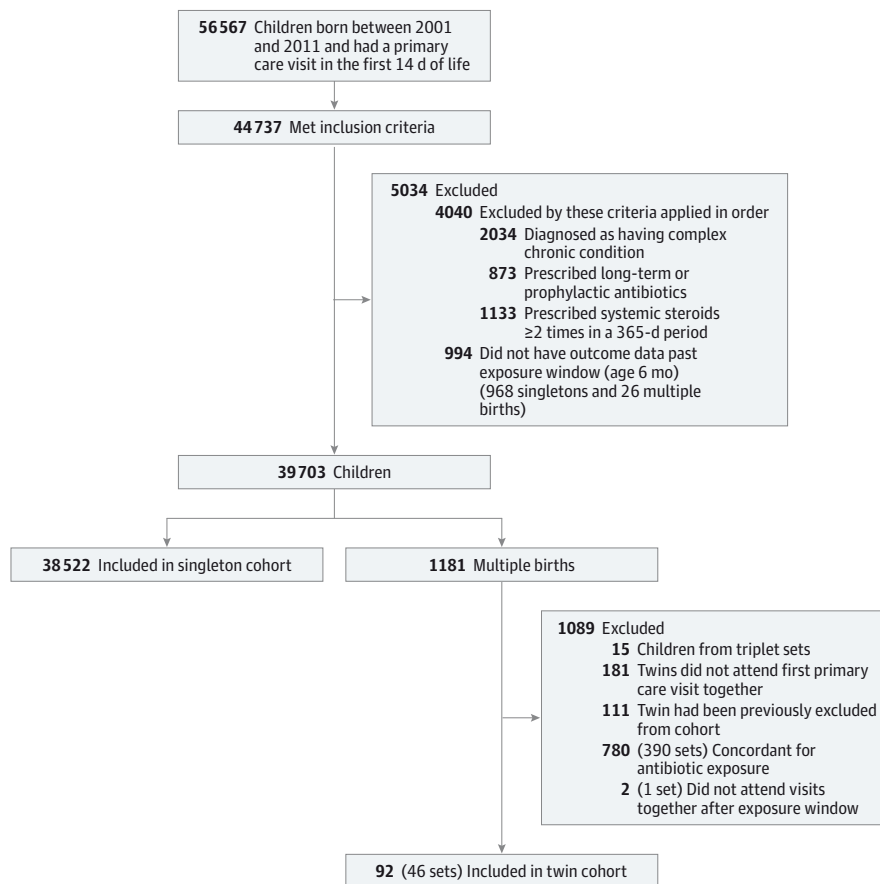
In the entire network, 56 567 children were born between 2001 and 2011 and had a primary care visit in the first 14 days of life. Of these, 44 737 children met inclusion criteria and 38 614 remained eligible for analyses after exclusions (38 522 singletons and 92 twins) (Figure 1). Demographic characteristics of the singleton and twin cohorts are shown in Table 1 and eTable 3 in the Supplement, respectively (for 24-month exposure windows, see eTables 4 and 5 in the Supplement).

Antibiotic Exposure

In the first 6 months of life, 5287 singleton children (14%) were exposed to antibiotics at a mean age of 4.3 months (eFigure in the Supplement), of whom 24% received broad-spectrum agents and 5% macrolides. Most of the exposed (79%) received only 1 course. The percentage of children exposed to any antibiotics increased to 67% by 24 months of age, of whom 52% received broad-spectrum agents and 19% macrolides.

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Figure 1. Antibiotic Exposure Cohorts for Singleton and Twin Births



Primary Exposure

Exposure to any antibiotic in the first 6 months was not associated with rate of change in weight (0.7%; 95% CI, -0.1% to 1.5%; $P = .07$) (Table 2). The estimated increase in the rate of change in weight was equivalent to 0.05 kg (95% CI, -0.004 to 0.11 kg) of attributable weight difference between 2 and 5 years of age. Subanalyses by number of antibiotic courses (1, 2, or ≥ 3) and by antibiotic type (narrow spectrum, broad spectrum, or macrolide) did not find significant associations between antibiotic exposure and rate of change in weight. The Wald test for overall differences in the rate effect across groups defined by antibiotic type did not approach conventional levels of statistical significance ($P = .51$).

Secondary Exposure

Exposure to any antibiotic in the first 24 months was associated with a 2.1% (95% CI, 0.8%-3.3%; $P = .001$) increase in the rate of change in weight (Table 2), equivalent to an attributable weight difference of 0.15 kg (95% CI, 0.06-0.24 kg) between 2 and 5 years of age (or gaining, on average, 7.34 kg instead of 7.19 kg during this 3-year period). Subanalyses by number of antibiotic courses and by antibiotic type revealed similar estimated changes in growth trajectory, ranging from a low of 1.8% (95% CI, 0.4%-3.3%; $P = .01$) for 1 antibiotic course to a high of 2.4% for 3 or more courses (95% CI, 0.9%-3.9%;

$P = .002$) and macrolides (95% CI, 0.6%-4.2%; $P = .009$). The Wald test for overall differences in the rate effect across groups defined by antibiotic type was statistically significant ($P = .01$). Figure 2 shows growth curves, adjusted for mean- and rate-level confounders, by antibiotic exposure in the first 6 months (panel A) and first 24 months (panel B).

Sensitivity Analyses

Analyses to assess the statistical effect of potential exposure misclassification assumed that misclassification was strongly associated with increased weight gain. For example, we assumed that some children who gained more weight but had no observed exposure to antibiotics actually were exposed and that some children who did not gain weight but were prescribed antibiotics actually did not take them. In this extreme scenario, the estimated upper bound for any antibiotic exposure was a 3.5% (95% CI, 2.7%-4.4%; $P < .001$) rate difference (0.26 kg [95% CI, 0.20-0.32 kg] attributable weight difference) for the 6-month exposure (eAppendix 2, eTable 6, and eTable 7 in the Supplement).

Cohort of Discordant Twins

For the 46 twin sets (92 children; 38% female; mean birth weight, 2.8 kg) discordant on antibiotic exposure in the first 6 months (mean age at exposure, 4.5 months), adjusted for

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Table 1. Singleton Cohort Demographic Characteristics by Antibiotic Exposure Within 6 Months of Life (N = 38 522)

Characteristics	Antibiotic Exposure in First 6 mo		Overall (n = 38 522)
	Exposed (n = 5287)	Unexposed (n = 33 235)	
Male, No. (%)	2891 (55)	16 538 (50)	19 429 (50)
Race, No. (%)			
Black	1023 (19)	11 860 (36)	12 883 (33)
Nonblack ^a	3545 (67)	16 950 (51)	20 495 (53)
Unknown	719 (14)	4425 (13)	5144 (13)
Medicaid insurance, No. (%)	1440 (27)	12 578 (38)	14 018 (36)
Older siblings in household, No. (%)			
None	2205 (42)	16 816 (51)	19 021 (49)
1-2	2788 (53)	14 824 (45)	17 612 (46)
3-4	260 (5)	1460 (4)	1720 (4)
≥5	34 (1)	135 (<1)	169 (<1)
Birth year, No. (%)			
2001	4 (<1)	18 (<1)	22 (<1)
2002	43 (1)	328 (1)	371 (1)
2003	62 (1)	510 (2)	572 (1)
2004	208 (4)	1229 (4)	1437 (4)
2005	500 (9)	2670 (8)	3170 (8)
2006	680 (13)	3762 (11)	4442 (12)
2007	749 (14)	4325 (13)	5074 (13)
2008	787 (15)	5024 (15)	5811 (15)
2009	776 (15)	4934 (15)	5710 (15)
2010	694 (13)	5045 (15)	5739 (15)
2011	784 (15)	5390 (16)	6174 (16)
Attends urban or faculty primary care practice, No. (%)	1008 (19)	13 115 (40)	14 123 (37)
Birth weight, mean (SD), kg	3.47 (0.46)	3.38 (0.46)	3.40 (0.46)
Baseline length, mean (SD), cm	51.34 (2.74)	50.70 (2.71)	50.79 (2.73)

^a Nonblack category includes American Indian, Alaskan Native, Asian, Native Hawaiian, Pacific Islander, white, and mixed race.

sex, birth weight, and baseline length, antibiotic exposure was not associated with a difference in weight change (−0.09-kg difference between exposed twin and unexposed twin per year; 95% CI, −0.26 to 0.08 kg; $P = .30$). Likewise, for twin sets discordant for antibiotic exposure in the first 24 months, exposure was not associated with a difference in weight change (−0.11-kg difference per year; 95% CI, −0.28 to 0.05 kg; $P = .18$).

Discussion

In a large, diverse birth cohort of 40 000 children within a comprehensive pediatric care network, a statistically significant association between antibiotic use in the first 6 months of life and weight trajectory was not observed. Secondary analyses of antibiotic exposure in the first 24 months was associated with a small but statistically significant increase in weight gain, equivalent to roughly 150 g over 3 years. These findings do not support a clinically meaningful association of early-life antibiotic use with childhood weight gain.

Previous studies reported associations between antibiotic use and obesity. A systematic review of 10 randomized clinical trials concluded that antibiotics had growth-

promoting effects on young children from middle- and low-income countries²⁷; however, given the fundamental differences observed in the structure and function of the microbiome in children with clinically significant malnutrition,²⁸ these findings may not be generalizable to all children. Studies of children from developed nations have reported mixed results. Ajslev et al⁹ found that exposure to antibiotics in the first 6 months of life was associated with a higher risk of being overweight at age 7 years in children with normal-weight mothers but a decreased risk in children with overweight mothers, and Trasande et al¹⁰ observed that antibiotic exposure in the first 6 months of life was associated with an increase in body mass between 10 and 38 months but not at 7 years. Both studies relied on parent recall of antibiotic use for the year preceding the interview, a possible source of bias. Bailey et al¹¹ found an association between one of several exposure categories tested (>3 broad-spectrum courses in the first 24 months) and obesity measured at any time during years 3 to 5, and Saari et al¹² found associations between infant antibiotic exposures and first BMI measurement at 24 months of age or older.

This study features important differences in design and analysis from prior studies. The primary exposure—antibiotics within the first 6 months of life—was chosen based

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Table 2. Differences in Growth Trajectories for Patients With Early-Life Antibiotic Exposure Compared With Unexposed Patients Followed Up to Age 8 Years^a

	No. of Patients	Difference in Rate of Weight Gain Associated With Exposure, % (95% CI)	P Value	Expected Weight Change Between Ages 2 and 5 y	
				Change in Unexposed Child, kg ^b	Attributable Weight Difference Due to Exposure, kg (95% CI)
6-mo Exposure					
No antibiotic	33 235				
Any antibiotic ^c	5287	0.7 (-0.1 to 1.5)	.07	7.39	0.05 (-0.004 to 0.11)
No. of courses of antibiotics					
1	4159	1.0 (0.1 to 1.8)	.03	7.39	0.07 (0.01 to 0.14)
2	866	0.3 (-1.5 to 2.1)	.72	7.39	0.02 (-0.11 to 0.16)
≥3	262	-1.7 (-4.9 to 1.5)	.30	7.39	-0.13 (-0.36 to 0.11)
Antibiotic type ^d					
Narrow spectrum	3979	0.4 (-0.6 to 1.3)	.45	7.68 ^e	0.03 (-0.05 to 0.10)
Broad spectrum (nonmacrolide)	1026	-0.3 (-2.1 to 1.5)	.72	7.68 ^e	-0.03 (-0.16 to 0.11)
Macrolide	282	2.2 (-1.2 to 5.7)	.20	7.68 ^e	0.17 (-0.09 to 0.44)
2-y Exposure					
No antibiotic	8969				
Any antibiotic	18 809	2.1 (0.8 to 3.3)	.001	7.19	0.15 (0.06 to 0.24)
No. of courses of antibiotics					
1	6109	1.8 (0.4 to 3.3)	.01	7.19	0.13 (0.03 to 0.24)
2	3995	1.9 (0.3 to 3.6)	.02	7.19	0.14 (0.02 to 0.26)
≥3	8705	2.4 (0.9 to 3.9)	.002	7.19	0.17 (0.06 to 0.28)
Antibiotic type ^f					
Narrow spectrum	8932	1.9 (0.5 to 3.2)	.007	7.19	0.14 (0.04 to 0.23)
Broad spectrum (nonmacrolide)	6273	2.2 (0.7 to 3.8)	.004	7.19	0.16 (0.05 to 0.27)
Macrolide	3604	2.4 (0.6 to 4.2)	.009	7.19	0.17 (0.04 to 0.30)

^a Longitudinal rate regression model results for weight against antibiotic exposures in separate models.

Mean- and rate-level adjustment included sex, birth weight, race, Medicaid insurance status, number of siblings, birth year, baseline length, and urban/faculty practices (full site adjustment at the mean level).

^b Weight change for a typical unexposed child was estimated based on the difference in model estimates of the reference time function at ages 5 years and 2 years.

^c Estimates are adjusted for missing race using multiple imputation with 5 replicates; all other models use single imputation because of minimal variation across replicates.

^d Wald test for overall group differences resulted in $P = .51$.

^e The observable difference in the estimated weight change for a typical unexposed child for this model compared with other models of 6-month antibiotic exposure is likely due to the small subsample of infants exposed to macrolides at 6 months (0.7% of the sample), which overly influenced the reference time function as a result of the proportional rate assumption.

^f Wald test for overall group differences resulted in $P = .01$.

on the biological mechanism through which antibiotics increase adiposity in experimental animals; perturbations in the developing gut microbiome.^{7,16} The lack of an association in subanalyses of children exposed to repeated antibiotic courses and those given agents that would target a broader range of gut microbiota supports our conclusions. Because prior studies reported associations between antibiotic exposure through 24 months of life and obesity,^{11,12} this time window was examined in secondary analyses to allow for comparison. Herein, the roughly 2% increase in weight trajectory was equivalent to a child gaining an additional 150 g between 2 and 5 years of age; the statistical significance likely reflects the robust statistical power afforded by the sample size instead of a clinically meaningful difference.

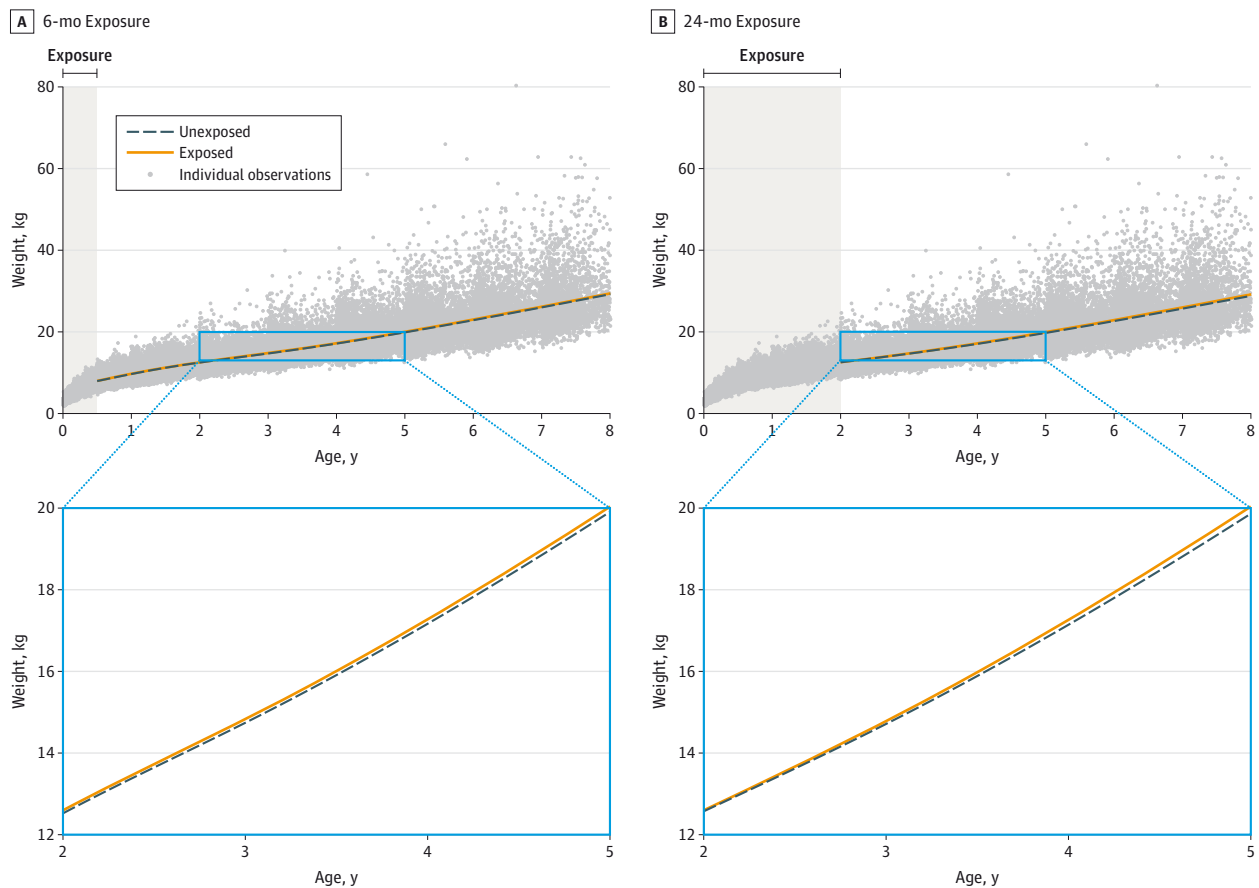
Additionally, twin pairs discordant in early antibiotic exposure were examined to address the potential influence of environmental and genetic factors that might not have been accounted for in the adjusted analyses of the singleton cohort. The narrow confidence intervals in the results from the twin cohort make clinically important weight gain associated with antibiotic exposure unlikely (either by 6 months or 24 months of age).

The primary outcome measure, weight trajectory over time, also differs from prior studies. Weight was selected as the primary outcome rather than BMI because BMI as a ratio

measure can introduce bias and spurious correlations in regression settings.¹⁷ Furthermore, modeling weight unadjusted for stature (length or height) was deemed a more appropriate outcome for addressing the question of whether antibiotic exposure is associated with overall increases in size. Because no association was found between antibiotic exposure and weight gain, additional adjustment for length or height would not be expected to affect the observed results unless antibiotic exposure affects stature, but this potential effect of antibiotic exposure lacks a biological basis. To reduce measurement error, only anthropometric measurements obtained at well-child visits were included, and an automated, reproducible method was used to exclude measurements identified as likely errors. Changes in weight trajectories over time were modeled to reflect the association of the exposure with weight gain based on a microbiome mechanism. The analysis of weight trajectories also avoids misclassification biases that can arise when continuous outcomes are dichotomized.²⁹ For example, if analyzing “time to obesity,” the outcome assesses only small (and potentially transient) weight increases in children on the borderline of the 95th percentile of weight (or other dichotomous criteria) but ignores subsequent weight changes that drop these children below this threshold and does not assess weight changes in nonoverweight children (ie, the majority of the

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Figure 2. Adjusted Change in Weight Over Time Associated With Early-Life Exposure to Antibiotics



Adjusted rates of growth in 6-month (panel A) and 24-month (panel B) exposure groups. Curves denote the fitted line within exposure groups as estimated by the longitudinal rate regression model. Indicated regions are shown magnified in

the lower plots. Dots indicate individual observations. For the 6-month exposure group, 33 235 were unexposed and 5257 were exposed; for the 24-month exposure group, 8969 were unexposed and 18 808 were exposed.

population). Thus, assessing the association of antibiotics with weight gain in all children was deemed most appropriate. The differences in results from prior studies highlight the sensitivity of conclusions in obesity studies to model specification and emphasizes the importance of selecting a model that reflects the biological mechanism in question.

Despite these strengths, this study has potential limitations. As with prior human studies (including those measuring BMI), adiposity could not be assessed. Therefore, it is possible that antibiotic exposure could lead to changes in adiposity without affecting overall weight or BMI. Misclassification of exposure may have occurred if antibiotics were obtained outside of the network or if prescribed antibiotics were not taken. Sensitivity analyses, however, suggest that this bias is insufficient to explain the lack of meaningful differences between exposed and unexposed children. Also, an alternative time window, duration, or spectrum of antimicrobial exposure not examined in the study could affect child weight gain.⁷ All possible factors that might be associated with both antibiotic use and weight gain, such as genetics, mode of delivery, and infant diet, could not be assessed. However, a matched twin study, which would account for many of these factors and was

well powered to find even small differences in weight gain, confirmed the results. Although confounding by indication is a common limitation, the indications for the vast majority of antibiotic use for these children were acute respiratory tract infections managed in the ambulatory setting, which have not previously been associated with long-term weight change in healthy children. In addition, although the network serves a population of diverse race, socioeconomic status, and medical setting (academic and community based) and has an overall antibiotic prescription rate similar to national estimates,^{2,30} it might not be generalizable to children outside of a North American health care setting, particularly to those with clinically significant malnutrition.

Conclusions

Exposure to antibiotics within the first 6 months of life compared with no exposure was not associated with a statistically significant difference in weight gain through age 7 years. There are many reasons to limit antibiotic exposure in young, healthy children, but weight gain is likely not one of them.

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Author Contributions: Drs Gerber and Bryan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.

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