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Early Antibiotic Exposure and Risk of Childhood Obesity in Latinos

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Abstract

We investigated the relationship between early antibiotic exposure before 6 months age and risk for obesity at 2 years in a high-risk, low-income, urban Latino cohort ($n=97$), with the hypothesis that antibiotic exposure would increase risk for obesity by 2 years. Data were collected through maternal report of infant 24-hour dietary intake at 4–6 weeks, 6 months, 1, and 2 years; and food frequency questionnaires at 4–6 weeks, 6 months, 1, and 2 years. Antibiotic use data, including type and frequency, were collected through maternal self-report at 6 months and 1 year. Cord blood levels of leptin and insulin were measured at birth. Chi-squared tests were used to assess the relationship between obesity and dichotomous predictors and Student's *t*-tests for continuous predictors. Multivariable logistic models were used to ascertain independent predictors of obesity at age 2. We found that early antibiotic exposure before 6 months was independently associated with increased risk for rapid infant weight gain [odds ratio (OR) 6.42, 95% confidence interval (CI, defined as the range in which sample will fall with 95% confidence: 1.17–35.06)] and obesity at age 2 [OR 6.15, 95% CI (1.03–36.70)]. These findings provide evidence promoting antibiotic stewardship in pediatric practices to minimize exposure in the first 6 months of life.

Keywords: infancy; pediatric; rapid infant weight gain

Introduction

Obesity has become a major public health concern. In 2011–2014, 17.0% of all American children were obese, with 21.9% prevalence in Latino children populations compared with 14.7% in non-Latino whites, 19.5% in non-Latino blacks, and 8.6% in non-Latino Asians.[1]

Recent studies suggest that antibiotic exposure before 12 months of age increases risk for obesity due to disruption of gut microbiota before it is completely established.[2] Multiple exposures to antibiotics within the first 2 years of life may have the most profound effect increasing BMI z-score,[3] specifically with three or more courses before age 2,[4] although not all studies have found increased risk with multiple exposures.[5] Other factors, including breastfeeding and mother's prepregnancy BMI, may modulate the impact on antibiotic exposure on child's weight gain due to inherited maternal microbial diversity.[6] However, the protective factor of breastfeeding may be diminished if the infant has exposure to antibiotics in the first months of life.[7]

Early feeding patterns can play a pivotal role in children's metabolome (the complete set of small-molecule metabolites from cellular processes), growth rates, body composition, and microbial colonization.[8] Breastfeeding allows hormone and bacterial exchange from mother to baby and thus provides antimicrobial, anti-inflammatory, and immunomodulatory agents, which help the infant's immune system establishment and function, improve overall health, and may lead to less antibiotic exposure and thus lower risk for obesity.[9]

No prior study has determined the impact of antibiotic exposure in high-risk, low-income, urban Latino infants and toddlers. We tested the hypothesis that antibiotic exposure in the first year of life leads to development of obesity by 2 years of age.

Methods

A cohort of 97 pregnant, self-identified Latina women were recruited before delivery at the prenatal clinics at San Francisco General Hospital (SFGH) in 2012 and 2013, as previously described.[10] The definition of Latina was self-defined based on maternal self-report and commonly included countries of origin, including Mexico, and those of Central and South America. Dietary intakes were collected by 24-hour dietary recall beginning at 6 months of age and 48-hour recall at 1 and 2 years of age. Food frequency questionnaires were used to gather information on introduction of solids,

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duration of breastfeeding, and frequency and volume of consumption of foods and beverages at 4–6 weeks, 6, 12, and 24 months of age.[11] Birth mode (cesarean section vs. vaginal) was noted from the medical record. Anthropometrics were assessed using standard digital scales for weight, stadiometer, and measuring boards for recumbent length and height. Data of type and frequency of antibiotics were collected through maternal self-report at 6 and 12 months of age. We did not have access to medical records to confirm or gain any additional prescription details. Cord blood was tested for adipocyte and gut hormones as previously described.[10] Written consent was provided by all mothers. The study was approved by the Committee on Human Research (CHR) at the University of California, San Francisco, CA.

Primary Predictors

Child. Obesity was defined as greater than or equal to 95th percentile BMI according to US CDC age and sex-standardized growth charts.[12] Antibiotic use was categorized as any use between 0 and less than 6, 6 and 12, and 0 and 12 months of age, including the duration of antibiotic course, number of courses (0, 1, >1), and specific antibiotic prescribed. A second set of predictors included child dietary intake, including any breastfeeding at 4–6 weeks, 6 months, and 1 year; exclusive breastfeeding at 4–6 weeks and 6 months; any 100% fruit juice at 4–6 weeks, 6 months, 1, and 2 years; any flavored milk at 1 and 2 years; and any sugar-sweetened beverage consumption (sugar-sweetened beverages [SSB] defined as colas, sodas, Koolaid, or Hi-C) at 6 months, 1, and 2 years. Beverage intake was also categorized as consistent 100% fruit juice consumption from 4 to 6 weeks until 2 years, high 100% fruit juice consumption at 2 years (≥highest quartile), high SSB consumption at 2 years (≥highest quartile), and high flavored milk consumption at 2 years (≥highest quartile). Other predictors included infant sex, Apgar scores at 1 and 5 minutes, infant gestational age, rapid infant weight gain defined as a change in weight for age z score between birth and 6 months ≥0.67,[13] child cord blood hormone levels, and multivitamin use at 2 years.

Maternal. Maternal predictors included advanced age (≥35 years old), ethnicity (Central/South American vs. Mexican), gestational diabetes mellitus, overweight (BMI 25–<30[10]), obese (BMI ≥30[14]), depressive symptoms as previously defined,[10] use of depression medications, education level, excessive pregnancy weight gain,[15] maternal smoking at 6 months and/or 1 year, home language (English versus Spanish), household income, and home ownership. Other predictors include maternal age and pre-pregnancy BMI, analyzed continuously.

Statistical Analysis

Our primary outcome of interest was child obesity at 2 years of age. The primary predictor of interest was antibiotic exposure from 0 to 6 months of age. Chi-squared tests were used to assess the relationship between obesity at 2 years and dichotomous predictors. Student's *t*-tests were applied to assess the relationship between obesity and continuous predictors.

Multivariable linear regression was used to explore independent predictors of obesity at 2 years. Variables with a statistical significance of $p < 0.05$ in bivariate analysis or that had potential biological plausibility, including maternal prepregnancy BMI[16] and breastfeeding at 6 months,[9] or those which previous studies have found significant, including infant sex,[5] were analyzed in a multivariable logistic regression model.

Results

Of the 97 participants, 46% was males, mean gestational age was 39.17 ± 1.27 weeks, mean birth weight was 3386.43 ± 473.32 grams, 50% reported Mexican origin, and 50% reported Central/South American.[10] Twenty-three percent were born by cesarean section and 76% were born by vaginal delivery, with 1% unknown.

Obesity and Antibiotic Exposure

Obesity was present in 7.2% of newborns, 13.4% at 6 months, 16.5% at 1 year, and 11.8% at 2 years. By 6 months of age, 18.4% (16/87) of children followed had been exposed to one course of antibiotics (most commonly amoxicillin, amoxicillin plus clavulanic acid, or erythromycin). Between 6 and 12 months of age, 31.4% were exposed to antibiotics, with 26.7%, 3.5%, and 1.2% having one, two, and three courses, respectively. Overall, from 0 to 12 months of age, 40.0% (34/85) were exposed to any antibiotics, with 26.0%, 7.8%, and 2.6% having one, two, and three courses, respectively. A small percentage of children (6.8%) were exposed to antibiotics at both 0–6 and >6–12 time frames.

Exposure to antibiotics in the first 6 months was greater among obese 2-year-olds (40.0%) compared with nonobese (13.0%; $p = 0.03$) (Table 1). Additionally, 30.0% of participants, obese at 2 years, had exposure at both time intervals (0–6) and (>6–12) months compared with 3.0% in nonobese ($p < 0.01$) (Table 1). Obese 2-year-olds also tended to have more antibiotic exposures with 22.2%, and 33.3% exposed to 1, and >1 courses of antibiotics compared with 27.2%, and 7.7% in nonobese ($p = 0.07$) (Table 1).

Leptin and insulin levels were higher at birth in children who were later obese at 2 years compared with nonobese. Rapid infant weight gain was associated with obesity at 2 years ($p < 0.01$) (Table 1).

Infant and Toddler Feeding

Breastfeeding was started in 95%; however, exclusive breastfeeding was maintained in only 33% at 4–6 weeks and 6% at 6 months. At 4–6 weeks, 25% were consuming non-milk replacement liquids or solids, most commonly sugar water and teas. While only 1% began consuming 100% fruit juice at 4–6 weeks, by 6 months, 27% consumed 100% fruit

Table 1. Child Characteristics and Risk for Obesity at 2 Years of Age (*N* = 97)

Variable	Mean ± SD or percentage (N/T)		*p*
	Obese	Nonobese	
Antibiotic use			
0–6 months	40.0 (4/10)	12.9 (9/70)	0.03
>6–12 months	50.0 (5/10)	29.6 (21/71)	0.20
Exposure to any antibiotics 0–12 months	50.0 (5/10)	38.2 (26/68)	0.48
Courses 0–12 months			0.07
0	44.4 (4/9)	64.6 (42/65)	
1	22.2 (2/9)	27.7 (18/65)	
>1	33.3 (3/9)	7.7 (5/65)	
Hormones			
Leptin	38354.1 ± 32063.5 (6)	21421.0 ± 16924.5 (52)	0.04
Insulin	1350.7 ± 482 (6)	858.7 ± 460.5 (54)	0.02
Growth			
Rapid infant weight gain	70.0 (7/10)	26.7 (20/75)	<0.01
Infant sex			0.75
Male	40.0 (4/10)	45.3 (34/75)	
Female	60.0 (6/10)	54.7 (41/75)	
Birth characteristics			
Apgar score ≥9 at 1 minute of life	30.0 (3/10)	29.7 (22/74)	0.99
Apgar score ≥9 at 5 minutes of life	80.0 (8/10)	82.4 (61/74)	0.85
Delivery type			0.54
Vaginal	66.7 (6/9)	76.0 (67/75)	
Cesarean section	33.3 (3/9)	24.0 (18/75)	
Breastfeeding			
Exclusive breastfeeding at 4–6 weeks	40.0 (4/10)	36.0 (27/75)	0.81
Any breastfeeding at 4–6 weeks	100.0 (10/10)	93.3 (70/75)	0.40
Any breastfeeding at 6 months	70.0 (7/10)	69.0 (49/71)	0.95
Any breastfeeding at 1 year	60.0 (6/10)	62.0 (44/71)	0.90
Beverage and solid consumption			
4–6 weeks			
Consuming foods or nonmilk liquids	20.0 (2/10)	24.0 (18/75)	0.78
6 months			
Any juice	40.0 (4/10)	27.1 (19/70)	0.40
Solid food	90.0 (9/10)	94.4 (67/71)	0.59
1 year			
Any juice	80.0 (8/10)	76.1 (54/71)	0.78
2 year			
Juice ≥4 × /week	50.0 (5/10)	34.8 (24/69)	0.35
Juice consumption at all time points 6 months–2 years	40.0 (4/10)	20.3 (14/69)	0.16
Multivitamins	60.0 (6/10)	34.3 (24/70)	0.12

This shows the main variables of interest and the correlation with obese and nonobese participants at 2 years in our cohort.
N/T, number out of total; SD, standard deviation.

Table 2. Multivariate Predictors of Obesity at 2 years (*N* = 74)

Variable	Odds ratio	95% Confidence interval	*p*
Antibiotic exposure 0–6 months	6.15	1.03–36.70	0.046
Maternal BMI	0.90	0.71–1.13	0.37
Birth weight for length Z score	1.50	0.74–3.06	0.26
Breastfeeding at 6 months	0.95	0.16–5.45	0.95
Rapid infant weight gain	6.42	1.17–35.06	0.03
Infant sex	1.23	0.25–5.97	0.80

This shows the statistically significant variables impacting obesity at 2 years for antibiotic exposure between 0 and 6 months ($p = 0.046$) and rapid infant weight gain ($p = 0.03$).

juice; by 1 and 2 years, this percentage increased to 77.0%, and 96.3%, respectively. SSBs were being consumed by 1% at 6 months, 24% at 1 year, and 62% at 2 years. Flavored milk consumption increased from 13% at 1 year to 31% at 2 years.

Obesity at 2 years did not correlate with infant sex ($p = 0.75$) or delivery type ($p = 0.54$) (Table 1), feeding variables, and dietary intake, including 100% fruit juice or SSB consumption, maternal age, pre-pregnancy maternal BMI, or exposure to maternal smoking at 6 months or 1 year (results not shown). For those who lost contact at 2 years ($n = 17$), the only significant difference compared with those who were maintained in the cohort was the presence of depressive symptoms in the mother at intake, with higher levels of depression in those who were maintained in the study ($p = 0.03$). We found no differences in maternal age, education level, country of origin (Central/South America vs. Mexico), household income, specific dietary intake factors, or antibiotic exposure in those lost to follow-up and those maintained in the study.

Multivariate Predictors of Obesity at 2 Years

Early antibiotic exposure during the first 6 months independently predicted obesity at 2 years, adjusting for maternal BMI, weight for length Z score at birth, any breastfeeding at 6 months, rapid infant weight gain, and infant sex [odds ratio (OR) = 6.15, 95% confidence interval (CI: 1.03–36.70)]. Rapid infant weight gain was also independently associated with obesity at 2 years of age [OR = 6.42, 95% CI (1.17–35.06)] (Table 2).

Discussion

Our study of urban Latino infants reveals increased risk for obesity at 2 years with antibiotic exposure within the first 6 months. This is the first study to report the association between early antibiotic exposure and risk for obesity in this population. Our results do not support an association between later antibiotic exposure or number of courses from 6 to 12 months and risk for obesity at 2 years, but these associations require further study. Our findings concur with prior studies showing greatest risk from early exposure[3] as gut microbiota is particularly sensitive during the formative time frame before homeostasis and the immune system become well established.[2]

Antibiotic prescription rates in our study (18.4% by 6 months of age) are within the range of prior studies from the United States, but toward the lower end of the spectrum of international studies. A large study from Philadelphia found that antibiotics were prescribed to 14% of children under 6 months ($n = 65{,}480$).[17] Studies in other countries, including Canada and Denmark, found that 7%–34% of children had antibiotic exposure within the first 6 months.[5,6] While previous studies have investigated this relationship in infants,[19] ours is the first study to evaluate antibiotic usage in a prospective infant/toddler Latino cohort.

Rapid infant weight gain is independently associated with obesity at 2 years in our population. We and others have previously reported that rapid infant weight gain is predictive of future obesity and thus is a potential target for prevention.[5,16,18,21] This risk factor may have a larger effect in Latino children compared with other populations.[21]

In contrast with other studies,[22,23] neither SSB intake nor breastfeeding in our cohort was related to obesity at age 2. Possibly, our population was too young and beverage patterns change during the preschool years. However, compared with 2-year-old US children, our study reveals slightly higher flavored milk (30% vs. 14%) and much higher SSB (62% vs. 29%) intake.[24]

Limitations of the study included data on type of early antibiotic exposure. We were unable to analyze the effects of the microbial spectrum of the prescribed antibiotics as we relied on self-reported data, and we only evaluated risk for any antibiotic exposure and obesity in Latino children. Future studies should analyze the relationship between specific antibiotics and time of exposure and associated risk for obesity. Another limitation was the potential recall bias from maternal self-report of child's antibiotic use.

Conclusions

Our study investigated the relationship between antibiotic exposure in the first 12 months of life and risk for obesity at 2 years. Our results showed a statistically significant increased risk for obesity at 2 years of age in our cohort with antibiotic exposure in the first 6 months of life, and rapid infant weight gain.

Pediatric antibiotic-prescribing patterns have been scrutinized for improvement with some success in reducing dispensing rates, but continued efforts are needed to decrease use of antibiotics, particularly broad-spectrum agents.[25] Our findings support recent calls for continued improvement in antimicrobial stewardship interventions for appropriate antibiotic use during infancy, especially to minimize exposure in the first 6 months and use of broad-spectrum agents.[3–5,18]

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Author Disclosure Statement

No competing financial interests exist.

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