Neonatal Ampicillin/Gentamicin Exposure and the Risk of Childhood Obesity in South Bronx Pediatric Population

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Abstract

Objective   This study aimed to assess the association between neonatal antibiotic exposure and the risk of childhood obesity.

Study Design   This retrospective cohort study enrolled neonates born between 2011 and 2015 and followed up until 5 years. The incidence of obesity at 5 years old, and other characteristics were compared between the antibiotic-exposed and unexposed groups. Chi-square test was conducted on categorical variables and Student's t-test for normally distributed continuous variable. Significant variables ($p < 0.05$) in bivariate analysis were modelled in a stepwise multivariate logistic regression analysis to ascertain independent predictors of obesity at 5 years.

Results   Of the 1,447 subjects, 749 (51.8%) received ampicillin and gentamicin, and 333 (23%) were obese. Neonates exposed to antibiotics were more likely to be obese compared with those unexposed (26 vs. 20%, $p = 0.01$). In the adjusted model, this association persisted (adjusted odds ratio: 1.37, $p = 0.02$).

Conclusion   Neonatal antibiotic exposure is associated with early childhood obesity and may play a significant role in the weight trajectories of these children. Hence, antibiotic stewardship in this period cannot be overemphasized.

Keywords
► antibiotics
► neonates
► obesity
► childhood
► gut microbiome

Key Points

- Findings from our study showed that neonatal antibiotic exposure is associated with early childhood obesity.
- The prevalence of childhood obesity at 5 years is high (23%).
- Further exploration of the role of antibiotics on the gut microbiome and its effect on weight trajectories is needed.

Obesity has reached epidemic proportions in the developed world, with one in three children in the United States considered overweight or obese.[1] It is estimated that 8.1% of infants and toddlers and 16.9% between the age of 2 to 19 years have a body mass index (BMI) greater than the 85th percentile,[2] making it one of the greatest public health threats in the country. South Bronx, a socially disadvantaged and medically underserved area in New York City, is known

to have some of the highest burdens of various medical conditions and a much higher prevalence of obesity (47%)[3] among children and adolescents compared with a national rate of 19.7%.[4] Aside from the significant risk of developing cardiometabolic conditions later in life, the increased prevalence of childhood obesity is associated with comorbidities previously considered "adult" diseases, including type 2 diabetes mellitus, hypertension, nonalcoholic fatty liver disease, obstructive sleep apnea, and dyslipidemia.[5]

The development of obesity in children is multifactorial and influenced by diet, physical activity, and socioeconomic factors. Lifestyle modifications, such as balancing calories and increasing physical activity, continue to be first-line strategies for preventing obesity in the pediatric population. However, this strategy has yielded a modest impact. Therefore, it is vital to seek and understand other modifiable risk factors leading to childhood obesity.[6] Research has identified that more intrinsic risk factors, including genetics and gut microbiome, play a role in the development of obesity.[7] Specifically, the human gut microbiome, which comprises more than 100 trillion microbial cells, has a wide-reaching metabolic, nutritional, and immunological effect.[8] It is known to influence overall metabolism through the regulation of energy expenditure, fat storage, and maintaining immune and gut barrier functions.[8] Development of the gut microbiome starts at birth and is influenced primarily by the mode of delivery and feeding practices, among other factors.[9] Studies have shown that microbiome composition is stable starting around 6 months of age. The neonatal period is a critical time point in the development of host and gut microbiome symbiosis, as it is the time of intense development and maturation of the immune system and microbial imprinting.[10] Alterations of the microbiome increase the risk of developing chronic medical conditions such as asthma, inflammatory bowel disease, allergic and inflammatory disorders, and obesity. Association between the gut microbiome composition and the development of these chronic medical conditions has been established in previous research.[11–13]

In animal models, changes in the microbiome brought about by antibiotics resulted in weight gain through direct effects on growth and metabolic pathways associated with fat production, metabolism, and storage.[14,15] Research in humans has produced mixed results, with some studies showing a significant association between early-life antibiotic exposure and increased risk of development of obesity.[7,14,16–20] In contrast, others report either marginal or no risk.[21–23]

However, studies are sparse on neonatal antibiotic exposure and the risk of overweight or obesity in early childhood. Dysbiosis in early infancy could potentially have long-lasting effects on weight trajectory later in childhood.[14] Hence, it is critical to explore the probability of antibiotic-induced dysbiosis within the first month of life, particularly in infants exposed to antibiotics in the neonatal intensive care unit (NICU), as it may provide additional impetus to limit unnecessary antibiotic use.

In this study, we assessed the association between neonatal antibiotic exposure and the risk of childhood obesity with a secondary dose–response assessment and comparison of antibiotic exposure effect between those exposed only in the first 72 hours of life and beyond 72 hours of life.

Materials and Methods

Study Design and Population
This is a retrospective cohort study on children born at BronxCare Health System or extramural deliveries admitted to the NICU/nursery who were exposed to antibiotics (ampicillin, gentamicin, or a cephalosporin) as well as a control group of infants who were unexposed during the birth admission and followed up annually with respect to the weight for length or BMI percentile from the second year of life through the age of 5. We reviewed medical records from 2011 to 2020 and extracted data for exposed and unexposed neonates.

Our study focused on children delivered, or that received care, at BronxCare Health System within the first 28 days of life and followed up in the BronxCare Health System outpatient clinics consistently through the age of 5. We included infants born at 34 to 41 completed weeks of gestation and excluded preterm neonates less than 34 weeks' gestational age, as they received antenatal steroids for fetal lung maturity. Postterm neonates and preterm neonates were excluded because of their possible confounding effect.[24,25] Children with congenital conditions affecting growth (i.e., Prader–Willi), congenital hypothyroidism, cystic fibrosis, and congenital immune deficiencies were also excluded.

Measurements

Measurement of Exposure
The exposure variable, neonatal antibiotic exposure, was extracted from electronic medical records (EMR) from the medication administration section indicating actual administration, including dose and length of antibiotic treatment. Ampicillin, gentamicin, cefotaxime, ceftazidime, antifungal, and antiviral agents were extracted for analysis. However, because ampicillin and gentamicin constituted greater than 98% of antibiotics used in our NICU, they were the primary exposure variables considered. The predominant reason for antibiotic administration was to rule out sepsis in neonates with fever, hypothermia, respiratory distress, and/or maternal chorioamnionitis. The exposure period was between 2011 and 2015, allowing a 5-year follow-up of children until 2020. Similarly, the control group, neonates in the NICU or nursery admitted at the same time and did not receive antibiotics, were extracted from the EMR, and followed up for the same duration. The total number of live births delivered in our hospital including extramural deliveries is 2,388 out of which 1,447 met our inclusion criteria. Preterm neonates (<34 weeks) and postterm neonates accounted for 399 of the excluded data and 542 did not have 5-year follow-up data.

Covariates
Our covariates included variables shown in previous literature to be significantly associated with childhood obesity or

based on biological plausibility. These included maternal age at delivery, ethnicity, pregravid maternal weight, mode of delivery, intrapartum prophylaxis against group B streptococcal disease (GBS), birth weight, neonatal gender, type of feeding (breastfeeding, formula, or both), and mother and child comorbidities. For the early feeding practices, we reviewed charts at health care maintenance visits at 0 to 2, 3 to 4, and 6 months of age to check if the infants were exclusively breastfed, formula fed, or both. For the intrapartum antibiotic prophylaxis (IAP) against GBS, adequate IAP was defined as administration of penicillin >4 hours before delivery and inadequate refers to antibiotics other than penicillin or penicillin administration for <4 hours before delivery. These variables were extracted by carefully reviewing the maternal and child records in the EMR database.

Measurement of Outcome

Ambulatory clinics visit records were reviewed for the identified exposed and unexposed cohorts. The documented CDC BMI percentile at the 5-year-old health care maintenance visit was used in the analysis. We also included those that missed the 5-year-old visit but were seen for acute ambulatory care or in the emergency department 5 months before or after their fifth birthday. Overweight was defined as BMI percentile at 85th to less than the 95th percentile for age and sex, and obesity was defined as BMI at or greater than the 95th percentile for age and sex. Some studies reviewed operationalized outcomes of relative body mass using BMI-for-age z-score,[16] weight-for-length z-score,[21] or weight-for-age z-score and categorized these outcomes based on set references. In this study, we used dichotomized BMI percentile (BMI percentile $\geq$ 95th percentile or BMI percentile < 95th percentile) at 5 years as the primary outcome variable.[26–28]

Statistical Analysis

Our sample consisted of 1,447 neonates admitted to the NICU or nursery and followed up in our outpatient clinics for at least 5 years. The maternal–child demographics, anthropometric measures, and other clinical characteristics were summarized using descriptive statistics. Categorical variables were presented in frequencies and percentages, and continuous variables were presented as mean (standard deviation). The normality of the variables was tested using the Kolmogorov–Smirnov test. A bivariate analysis was done to examine if the risk of the outcome variable (childhood obesity) significantly differs between the two cohorts based on different predictor variables. Chi-square statistics analyzed the categorical variables, and the continuous variables were analyzed by Student's t-test since they are normally distributed. Statistical significance was set at a $p < 0.05$. All the statistically significant variables in the bivariate analysis were modeled in a stepwise multivariate logistic regression analysis to determine whether neonatal ampicillin–gentamicin exposure is an independent predictor of early childhood obesity. In our analysis, we used the stepwise selection method, a flexible method that can be directly applied to mixed continuous and categorical predictors and allows the

selection of significant variables at a $p < 0.05$. The stepwise selection method is very attractive because of its tractability and gives a good sequence of models that helped us identify predictive factors associated with early childhood obesity. A receiver operator characteristic (ROC) curve was plotted for the final models predicting our outcome variable. The goodness of fit of the multivariate logistic model using the Hosmer–Lemeshow test, Cox and Snell R-square, and max rescaled R-square were also evaluated. The multicollinearity of variables was checked to identify and adjust for colinear independent variables in the regression model. We also did an ad hoc analysis, where we stratified neonates that were exposed to antibiotics into two groups; exposure less than or equal to 72 hours and greater than 72 hours and we did a bivariate analysis to determine whether there is an association with childhood obesity based on the duration of exposure. We chose 72 hours because, during the time frame when our exposure cohorts were extracted, 2011 to 2015, we administered prophylactic antibiotic treatment for 72 hours pending blood culture results for neonates with suspected neonatal sepsis, unlike 48 hours of treatment with negative blood culture result that we currently practice. Statistical analysis was conducted using SAS version 9.4 software (Cary, NC), with statistical significance set at $p < 0.05$.

Results

Characteristics of Study Participants

A total of 1,447 neonates were examined. A total of 749 (51.8%) were exposed to ampicillin–gentamicin, and 698 (48.2%) were not exposed to antibiotics. Of the total subjects, 333 (23%) were obese, and 1,114 (77%) were not obese at 5 years of age. Other chronic inflammatory conditions like childhood asthma and atopic diseases constituted 12%. Demographic characteristics were similarly distributed based on maternal age, gestational age, and gender. A total of 54% of mothers were of Hispanic origin. Vaginal delivery was the prevalent route of delivery (61.3%). Only 7.4% were exclusively breastfed for at least 4 months, and most of the early feeding practice was formula (49.2%) and mixed (43.5%). Of the 350 (25%) mothers who required GBS IAP, 244 (69.7%) received adequate IAP. Approximately 9, 8, and 33% of the mothers had diabetes mellitus, hypertension, and obesity, respectively (►Table 1).

Factors Associated with Childhood Obesity at 5 Years
►Table 2 shows the baseline demographics and other clinical characteristics associated with childhood obesity at 5 years based on ampicillin–gentamicin exposure status. Compared with the children without antibiotic exposure, those exposed had a higher incidence of obesity (25.8 vs. 20.1%, $p < 0.01$). Infants that were formula-fed or got mixed feeding had a higher incidence of obesity (22.8 and 25.9%, respectively) compared with breastfed infants (15.4%, $p < 0.05$). Compared with no atopy, those with childhood atopic disease were more likely to be obese (32.2 vs. 20.5%, $p < 0.01$). The incidence of obesity was higher among children exposed to maternal pregestational and gestational diabetes compared

Table 1 Baseline and maternal–child characteristics by obesity status

Characteristics	All, N (%)	Obese		p-Value
		Yes, n = 333	No, n = 1,114	
Gender				0.48
Male	732 (50.7)	163 (22.3)	569 (77.7)	
Female	713 (49.3)	170 (233.8)	543 (76.2)	
Maternal race				<0.01[a]
Black/African	562 (38.9)	76 (13.5)	486 (86.5)	
Hispanics	782 (54.1)	226 (28.9)	556 (71.1)	
Others	101 (7.0)	31 (30.7)	70 (69.3)	
Maternal age (y)	1,445	28.56 (6.61)	28.32 (6.68)	0.56
Birth weight (g), mean (± SD)	1,437	3,318.22 (688.9)	3,132.93 (619.0)	<0.01[a]
Length of stay (d), mean (± SD)	1,447	5.80 (6.6)	5.93 (7.55)	0.77
Delivery route				0.12
C-section	553 (38.8)	140 (25.3)	413 (74.7)	
Vaginal	874 (61.3)	190 (21.7)	684 (78.3)	
Ampicillin–gentamicin				0.01[a]
Yes	749 (51.8)	193 (25.8)	556 (74.2)	
No	698 (48.2)	140 (20.1)	558 (79.9)	
Ampicillin count[b]		7.81 (3.87)	8.21 (4.11)	0.23
Gentamicin count[b]		3.60 (1.88)	3.85 (1.92)	0.12
Early feeding				0.05[a]
Breastfed	104 (7.4)	16 (15.4)	88 (84.6)	
Formula	690 (49.2)	157 (22.8)	533 (77.2)	
Mixed	610 (43.5)	158 (25.9)	452 (74.1)	
Intrapartum GBS prophylaxis				0.38
Adequate	244 (17.1)	65 (26.6)	179 (73.4)	
inadequate	106 (7.4)	23 (31.7)	83 (78.3)	
None	1,076 (75.5)	244 (22.7)	832 (77.3)	
Childhood asthma				0.39
Yes	185 (12.8)	38 (20.5)	147 (79.5)	
No	1,261 (87.2)	295 (23.4)	966 (76.6)	
Child atopic disease				<0.01[a]
Yes	307 (21.2)	99 (32.2)	208 (67.8)	
No	1,139 (78.8)	234 (20.5)	905 (79.5)	
Maternal diabetes				<0.01[a]
Pregestational	28 (1.9)	10 (35.7)	18 (64.3)	
Gestational	106 (7.3)	40 (37.7)	66 (62.3)	
None	1313 (90.7)	283 (21.6)	1,030 (78.4)	
Maternal hypertension				0.05[a]
Chronic hypertension	63 (4.4)	14 (22.2)	49 (77.8)	
Gestational hypertension	48 (3.3)	18 (37.5)	30 (62.5)	
None	1,336 (92.3)	301 (22.5)	1,035 (77.5)	
Maternal asthma				0.83
Yes	41 (2.8)	10 (24.4)	31 (75.6)	
No	1,406 (97.2)	323 (23.0)	1,083 (77.0)	

(Continued)

Table 1 (*Continued*)

Characteristics	All, *N* (%)	Obese Yes, *n* = 333	No, *n* = 1,114	*p*-Value
Maternal obesity				<0.01[a]
Yes	473 (32.7)	138 (29.2)	335 (70.8)	
No	974 (67.3)	195 (20.0)	779 (80.0)	
Maternal BMI, kg/m² mean (± SD)	1,447	29.85 (6.46)	28.25 (6.36)	<0.01[a]

Abbreviations: BMI, body mass index; GBS, group B streptococcal disease; SD, standard deviation.
Notes: Descriptive and bivariate analysis. Comparing baseline characteristics and other clinical factors of mother–child dyad based on child obesity status at 5 years. Results for categorical data are presented as percentage and frequency. Pearson's chi-square is used to compare differences between demographic and clinical characteristics among the children based on their obesity status, and the result of normally distributed continuous variable are presented as mean ± SD. Student's *t*-test was used to compare differences between clinical characteristics among the children based on their obesity status. Clinical diagnoses mentioned are based on entries in the medical record and not on any prespecified diagnostic criteria.
[a]Statistical significance (*p* < 0.05).
[b]The ampicillin/gentamicin counts refers the number of times ampicillin at 50 mg/kg/dose and gentamicin at 4 mg/kg/dose was given.

with no diabetes (35.7 and 37.7 vs. 21.6%, *p* < 0.01). Also, children exposed to maternal gestational hypertension had a higher incidence of obesity (37.5%) compared with chronic hypertension or no hypertension (22.2 and 22.5%, respectively, *p* = 0.05). Compared with vaginal delivery, more infants delivered via cesarean section were obese at 5 years (25.3 vs. 21.7%), but the difference was not statistically significant. The maternal age, neonatal length of hospital stay, gestational age, ampicillin, and gentamicin dose, GBS IAP, and maternal and childhood asthma were not statistically different among the children with and without obesity (►Table 1).

►Table 3 shows factors independently associated with childhood obesity at 5 years. Following a stepwise multivariable logistic regression analysis, ampicillin and gentamicin exposure remains an independent predictor of childhood obesity, with a 37% increase in the risk of obesity among the exposed compared with the unexposed group (adjusted odds ratio: 1.37, 95% confidence interval: 1.055–1.775).

We further stratified the antibiotic-exposed group by the duration of exposure, less than or equal to 72 versus greater than 72 hours. Obesity among the ampicillin and gentamicin exposed group was 26.7 versus 23.1% for exposure less than or equal to 72 hours and greater than 72 hours, respectively. However, this difference was not statistically significant (►Table 2).

Discussion

In our retrospective study of a large cohort of children born in a community with a high prevalence of obesity, we found that those exposed to antibiotics during the birth admission were more likely to be obese at 5 years of age compared with those who were not exposed. To our knowledge, this is the first study to report an association between neonatal exposure to penicillin-based and aminoglycoside antibiotics and obesity in early childhood. Our study is consistent with some studies, which showed a similar association between antibiotic exposure in early childhood and an increased risk of obesity.[6,13,15,19,22,25] Scott et al found a similar association to our study, reporting that antibiotic exposure before the age of 2 years increased the odds of childhood obesity at 4 years by 21%, consistent with our study, where antibiotic exposed neonate showed a 37% increase in the risk of obesity at 5 years. An earlier study found the obesity rate among children and adolescents (3–21 years) to be about 47% in the South Bronx.[3] However, our study presents the prevalence of obesity at age 5, which may explain the relatively lower rate (23%).

A few studies have shown a negative association between early antibiotic exposure and childhood obesity.[20–22,26–28] The differing methodologies and exposure time to outcome evaluation used in these studies could explain the inconsistent findings. For example, Rogawski et al and Gerber et al extracted their antibiotic exposure variable from the prescription database,[21] caregiver verbal report, and prescription data (20) with no means of verification, which could lead to misclassification bias. We have minimized this bias by utilizing data that was extracted directly from the EMR, including the record of actual administration of antibiotics with standardized weight-based dosing and duration of treatment. Pyle et al and Kamphorst et al reported decreased weight gain with neonatal antibiotic exposure. It is

Table 2 Obesity at 5 years based on the duration of antibiotic exposure

		Obese Yes	No	*p*-Value
Ampicillin–gentamicin use duration (*n* = 749)	≤ 72 h	200 (26.7)	549 (73.3)	0.31
	> 72 h	173 (23.2)	576 (76.8)	

Note: Ampicillin–gentamicin exposure stratified into ≤ 72 and > 72 hours and obesity status at 5 years.

Table 3 Factors independently associated with childhood obesity

Variable	Adjusted odds ratio (aOR)	95% Confidence interval		p-Value
		Lower	Upper	
Ampicillin–gentamicin	1.368	1.055	1.775	0.02[a]
Maternal obesity	1.664	1.274	2.174	<0.01[a]
Child atopy	1.744	1.302	2.336	<0.01[a]
Maternal diabetes				<0.01[a]
None	Reference			
Gestational	2.295	1.474	3.573	<0.01[a]
Pregestational	2.037	0.867	4.788	0.10
Maternal race				<0.01[a]
Hispanics	Reference			
Black/African	0.357	0.265	0.480	<0.01[a]
Others	1.131	0.712	1.797	0.60

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio.
Notes: Factors associated with childhood obesity at 5 years. Adjusted OR were presented. Adjusted OR < 1 denotes factors that are associated with a lesser risk of childhood obesity while OR > 1 denotes factors that are associated with a higher risk of childhood obesity. Hosmer–Lemeshow test ($p = 0.7431$), indicates that our models fit the data. Max-rescaled R-square ($R^2 = 0.1073$) was used to assess how well our model explains the variability in the ambulatory outcome.
[a]Statistical significance ($p < 0.05$) with a 95% confidence interval that excludes null value of 1.

important to highlight the differences in the population characteristics, wherein preterm (<32 weeks) and very low birth weight infants were included[29] and exposure time to outcome evaluation was 12 months.[30] We believe the differences in population characteristics and exposure time to outcome evaluation resulted in the differing findings. Li et al also suggested that the differences among studies may result from a lack of differentiation between exposure to maternal infection (especially GBS) versus antibiotic administration, for which superior study designs or a propensity score analysis may be required to further explore the association.[31]

Increased exposure to antibiotics through longer or multiple courses is thought to lead to more pronounced alterations in the gut microbiome and potentially more effects on the metabolic pathways. Previous studies[7,19] have demonstrated a dose-dependent association between antibiotic use and childhood obesity when utilizing data with multiple antibiotic exposures over a prolonged time throughout childhood. However, we did not find a significant difference between the incidence of obesity between infants exposed for less than or equal to 72 versus greater than 72 hours, suggesting that mere exposure, regardless of duration and dose, is impactful in the neonatal period. However, the effect we found in our study may also be limited to the timing of antibiotic exposure in our cohort, as animal models suggest that earlier exposure may lead to more significant alterations.[32] The risk of developing obesity with antibiotic exposure in the first month of life emphasizes that the neonatal microbiome is a dynamic environment that is extremely inducible by external factors like antibiotics.[21–23]

This emphasis on exposure timing is fundamental. For instance, some studies[16,17] found a positive association in children exposed to antibiotics before 6 months. Scott et al found increasing risk of obesity as the timing of exposure shortens from 2 to 1 year to <6 months.[7] Others, like Block et al, reported a marginal association between antibiotic exposure in infants exposed under 24 months of age and being overweight or obese at 5 years of age.[14] It is important to highlight that in the population we studied, antibiotics were administered in the first few days, if not first hours, of life. By focusing solely on the neonatal period, we were able to explore the effects of antibiotic exposure on the formative period of gut microbiome development and confirm that alterations at this time may have been impactful on the future weight trajectories of the children included in the study. Hence, neonatal antibiotic exposure is a modifiable risk factor for obesity in our population, and cautious use of antibiotics at this time may have critical importance in preventing childhood obesity.

In our study, the association between antibiotic exposure and childhood obesity remained significant after controlling for covariates, some of which include maternal comorbidities and feeding practices. We found that maternal obesity and gestational diabetes were significantly associated with childhood obesity at 5 years. This association is intuitive as maternal genetic or environmental predispositions that led to maternal comorbidities can easily influence weight trajectories in their offspring.[33] Additionally, in our study, the unadjusted analysis showed an association between feeding practices and childhood obesity; the variable was removed in the stepwise multivariate analysis model due to nonsignificance at 0.05 significance level. This finding is inconsistent with previous studies, which suggested that breastfeeding is an important early contributor to gut microbiota.[20,21] These studies surmised that antibiotic exposure might attenuate

the beneficial effect of breastfeeding. However, since only 7.4% of our study population were exclusively breastfed, that conclusion is difficult to ascertain from our study population.

The initial development and maturation of the neonatal microbiome is closely related to the maternal microbiome, which is influenced by diet, infection, antibiotic use, and a host of other factors. During the perinatal period, there is transfer of the maternal microbiota, especially from vaginal fluid and gastrointestinal tract to the neonate's gut during vaginal delivery, forming the core of the neonatal gut microbiome. Skin bacteria colonize infants born via cesarean section.[34] Delivery route was not significantly related to child obesity status in our bivariate analysis and was not included in our final model. The noninclusion of the delivery route as a confounder in our model is a potential limitation.

Strengths and Limitations

Strengths of this study include large sample size and the retrospective cohort design, which provides a means of estimating risk, as opposed to a cross-sectional or case–control design that suggests only association. Additionally, the direct extraction of our primary independent variable (ampicillin/gentamycin exposure) from the administered medication section of the EMR reduced misclassification bias, added to the exposure classification's validity, and improved our ability to detect a true effect. We also included multiple covariates (including variables previously established as risk factors or based on biological plausibility) in our analysis. This helped us to account for their possible effect on our outcome variable, obesity at 5 years.

Some potential limitations of this study include a single-center analysis and the study design, which only suggested association but was not equipped to validate causation. Hence, prospective studies will be needed to establish the potential risk of neonatal antibiotic exposure in the development of early childhood obesity. The lack of exploration of additional antibiotic use after the birth admission and the failure to evaluate the possible effect of such exposure on the outcome variable is another potential limitation. In addition, selection bias, which is inherent in retrospective studies, may have influenced our result. Therefore, we tried to strengthen our design by adopting a retrospective cohort design, which provides a higher level of evidence for the association between early antibiotic exposure and obesity compared with the case–control approach employed by Azad et al,[35] which was lacking in the precision of the effect size (wide confidence interval), albeit statistically significant. Although we adjusted for many potentially confounding variables, variables such as GBS IAP and race or ethnicity had poor documentation, which may have impacted our findings.

Conclusion

Neonatal antibiotic exposure (specifically ampicillin–gentamicin) was associated with early childhood obesity at 5 years.

However, we did not find a significant impact from the duration of antibiotic exposure. Our findings lend credence to previous studies on the effect of antibiotics on weight gain. Given the high rate of neonatal antibiotic exposure in our cohort, cautious use of antibiotics in this critical period cannot be overemphasized, especially among the vulnerable population in the South Bronx. This will be an area of intervention that might have long-term implications for this population. Finally, with the high incidence of obesity among our cohort compared with the national average, augmenting current efforts at controlling and preventing traditional obesity risk factors with cautious antibiotic use may reduce the prevalence of childhood obesity and the attendant cardiovascular comorbidities.

Ethics Approval and Patient Consent
This retrospective cohort study was approved by the BronxCare Health System Institutional Review Board (approval number: 01142111).

Authors' Contributions
A.A. conceptualization, data management, and statistical analysis, manuscript writing, and editing. A.P.T. conceptualization, data extraction, manuscript writing, and editing. M.A.A.G. conceptualization, data extraction, and manuscript editing. N.M. conceptualization, data extraction, and manuscript editing. T.O. data extraction and manuscript editing, S.D. data extraction and manuscript editing. M.A. manuscript writing and editing. O.P. manuscript writing and editing. A.P. conceptualization, supervision of project, manuscript editing.

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