Original Investigation

Association of Antibiotics in Infancy With Early Childhood Obesity

L. Charles Bailey, MD, PhD; Christopher B. Forrest, MD, PhD; Peixin Zhang, PhD; Thomas M. Richards, MS; Alice Livshits, BS; Patricia A. DeRusso, MD, MS

Related article page 1084

IMPORTANCE Obesity in children and adults is associated with significant health burdens, making prevention a public health imperative. Infancy may be a critical period when environmental factors exert a lasting effect on the risk for obesity; identifying modifiable factors may help to reduce this risk.

OBJECTIVE To assess the impact of antibiotics prescribed in infancy (ages 0-23 months) on obesity in early childhood (ages 24-59 months).

DESIGN, SETTING, AND PARTICIPANTS We conducted a cohort study spanning 2001-2013 using electronic health records. Cox proportional hazard models were used to adjust for demographic, practice, and clinical covariates. The study spanned a network of primary care practices affiliated with the Children's Hospital of Philadelphia including both teaching clinics and private practices in urban Philadelphia, Pennsylvania, and the surrounding region. All children with annual visits at ages 0 to 23 months, as well 1 or more visits at ages 24 to 59 months, were enrolled. The cohort comprised 64 580 children.

EXPOSURES Treatment episodes for prescribed antibiotics were ascertained up to 23 months of age.

MAIN OUTCOMES AND MEASURES Obesity outcomes were determined directly from anthropometric measurements using National Health and Nutrition Examination Survey 2000 body mass index norms.

RESULTS Sixty-nine percent of children were exposed to antibiotics before age 24 months, with a mean (SD) of 2.3 (1.5) episodes per child. Cumulative exposure to antibiotics was associated with later obesity (rate ratio [RR], 1.11; 95% CI, 1.02-1.21 for ≥4 episodes); this effect was stronger for broad-spectrum antibiotics (RR, 1.16; 95% CI, 1.06-1.29). Early exposure to broad-spectrum antibiotics was also associated with obesity (RR, 1.11; 95% CI, 1.03-1.19 at 0-5 months of age and RR, 1.09; 95% CI, 1.04-1.14 at 6-11 months of age) but narrow-spectrum drugs were not at any age or frequency. Steroid use, male sex, urban practice, public insurance, Hispanic ethnicity, and diagnosed asthma or wheezing were also predictors of obesity; common infectious diagnoses and antireflux medications were not.

CONCLUSIONS AND RELEVANCE Repeated exposure to broad-spectrum antibiotics at ages 0 to 23 months is associated with early childhood obesity. Because common childhood infections were the most frequent diagnoses co-occurring with broad-spectrum antibiotic prescription, narrowing antibiotic selection is potentially a modifiable risk factor for childhood obesity.

JAMA Pediatr. 2014;168(11):1063-1069. doi:10.1001/jamapediatrics.2014.1539
Published online September 29, 2014.

Author Affiliations: Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Bailey, Forrest, Zhang, Richards, Livshits, DeRusso); Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Bailey, Forrest, DeRusso); Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Richards).

Corresponding Author: L. Charles Bailey, MD, PhD, Division of Oncology/CTRB 10407, Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (baileyc@email.chop.edu).

Obesity is a major public health problem, with 1 in 3 children and adolescents in the United States either overweight or obese.[1,2] Obesity is associated with cardiometabolic outcomes such as type 2 diabetes mellitus, hyperlipidemia, hypertension, and other long-term consequences.[3] No age group is spared, with 10% of children obese by 24 months of age.[2] Additional work is needed to identify modifiable risk factors to mitigate the impact of this disease.

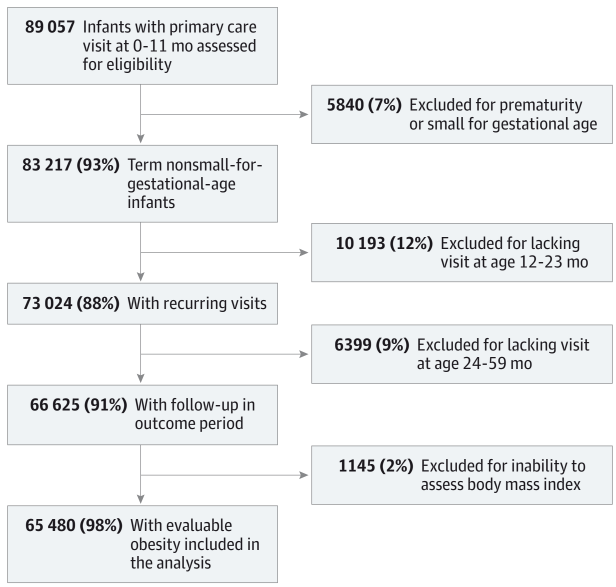
Early childhood obesity has been associated with several factors. Maternal prepregnancy body mass index (BMI), nutritional intake, physical activity, sleep duration, and screen time were identified by the Institute of Medicine Committee on Obesity Prevention Policies for Young Children.[4] One emerging factor noted by the committee is the role of microbial populations in the intestine. Colonization of the gut begins at birth and is influenced by a variety of dietary and environmental factors. Recent evidence suggests bacteria differ in their ability to extract energy, and colonization patterns can influence growth in both animal models and humans.[5-9] The intestinal microbiome plays an important role in host energy metabolism including the expression of genes influencing energy available from short-chain fatty acids and for processing otherwise indigestible polysaccharides.[5]

Previous studies have suggested intestinal microflora are associated with obesity later in life[7-10] and that antibiotic exposure influences microbial diversity and composition.[11-13] Given the modifiable nature of the intestinal microflora, the large shifts in diet and environmental contacts in infancy, the national burden of disease, and ample opportunity for improved antimicrobial use,[14] there is a need to determine the influence of antibiotic use on early childhood obesity.

In a large longitudinal birth cohort study of approximately 11 500 children born in the United Kingdom in 1991-1992, infants receiving antibiotics before age 6 months had a greater risk for being obese at 38 months of age (odds ratio, 1.22).[15] This study modeled antibiotic exposure as a binary outcome based on parent surveys. Covariates included parental obesity, socioeconomic status, and several aspects of early diet and lifestyle that may contribute to obesity risk. However, detailed information about the duration or type of antibiotics used was not available. Ajslev et al[8] included antibiotic exposure before 6 months as a variable in their analysis of the Danish National Birth Cohort, although they found significant association with later obesity in only subsets of children.

To further investigate the role of health care–related factors in this association, we undertook an observational study of early childhood obesity in the population of children followed up in a large pediatric primary care network covering parts of Pennsylvania, New Jersey, and Delaware in the eastern United States. The network has used a common electronic health record (EHR) system since 2001 for outpatient visits, with new practices adopting the EHR as they entered the network. Discretely captured data elements include patient demographics, anthropometric measurements, visit diagnoses, and medications. We used these data to assess the relationships between antibiotic prescription and related diagnoses before age 24 months and the development of obesity in the following 3 years, hypothesizing that antibiotic use in infancy is associated with early childhood obesity.

Figure 1. Construction of Study Sample



Percentages at each step in selection are computed by reference to the prior step.

Methods

Study Population

This study was reviewed and approved by the Children's Hospital of Philadelphia institutional review board, which granted waivers of both patient consent and Health Insurance Portability and Accountability Act authorization. Electronic health records for 2001 to 2013 from the primary care practice network affiliated with the Children's Hospital of Philadelphia were screened for potential cases. Because other hospital departments began using the EHR in stages from 2008 to 2012, records from these sources were not used to avoid creating substantial period effects in this interval. Children were eligible if they had at least 1 primary care visit at 0 to 11 months and 12 to 23 months of age to select for a level of continuous contact with the network during the medication exposure window, as well as at least 1 additional visit between 24 and 59 months for which BMI could be computed. Children with a diagnosis of prematurity (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 765.xx) or low birth weight (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 764.xx, V21.3x) at any visit in the first year of life were excluded. All other eligible children contributed to the analyses (**Figure 1**).

Data Retrieval

For each child, data were retrieved for all primary care visits from birth through the last available visit up to 59 months of age. Data from visits between 0 and 23 months of age were used to characterize potential predictors of obesity, while visits between 24 and 59 months were used to assess obesity outcomes.

Patient-level practice location was assigned using the practice first visited by the child. Race and ethnicity were patient-reported values collected using the EHR vendor's categories. Practices located within the city limits of Philadelphia, Pennsylvania, were classified as urban, while those outside the city were suburban. A child's insurance type was obtained by integrating payer information available for all visits before his or her second birthday. If the payer at any visit was a public insurance plan, the child was assigned to public insurance. Otherwise, children with at least 1 commercial payer recorded were scored as privately insured, and those without insurance recorded at any visit were classified as self-pay.

Medication Exposures

Antibiotic and other medication exposure was assessed using outpatient prescriptions and patient-reported medications recorded at all primary care visits between birth and 23 months of age. To limit bias from incomplete capture of over-the-counter medications, these were eliminated from analyses. Because specific doses were not always present, particularly for older records and for patient-reported medications, we recorded exposure to a medication categorically rather than as a specific dose. The duration of exposure was determined as all days from the prescribed start to end date or as a single day for prescriptions without a specific ending date.

Antibiotic exposures comprised systemic medications with primarily antibacterial activity; drugs with primarily antiviral or antifungal activity were not included. A single episode of antibiotic exposure was defined as all days from the start of a course through the beginning of a 14-day antibiotic-free interval.

Based on recommended use of narrower-spectrum antibacterials as first-line therapy for common pediatric infections,[16-19] penicillin and amoxicillin were operationally classified as narrow spectrum. Antibiotics recommended in guidelines as second-line therapy, which typically have broader antibacterial spectra, and all other systemic antibacterial medications were classified as broad spectrum.

Steroid exposure included prescriptions for systemic prednisone, dexamethasone, hydrocortisone, and their derivatives; topical and inhaled steroids were excluded. Antireflux medication exposure comprised both H_2 antagonists and proton pump inhibitors.

Clinical Diagnoses

Children were classified as having a given diagnosis if any of the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes in the cluster for that diagnosis were recorded at any visit before age 24 months. Asthma comprised all of the codes in the 493.xx subtree. Wheezing was assigned separately as the presence of 786.07. Bronchiolitis was indicated by the presence of 466 or 466.1x. Croup included 464 and 464.4. Otitis media included 055.2, 381, 381.x, 382.x, 384.x, 388.6x, 388.7x, and 388.9, while pharyngitis included 472, 472.1, and 474.x.

Outcomes

Body mass index was calculated as weight in kilograms divided by height in meters squared at visits occurring between 24 and 59 months of age as described[1] and compared with appropriate 2000 National Health and Nutrition Examination Survey growth norms.[20] A child was considered obese if the percentile was 95 or greater and overweight if the percentile was at least 85 but less than 95. For patient-level analyses, a child was scored as reaching the indicated outcome if the BMI percentile for any visit met the necessary criterion.

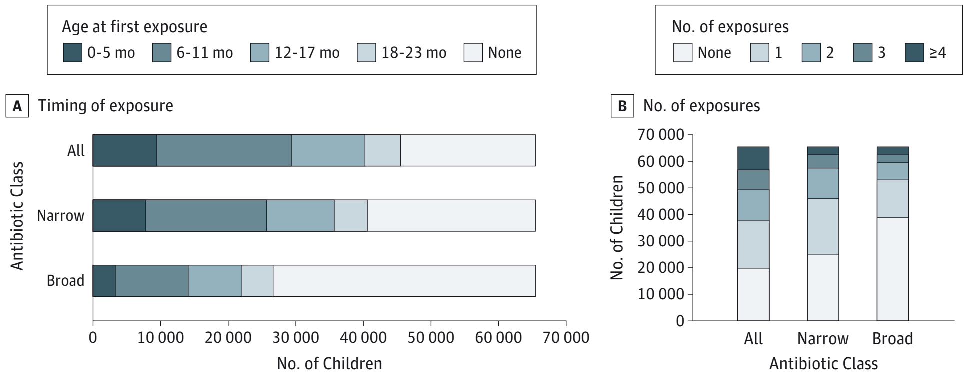
Data Analyses

Data management was done using Perl 5.12-5.18 (The Perl Foundation) and MySQL 5.5-5.7 (MySQL). Analyses were done using

Table 1. Baseline Characteristics of Study Population Assessed Over Ages 0 to 23 Months

Characteristic	No. (%)
Total	65 480 (100)
Sex	
Male	33 353 (51)
Female	32 127 (49)
Race	
White	33 337 (51)
Black	21 526 (33)
Other	10 617 (16)
Ethnicity	
Hispanic	2370 (4)
Non-Hispanic	63 110 (96)
Age at first primary care visit, mo	
<1	50 629 (77)
1-3	3474 (5)
4-6	3868 (6)
7-9	3995 (6)
10-12	3514 (5)
No. of primary care visits	
1-10	14 507 (22)
11-14	17 231 (26)
15-19	16 848 (26)
≥20	16 894 (26)
Practice location at first visit	
Urban	22 466 (34)
Suburban	43 014 (66)
Insurance coverage	
Medicaid/public	26 975 (41)
Commercial/private	38 060 (58)
Self-pay	95 (0)
Other	350 (1)
Calendar year of first visit	
2001	206 (0)
2002	2007 (3)
2003	2661 (4)
2004	5619 (9)
2005	10 315 (16)
2006	11 669 (18)
2007	11 144 (17)
2008	11 170 (17)
2009	10 689 (16)

Figure 2. Antibiotic Exposures at 0 to 23 Months



A, Timing of first antibiotic exposure. B, Total number of exposures.

R 2.14 or 2.15 (The R Project for Statistical Computing). Multivariate analysis was done in R and SAS 9.3 (SAS Institute Inc) with Cox proportional hazards models, using the first visit meeting BMI criteria for obesity (or overweight, where noted) as the event of interest. Patients were clustered by practice of their first visit in Cox models. Results are reported as rate ratios with 95% CIs and *P* values.

Results

Sample Construction

During the interval from 2001 through 2009, we identified 89 057 children seen as infants in the Children's Hospital of Philadelphia primary care network. Seventy-four percent had sufficient follow-up to meet inclusion criteria, yielding a cohort of 65 480 children (Figure 1). Baseline characteristics of the cohort are shown in **Table 1**. Comparison with patients excluded for lack of follow-up data indicated that the latter had highly similar distributions of sex, location, Hispanic ethnicity, and age at first visit; 7% less had private insurance and 5% more reported nonwhite race.

The cohort included significant representation from both urban (Philadelphia) and suburban practices, as well as from public and private insurance, with proportions by sex and race/ethnicity expected for the region. Patients had an average of 16 (median [SD],15 [7.2]) primary care visits from ages 0 to 23 months. Follow-up data were available for 98% of patients at 24 to 35 months of age, 79% of patients at 36 to 47 months, and 61% of patients at 48 to 59 months. For all children, the prevalence of obesity was 10% at 2 years of age, 14% at 3 years, and 15% at 4 years; corresponding values for overweight/obese were 23%, 30%, and 33%, respectively.

Antibiotic Exposures

Antibiotics were the most commonly prescribed medication at ages 0 to 23 months, with 69% of children exposed (**Figure 2**). On average, children received 2.3 (median [SD], 1 [1.5]) antibiotic treatment episodes. Overall, 62% of children had at least 1 exposure to narrow-spectrum antibiotics and 41% to broad-spectrum antibiotics. While antibiotics were prescribed to only 14% of children younger than 6 months, in each of the 3 subsequent 6-month periods, between 40% and 45% of children received antibiotics. Children exposed to antibiotics had weight-for-length *z* scores at the time of entry into the cohort similar to those for children not exposed to antibiotics (data not shown).

Risk Factors for Early Childhood Obesity

We constructed Cox proportional hazard models to evaluate the impact of antibiotic exposure on the risk for obesity (BMI≥95% percentile for age and sex). In addition to demographic factors, these models also incorporated calendar year and primary care practice at entry into the primary care network as covariates reflecting network evolution. We included oral steroids and antireflux medications, the second and third most commonly prescribed classes of medication in this age group, as clinical covariates addressing potential effects of overall medication use. To account for potential effects of underlying conditions on the risk for obesity, we also included as covariates common indications for use of these medications: otitis media and pharyngitis for antibiotics, and asthma, wheezing, croup, and bronchiolitis for steroids. Because we found no association between obesity and antireflux medications in both bivariate and multivariate analyses, related diagnoses were not included.

Table 2 summarizes the results of these analyses for a model incorporating all antibiotic exposures. We observed increased risk with greater antibiotic use, particularly for children with 4 or more exposures, when examining all antibiotics or broad-spectrum drugs only (**Figure 3**A). However, no significant association was seen between obesity and narrow-spectrum drugs. Neither pharyngitis nor otitis media, the 2 most common indications for antibiotics in early childhood, had significant association with obesity.

Models incorporating any antibiotic use in each of the periods of 0 to 5, 6 to 11, 12 to 17, and 18 to 23 months did not yield significant association between obesity and any single interval for any subset of antibiotics (data not shown). However, focusing the analysis on age at first antibiotic use showed greater effects for earlier exposure, with results reaching significance for broad-spectrum medications (Figure 3B). This effect was again absent for narrow-spectrum drugs. There was no interaction effect between age at first exposure and number of exposures (data not shown).

These models also demonstrated previously identified associations with several other obesity risk factors. Among nonclinical variables, male sex and urban practice environment were associated with a moderately increased risk for obesity, as was public insurance. We did not see a significant association with race, but Hispanic ethnicity was strongly associated with obesity. No time-dependent interaction between exposure and outcome was observed. Segmenting the exposure window into 3- or 4-month rather than 6-month intervals; limiting analyses to BMI measurement at each of 3, 4, or 5 years of age; or restricting the cohort to only patients with a full 5 years of follow-up produced similar results, as did use of logistic regression rather than Cox proportional hazards models.

Thirteen percent of children received systemic steroids, although only 3% had more than 1 episode of steroid use. Steroids had an effect size similar to that seen with frequent use of antibiotics. In contrast, antireflux medications were not associated with increased risk for later obesity; this group comprised 14% of all children, with use being more common at younger ages. Diagnosis of asthma or wheezing before 24 months was also associated with obesity. These were only partially overlapping groups, with 46% of the former and 48% of the latter having both diagnoses. Neither croup nor bronchiolitis were linked to obesity.

Table 2. Multivariate Analysis of the Risk for Early Childhood Obesity[a]

Variable	Rate Ratio (95% CI)	*P* Value
Any antibiotic use, No. of treatment episodes		
None	1 [Reference]	
1	1.030 (0.973-1.091)	.31
2	1.039 (0.958-1.128)	.36
3	1.042 (0.952-1.140)	.37
≥4[b]	1.110 (1.015-1.213)	.02
Sex		
Female	1 [Reference]	
Male[b]	1.144 (1.099-1.191)	<.001
Race		
White	1 [Reference]	
Black	1.026 (0.942-1.118)	.56
Other	1.025 (0.968-1.085)	.40
Ethnicity		
Non-Hispanic	1 [Reference]	
Hispanic[b]	1.626 (1.465-1.805)	<.001
Age at first primary care visit[b]	1.012 (1.006-1.019)	<.001
No. of primary care visits		
≤10	1 [Reference]	
11-14	1.012 (0.937-1.092)	.76
15-19	1.090 (0.999-1.188)	.05
≥20[b]	1.131 (1.039-1.231)	.004
Practice location at first visit		
Suburban Philadelphia	1 [Reference]	
City of Philadelphia[b]	1.066 (1.010-1.125)	.02
Insurance coverage		
Private/commercial	1 [Reference]	
Medicaid/public[b]	1.345 (1.256-1.440)	<.001
Self-pay at any visit	1.104 (0.678-1.798)	.69
Other non-Medicaid[b]	1.316 (1.028-1.684)	.03
Diagnoses in first 2 years		
Croup	1.049 (0.972-1.131)	.22
Bronchiolitis	1.028 (0.975-1.084)	.31
Asthma[b]	1.213 (1.141-1.289)	<.001
Wheezing[b]	1.127 (1.069-1.189)	<.001
Otitis media	1.014 (0.954-1.078)	.65
Pharyngitis	1.015 (0.964-1.069)	.57
Any steroid use		
No	1 [Reference]	
Yes[b]	1.089 (1.023-1.160)	.008
Any antireflux medication use		
No	1 [Reference]	
Yes	1.032 (0.994-1.072)	.10

[a] Results are shown for Cox proportional hazards model incorporating exposure to any antibiotic. In addition to the variables shown, the model included year and practice of entry into the cohort to account for site-specific effects.

[b] Effects with *P* < .05.

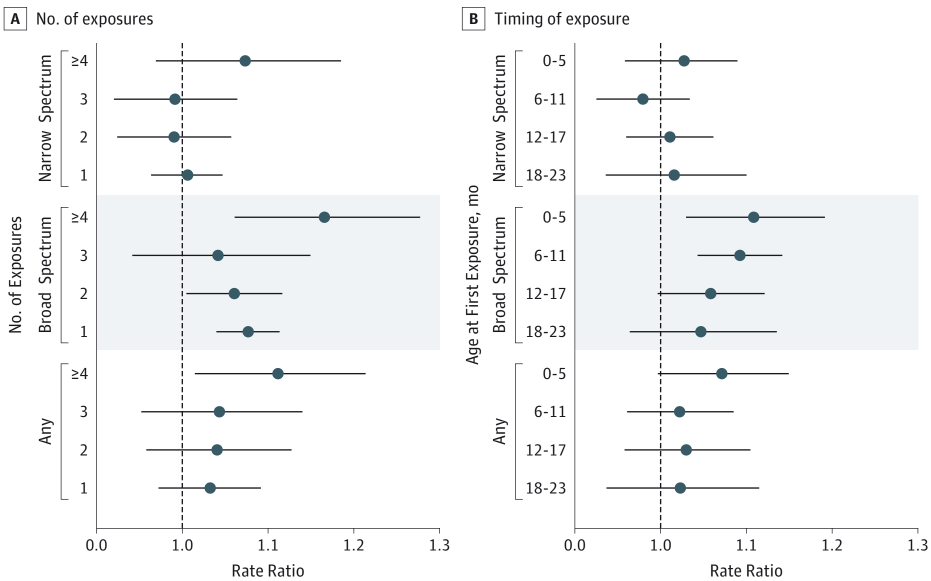
Discussion

Using primary care visit data from the EHR, we performed a longitudinal study evaluating exposure to antibiotics during infancy and the risk for obesity in early childhood for a large cohort of children in the mid-Atlantic region of the United States. In this context, we have shown that repeated use of antibiotics, particularly broader-spectrum drugs, at younger than 24 months old is a risk factor for later obesity. This association persists after accounting for a number of known risk factors including sex, urban primary care practice, insurance type, diagnosis of asthma, and steroid use.

Narrow-spectrum antibiotics, recommended as first-line treatment for common childhood infections,[16-19] are not associated with obesity even after multiple exposures. If validated in other studies, this observation suggests a potentially modifiable risk factor for childhood obesity, given the relatively high use of broad-spectrum drugs, although interventions in this area have proven difficult in practice.[14]

Because the first 24 months of life comprise major shifts in diet, growth, and establishment of the intestinal microbiome, this interval may comprise a window of particular susceptibility to antibiotic effects. We speculate that repeated use of antibiotics may have an impact on intestinal flora that alters long-term energy homeostasis as one factor in a complex mixture of physiologic, environmental, socioeconomic, and medical factors affecting a particular child's risk for obesity. However, this observational study cannot exclude the possibility that our results reflect the impact of

Figure 3. Impact of Antibiotic Class, Frequency, and Timing on the Risk for Obesity



Points indicate rate ratios, with 95% CIs shown by lines, derived from multivariate models examining number of exposures (A) or timing of first antibiotic exposure at 0 to 23 months (B).

underlying medical conditions that require repeated antibiotic treatment or that other covariates not available through our EHR, such as delivery method, are related to the use of antibiotics at later primary care visits.

Although there were differences in data provenance and specific analyses, our results reinforce those reported by Trasande et al.[15] We identified particularly strong associations with use of broad-spectrum antibiotics; small differences in our overall effect sizes may in part reflect different patterns of antibiotic selection in the 2 cohorts. The covariates available for each group's models differ in other ways as well, representing different aspects of a highly complex process. Because our study relies on structured data available in the EHR, we were not able to accurately capture details regarding family structure, activity, or diet. While biologic and behavioral factors may be closely interrelated and contribute to the development of obesity, we are not aware of known direct effects on antibiotic exposure of maternal prepregnancy body weight, infant birth weight, nutritional intake, physical activity, or screen time that would confound our analyses. We expect our data to be less sensitive to parents' recall bias around antibiotic use but subject to poor capture of medications prescribed at out-of-network visits, which we would only detect if recorded at a follow-up primary care visit. Conversely, Trasande et al[15] used birth weight to directly exclude children less than 2500 g from further analysis. Because our primary care records began at first outpatient follow-up visit, we used diagnoses of low birth weight or prematurity as exclusion criteria, which may have reduced our sensitivity to these conditions. Finally, the cohorts studied differed not only in size (11 532 vs 65 480), but also in location (United Kingdom vs United States), epoch (1990s vs 2000s), and sociodemographics (primarily white, "slightly more affluent than the general UK population"[15] vs 50% nonwhite and 41% Medicaid insured). Each of these factors may lead to results more reflective of a particular geographic, social, or clinical context.

With these limitations in mind, both studies suggest that antibiotic exposure during infancy influences the risk for childhood obesity. Additional investigation will be required to address the relationships among these factors. In particular, the ability to study a large cohort of patients where both comprehensive health services and nonmedical data were reliably available would permit simultaneous evaluation of potential confounders that could be directly addressed in only one of our or Trasande and colleagues' analyses. It will also be important to obtain results from a greater variety of clinical and demographic contexts to better distinguish between general and site-specific conclusions. Finally, the strong association with respiratory diagnoses separately from steroid use suggests that further investigation of other factors, including reduced activity, school participation, and controller medication use, is warranted.

In the United States, increasing use of EHRs and the ability to share population-level health information will facilitate this process. In future studies, it will be important to determine not only which factors contribute to the biology of obesity, but which represent modifiable risks that can be addressed through changes in clinical practice or lifestyle. Both characteristics will be important in developing health systems that more effectively reduce the risk for obesity and related comorbidities.

Conclusions

Because obesity is a multifactorial condition, reducing prevalence depends on identifying and managing multiple risk factors whose individual effects may be small but modifiable. Our results suggest that the use of broad-spectrum outpatient antibiotics before age 24 months may be one such factor. This provides additional support for the adoption of treatment guidelines for common pediatric conditions that emphasize limiting antibiotic use to cases where efficacy is well demonstrated and preferring narrow-spectrum drugs in the absence of specific indications for broader coverage.

ARTICLE INFORMATION

Accepted for Publication: June 26, 2014.

Published Online: September 29, 2014. doi:10.1001/jamapediatrics.2014.1539.

Author Contributions: Dr Bailey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bailey, Forrest, Zhang, DeRusso.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bailey, Forrest, DeRusso.
Critical revision of the manuscript for important intellectual content: Zhang, Richards, Livshits, DeRusso.
Statistical analysis: Bailey, Forrest, Zhang.
Obtained funding: Bailey, Forrest.
Administrative, technical, or material support: Bailey, Forrest, Richards, Livshits, DeRusso.
Study supervision: Bailey, Forrest, DeRusso.

Conflict of Interest Disclosures: None reported.

Funding/Support: Funding was provided by an unrestricted donation from the American Beverage Foundation for a Healthy America to the Children's Hospital of Philadelphia to support the Healthy Weight Program.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We are grateful to Brandon Becker, MPH (Department of Pediatrics, Children's Hospital of Philadelphia), for additional statistical support. He did not receive compensation from a funder for his contribution.

REFERENCES

1. Bailey LC, Milov DE, Kelleher K, et al. Multi-institutional sharing of electronic health record data to assess childhood obesity. *PLoS One*. 2013;8(6):e66192.

2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA*. 2012;307(5):483-490.

3. Steinberger J, Daniels SR; American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young); American Heart Association Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). Obesity, insulin resistance, diabetes, and cardiovascular risk in children: an American Heart Association scientific statement from the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). *Circulation*. 2003;107(10):1448-1453.

4. Committee on Obesity Prevention Policies for Young Children. *Early Childhood Obesity Prevention Policies.* Washington, DC: Institute of Medicine; 2011.

5. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444(7122):1027-1031.

6. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005;102(31): 11070-11075.

7. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature*. 2009;457(7228):480-484.

8. Ajslev TA, Andersen CS, Gamborg M, Sørensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *Int J Obes (Lond)*. 2011;35(4):522-529.

9. Vael C, Verhulst SL, Nelen V, Goossens H, Desager KN. Intestinal microflora and body mass index during the first three years of life: an observational study. *Gut Pathog*. 2011;3(1):8.

10. Cox LM, Yamanishi S, Sohn J, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell*. 2014;158(4):705-721.

11. Cho I, Yamanishi S, Cox L, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature*. 2012;488(7413):621-626.

12. Pérez-Cobas AE, Artacho A, Knecht H, et al. Differential effects of antibiotic therapy on the structure and function of human gut microbiota. *PLoS One*. 2013;8(11):e80201.

13. Pérez-Cobas AE, Gosalbes MJ, Friedrichs A, et al. Gut microbiota disturbance during antibiotic therapy: a multi-omic approach. *Gut*. 2013;62(11): 1591-1601.

14. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev*. 2005;(4):CD003539.

15. Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. Infant antibiotic exposures and early-life body mass. *Int J Obes (Lond)*. 2013;37(1):16-23.

16. American Academy of Family Physicians; American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Pediatrics Subcommittee on Otitis Media With Effusion. Otitis media with effusion. *Pediatrics*. 2004;113(5):1412-1429.

17. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. *Pediatrics*. 2004;113(5):1451-1465.

18. Bradley JS, Byington CL, Shah SS, et al; Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53 (7):e25-e76.

19. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):1279-1282.

20. Kuczmarski RJ, Ogden CL, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Statist*. 2002(246):1-190.