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Antibiotic use in early life, rural residence, and allergic diseases in Argentinean children

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Abstract

Background—Little is known about differential effects of antibiotic use on allergic diseases in rural versus urban environments. **Objective:** To examine whether area of residence in the first year of life modifies the relation between antibiotic use in early life and allergic diseases during childhood.

Methods—Cross-sectional study of allergic diseases in 1,517 children (ages 6–7 years) attending 101 schools in urban and rural areas of San Francisco (Córdoba, Argentina). Current asthma, wheeze, and allergic rhino-conjunctivitis were defined on the basis of responses to a validated questionnaire from the International Study of Asthma and Allergies in Childhood (ISAAC). Multivariate logistic regression was used for the analysis of antibiotic use and allergic diseases.

Results—After adjustment for paracetamol use, bronchiolitis, and other covariates, antibiotic use in the first year of life was associated with increased odds of current wheeze (odds ratio [OR]=1.8, 95% confidence interval [CI]=1.3–2.6) and allergic rhino-conjunctivitis (OR=1.9, 95% CI=1.3–2.7). After stratification by area of residence, antibiotic use was associated with current wheeze (OR=2.4, 95% CI=1.5–4.0) and allergic rhino-conjunctivitis (OR=2.1, 95% CI=1.3–3.4) among children who lived in an urban area in their first year of life, but not among those who lived in a rural area in their first year of life.

Conclusions—Early-life antibiotic use is associated with current wheeze and allergic rhino-conjunctivitis in Argentinean children who lived in urban areas during their first year of life.

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Exposure to a rural environment early in life may protect against the adverse effects of antibiotics on atopic diseases in children.

Keywords

antibiotics; rural residence; wheeze; asthma; hay fever; children

INTRODUCTION

Allergic diseases such as asthma and allergic rhino-conjunctivitis are an important public health issue worldwide^{1, 2}. A previously noted upward trend in asthma prevalence may have reached a plateau in industrialized countries, but this rising trend continues in developing countries². The causes of this “asthma epidemic” are unclear but most likely due to changes in environment or lifestyle.

Over the past decade, antibiotic use has substantially increased worldwide, especially in developing countries³. This is concerning, since antibiotics can disturb the normal gut microbiome, which could alter immune programming and predispose to allergic diseases in children^{4, 5}. To date, however, epidemiologic studies have provided inconclusive evidence of a causal link between antibiotic use in early life and asthma or allergic diseases in childhood^{6, 7}. For example, a meta-analysis of data from over 600,000 subjects in 22 studies showed that antibiotic use in the first year of life was significantly associated with 1.5-fold increased odds of childhood asthma (95% confidence interval [CI] for odds ratio [OR]=1.30–1.77)⁷. However, this association became much weaker and non-statistically significant when the analysis was restricted to data from longitudinal studies (n=9) and adjusted for confounding by indication (OR=1.12, 95% CI= 0.98 to 1.26)⁶.

Conflicting results from meta-analyses of epidemiologic studies of antibiotic use and asthma or allergic diseases^{6, 7} may be partly due to heterogeneity in population demographics, geographic location, and environmental exposures across studies. Indeed, one study reported that antibiotic use in the first six months of life was more strongly and significantly associated with atopy (defined as skin test reactivity to at least one allergen) in school-aged children who had fewer than two pets (OR=1.73, 95% CI=1.07 to 2.80, P=0.02) than in those with at least two pets (OR=0.25, 95% CI= 0.05 to 1.20)⁸, a finding that may be explained by immune modulatory effects of bacterial products in mammalian feces or increased richness and diversity of the gut microbiome among children living with pets⁹.

In 2007, Argentina had the highest rate of antibiotic use of all countries in Latin America¹⁰, a region of the world where both asthma and allergic rhino-conjunctivitis are common^{11–13}. In a previous study, we reported that rural residence was associated with reduced odds of current wheeze and allergic rhino-conjunctivitis among adolescents (ages 13 to 14 years) living in the province of Córdoba (Argentina)¹⁴. Given that finding, as well as a prior report of potential effect modification of the effect of antibiotic use on atopy by presence of animals (pets) in the home⁸, we hypothesized that antibiotic use would affect the risk of atopic diseases (current wheeze or allergic rhino-conjunctivitis) among children living in urban areas in early life, but not among those living in rural areas in early life (who are often exposed to farm animals and pets, and thus may be less susceptible to the detrimental effects

of antibiotics by virtue of a richer and more robust gut microbiota). To test this hypothesis, we examined the relation between antibiotic use in early life and current asthma, current wheeze, and allergic rhino-conjunctivitis among children ages 6 to 7 years in Córdoba, first in all children, and then separately in children who lived in rural vs. urban areas during their first year of life.

METHODS

Study population and design

From May to June 2007, all children aged 6 to 7 years who were enrolled in school and resided in the city of San Francisco and the surrounding rural areas (Province of Córdoba, Argentina) were invited to participate in this study. Located in the center of Argentina, on a plain area with mild climate, San Francisco has about 60,000 inhabitants and is an industrial center with low levels of air pollution. The surrounding rural areas have a similar climate, and dairy farm activities and grain harvests (soya, corn and wheat) are common.

The Education Ministry of the Province of Córdoba agreed to facilitate enrollment of all urban and rural students in public schools. A total of 101 public and private schools (22 urban and 79 rural) were contacted by the researchers and agreed to participate. A written questionnaire was then distributed to all children at their school, for completion by their parents. Of the 2,197 questionnaires distributed, 1,887 (85.9%) were completed (1,686 (89.3%) by the child's mother and 201 (10.7%) by the child's father or another caretaker), as follows: 1,315 (83.8%) of 1,569 from urban schools, and 572 (91.1%) of 628 from rural schools. Of the 1,887 participants, 370 (19.6%) had missing data for at least one of the study outcomes (current asthma, wheeze, or allergic rhino-conjunctivitis), leaving 1,517 (80.4 %) with complete data in the current analysis.

Study protocol

The Spanish version of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III core questionnaire was completed for all participants¹. This questionnaire, widely used in Argentina and other countries, has been shown to be a reliable tool to estimate the prevalence of allergic diseases. Information on any use of antibiotics in the first year of life, any use of paracetamol in the first year of life, and at least one hospitalization or visit to the Emergency Department for bronchiolitis in the first year of life, was obtained from the core questionnaire, which was supplemented with questions on socio-demographic and household characteristics, history of allergic diseases, and the living environment. Height and weight were measured by trained personnel after each participant completed the study questionnaire, and approximated to the nearest centimeter and pound, respectively.

The study was approved by the Ethics Committee of the Regional Hospital and informed consent/assent was obtained from study participants.

Statistical analysis

Residence within the limits of San Francisco city was classified as urban, and residence in the area outside any city or population within the San Justo Department was classified as rural (the Province of Córdoba is divided into departments, and San Francisco is the Head of the San Justo Department). Current wheeze was defined as parental report of any wheeze in the previous year. Current asthma was defined as parental report of physician-diagnosed asthma and current wheeze. Current allergic rhino-conjunctivitis was defined as parental report of naso-ocular symptoms apart from colds in the previous year.

Variables included in bivariate analyses were age, gender, body mass index (BMI), maternal education (completion of high school vs. non-completion of high school), birth weight (<2,500 grams vs. ≥2500 grams), breastfeeding (never, <6 months, ≥6 months), number of older siblings (none, 1–2, 3 or more), maternal smoking, paternal smoking, any second-hand smoke at home, parental history of allergy, maternal exposure to farm animals during pregnancy, and current place of residence (rural vs. urban). Reported environmental exposures in the first year of life included place of residence (rural vs. urban), presence of a cat or dog in the home, consumption of unpasteurized milk (categorized as ever, and also as regular [at least once a week] or not), contact with farm animals (poultry, cows, lambs, horses or pigs, categorized as ever, and also as regular (at least once a week) vs. not), contact with silos of cereal, residence near a dairy farm, and day care attendance.

Wald chi-square tests and Student *t*-tests were used for unadjusted analyses of binary and continuous variables, respectively. Logistic regression was used for the multivariable analysis of antibiotic use in the first year of life and: current asthma, current wheeze, and allergic rhino-conjunctivitis. A stepwise approach was used to build the multivariable models. Variables associated with the outcome of interest at $P < 0.25$ were included in the initial models. All final models included age, gender, parental history of allergy, and any other variable that was either significantly associated with the outcome of interest (at $P < 0.05$) or changed the estimate of effect (the odds ratio) by ≥10%. After the final models were built, we also included an interaction term for early-life antibiotic use and area of residence. All statistical analyses were conducted using SAS 9.3 software (SAS Institute Inc., Cary, NC).

RESULTS

Supplemental Table 1 shows a comparison of the characteristics of children who were (n=1,517) and were not (n=370) included in the current analysis. Compared with children who were included in the current analysis, those who were excluded were significantly more likely to have used any antibiotics, to have had bronchiolitis, or to have lived with a pet in the first year of life, and to have current wheeze. There were no other significant differences between children who were and were not included in this analysis.

The main characteristics of study participants are shown in Table 1. Current asthma, current wheeze, and allergic rhino-conjunctivitis were reported by 3.8%, 14.8.3% and 13.6% of the 1,517 participating children, respectively. Compared to children without current asthma, those with current asthma were more likely to have a parental history of allergy, and to have

taken paracetamol and had bronchiolitis in the first year of life, but less likely to have consumed unpasteurized milk in the first year of life. Compared with children without current wheeze, those with current wheeze had a higher BMI and were more likely to have been exposed to maternal smoking or any second-hand smoke at home, and to have a parental history of allergy, to have used paracetamol or antibiotics in the first year of life, and to have had bronchiolitis and regular contact with silos of cereal in the first year of life. Compared with children without allergic rhino-conjunctivitis, those with allergic rhino-conjunctivitis were more likely to have a parental history of allergy, to currently live in a rural area, to have used antibiotics and to have had bronchiolitis in the first year of life, and to have had contact with silos of cereal in the first year of life.

Table 2 shows the multivariable analysis of antibiotic use in the first year of life and allergic diseases among participating children. After adjusting for age, gender, parental history of allergy, and rural residence in the first year of life, antibiotic use in the first year of life was significantly associated with 2.1 to 2.4 fold increased odds of current allergic rhino-conjunctivitis and current wheeze (**Model 1**). After additional adjustment for both paracetamol uses in the first year of life and bronchiolitis in the first year of life, antibiotic use in the first year of life was significantly associated with 1.8 to 1.9 fold increased odds of current wheeze and current allergic rhino-conjunctivitis (**Model 2**). After adding an interaction term between antibiotic use in the first year of life and area of residence in the first year of life to Model 2 for current wheeze and current allergic rhino-conjunctivitis, we found evidence of significant modification of the estimated effect of antibiotic use on current wheeze by area of residence ($P = 0.03$ in both instances).

Next, we repeated the multivariable analysis of antibiotic use in the first year of life and current wheeze after stratification by area of residence in the first year of life (Figure 1). In this stratified analysis, antibiotic use in the first year of life was significantly associated with 2.4 fold increased odds of current wheeze among children who lived in an urban area in their first year of life. In contrast, antibiotic use in the first year of life was not significantly associated with current wheeze among children who lived in a rural area during their first year of life. In the multivariable analysis, bronchiolitis in the first year of life was significantly associated with increased odds of current wheeze among children who lived in either an urban area or a rural area in their first year of life, while paracetamol use in the first year of life was not significantly associated with current wheeze in either group.

Figure 2 depicts the results of our multivariable analysis of antibiotic use in the first year of life and allergic rhino-conjunctivitis, stratified by area of residence in the first year of life. Among children who lived in an urban area in their first year of life, antibiotic use was significantly associated with 2.1 fold increased odds of allergic rhino-conjunctivitis. Similar to our findings for current wheeze, antibiotic use was not significantly associated with allergic rhino-conjunctivitis among children who lived in a rural area in their first year of life. Moreover, bronchiolitis in the first year of life was significantly associated with allergic rhino-conjunctivitis among children living in either an urban or a rural area in their first year of life, while paracetamol use in the first year of life was not significantly associated with allergic rhino-conjunctivitis in either group.

Supplemental Table 2 shows a comparison of the characteristics of children who resided in rural (n=403) and urban (n=1,114) areas. Compared with children who resided in rural areas, those who resided in urban areas had significantly lower BMI and fewer older siblings, and were significantly more likely to have a parental history of allergy, to have higher maternal education and more frequent exposure to maternal smoking, to have been unexposed to a cat or a dog in the house in the first year of life, and to not have consumed unpasteurized milk. Of note, confirmatory analyses with additional adjustment for all covariates above yielded results that were very similar to those of the more parsimonious models shown in figures 1 and 2 (data not shown).

DISCUSSION

Among school-aged children who lived in an urban area of Córdoba (Argentina) early in their lives, antibiotic use in the first year of life was significantly associated with current wheeze and allergic rhino-conjunctivitis. In contrast, antibiotic use in the first year of life was not significantly associated with current wheeze or allergic rhino-conjunctivitis among children who lived in a rural area early in their lives. To our knowledge, this is the first report of modification of the estimated effect of antibiotic use in early life on allergic diseases by area of residence (rural vs. urban) in early life.

Deviation of microbial homeostasis has been associated with human health that prenatal and postnatal factors such as mode of delivery, antibiotic use, breast-feeding, and environmental exposure can configure the microbiome during early life¹⁵. Emerging evidence from human and animal studies suggests that the gut microbiome plays a major role in regulating Th2 and Treg immune responses, which are relevant to the development of allergic diseases in early life^{16, 17}. In murine models, alteration of commensal gut bacteria by oral antibiotics leads to elevated total serum IgE and circulating basophils, basophil-mediated Th2 cytokine responses, and allergic inflammation¹⁸. In another experimental model, neonatal vancomycin treatment significantly shifted the composition of gut bacteria, decreased microbial diversity, reduced T-reg cells in the colon, and increased the severity of allergic airway inflammation in ovalbumin-challenged mice¹⁹. In young children, the use of macrolides has been associated with asthma and overweight, perhaps through long-lasting effects on the composition and function of the gut microbiome²⁰.

Lower respiratory tract infections (LRTIs) and bronchiolitis in early life have been associated with increased risk of subsequent asthma and asthma exacerbations^{21–23}. Consistent with our findings among children living in urban areas, birth cohort studies in Europe and the United States have shown that antibiotic use in early life is associated with asthma or current wheeze, even after adjustment for respiratory infections in early life^{15, 24–28}. Unlike our study, however, most of those prior studies did not account for paracetamol use, which has been linked to asthma and allergic rhino-conjunctivitis in young children^{29, 30}. Likewise, antibiotic use in the first year of life was associated with current symptoms of allergic rhino-conjunctivitis among children aged 6–7 years old in New Zealand (OR=1.94, 95% CI=1.69, 2.24)³¹ and Colombia (OR=1.7, 95% CI=1.3, 2.3)³², but those studies did not account for bronchiolitis^{31, 32} or paracetamol use³¹ in early life. Although less studied, the gut virome includes eukaryotic viruses and bacterial viruses,

which may interact with bacteria to affect host immune system and susceptibility to viral infection²¹. There is a need for more complete time-series analysis of how disrupted host-microbiota homeostasis caused by antibiotics may lead to LRTIs or airway diseases.

The lack of a significant association between antibiotic use and current wheeze or allergic rhino-conjunctivitis among children who lived in a rural area in their first year of life is intriguing. Because of relatively small sample size and thus limited statistical power, we cannot completely exclude a weak or modest association between antibiotic use and allergic diseases in this group of children. However, insufficient power is an unlikely explanation for our findings, as we obtained similar results in a confirmatory analysis in which we replaced “rural residence in the first year of life” with “regular contact with farm animals in the first year of life” (Supplemental Figure 1).

A farming environment has been shown to be inversely associated with allergic diseases (asthma, wheeze, hay fever, and atopic dermatitis) in Alpine regions of Central Europe^{33, 34}. This protective effect against allergic diseases may be explained by bacterial or fungal exposures resulting from contact with livestock or animal feed/shed and raw milk consumption among children living in farms^{35, 36}. A few studies in Latin America have also shown rural residence to be associated with lower risk of current wheeze and allergic rhino-conjunctivitis^{14, 37, 38}. In an exploratory analysis conducted as part of a study of Mexican American children, antibiotic use was associated with asthma or current wheeze in children who were born in rural areas of Mexico, but not in those born in urban areas of Mexico³⁹. However, those findings must be cautiously interpreted in the context of an exploratory analysis unadjusted for bronchiolitis and other potential confounders.

Our study has several strengths, including a sample representative of children in Córdoba, Argentina, and the ability to adjust for confounders such as paracetamol use and bronchiolitis in early life. We also acknowledge several limitations. First, we cannot assess temporal relationships, given a cross-sectional design. Second, recall bias is possible if parents of children with asthma or allergies were more likely to recall antibiotic use in the first year of life than parents of children without asthma or allergies. Of note, however, physicians are nearly always responsible for prescribing antibiotics to newborns and infants in Argentina, where such antibiotic use reflects an illness requiring medical attention, and thus less susceptible to recall bias, even in children without asthma or allergies. Third, we lack detailed information on antibiotic use (e.g., timing, type and number of courses of antibiotics used) and some potential modifiers or confounders of the effect of antibiotics on allergic diseases (e.g., air pollution and diet). Fourth, selection bias is possible in any observational study. However, selection bias is unlikely to be a major explanation for our results, since the proportion of children who used antibiotics in the first year of life was significant but modestly different between those who were and were not included in this analysis. Moreover, we obtained similar results in secondary analyses including children missing data for 1 outcome (e.g., findings for current wheeze were unchanged in an analysis including children missing data for current asthma or allergic rhino-conjunctivitis). Fifth, we had no objective measures of atopy (e.g., allergy skin testing or allergen-specific IgEs). However, all outcomes were assessed using a well-validated questionnaire. Sixth, self-administered questionnaires can yield less accurate data than those administered by an

interviewer. Finally, we had limited statistical power for the analysis of current asthma, due to both a relatively small number of cases and potential under-diagnosis. Nonetheless, current wheeze is strongly correlated with airway responsiveness and asthma in school-aged children.

In summary, antibiotic use in the first year of life was associated with increased odds of current wheeze and allergic rhino-conjunctivitis in Argentinean children, but only if they lived in an urban area in their first year of life. Our findings suggest that rural residence in early life may protect against detrimental effects of antibiotic use on allergic diseases, perhaps through immune modulation by a more robust and diverse gut microbiome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
ISAAC	International Study of Asthma and Allergies in Childhood
LRTIs	Lower respiratory tract infections

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Highlights

What is already known about this topic?

Antibiotic use in early life has been associated with allergic diseases in some studies but not in others, perhaps due to the effects of concurrent environmental exposures.

What does this article add to our knowledge?

Antibiotic use in the first year of life is associated with current wheeze and allergic rhinoconjunctivitis among school-aged children who lived in an urban area of Córdoba (Argentina) early in their lives, but not among children who lived in a rural area early in their lives, suggesting that rural residence in early life may protect against detrimental effects of antibiotic use on allergic diseases.

How does this study impact current management guidelines?

Since the link between antibiotic use and allergic diseases requires further investigation, clinicians should adhere to current guidelines for prescribing antibiotics, while educating patients about detrimental effects of inadequate antibiotic use in children, including treatment resistance and alterations of the gut microbiome.

Figure 1. Multivariable analysis of antibiotic use in the first year of life and current wheeze at age 6–7 years, stratified by rural vs. urban residence in the first year of life.

Figure 2.

Multivariable analysis of antibiotic use in the first year of life and allergic rhino-conjunctivitis at age 6–7 years, stratified by rural vs. urban residence in the first year of life

Table 1

Characteristics of participating children, according to reported allergic diseases

Characteristic	Current asthma			Current wheeze		Allergic rhino-conjunctivitis	
	No (n=1,459)	Yes (n=58)	No (n=1,293)	Yes (n=224)	No (n=1,310)	Yes (n=207)	
Age, years	6.6 ± 0.5	6.5 ± 0.5	6.6 ± 0.5	6.5 ± 0.5	6.6 ± 0.5	6.6 ± 0.5	
Male gender	711 (48.9)	33 (56.9)	621 (48.3)	123 (54.9)	642 (49.3)	102 (49.3)	
Body mass index	17.0 ± 3.8	17.5 ± 3.0	16.9 ± 3.4	17.6 ± 4.9 [‡]	17.0 ± 3.6	17.6 ± 4.7	
Mother completed high school	504 (34.6)	24 (41.4)	450 (34.8)	78 (35.0)	454 (34.7)	74 (35.8)	
Birth weight <2,500g	91 (6.4)	6 (10.5)	82 (6.5)	15 (6.8)	87 (6.9)	10 (5.0)	
Breastfeeding							
Never	237 (16.7)	7 (12.3)	211 (16.8)	33 (15.1)	217 (17.0)	27 (13.6)	
< 6 months	469 (33.1)	14 (24.6)	416 (33.1)	67 (30.7)	416 (32.6)	67 (33.8)	
6 months	713 (50.3)	36 (63.2)	631 (50.2)	118 (54.1)	645 (50.5)	104 (52.5)	
Number of older siblings							
None	550 (37.7)	26 (44.8)	490 (37.9)	86 (38.4)	495 (37.8)	81 (39.1)	
1–2	659 (45.2)	26 (44.8)	584 (45.2)	101 (45.1)	599 (45.7)	86 (41.6)	
3	250 (17.1)	6 (10.3)	219 (16.9)	37 (16.5)	216 (16.5)	40 (19.3)	
Maternal smoking	260 (18.1)	10 (17.2)	219 (17.1)	51 (23.2) [‡]	228 (17.6)	42 (20.6)	
Paternal smoking	423 (29.7)	19 (34.6)	369 (29.2)	73 (33.8)	376 (29.4)	66 (32.8)	
Second-hand smoke at home	483 (33.1)	21 (36.2)	413 (31.9)	91 (40.6) [‡]	426 (32.5)	78 (37.7)	
Parental history of allergy	396 (28.1)	32 (58.2) [‡]	325 (26.0)	103 (49.1) [‡]	333 (26.3)	95 (48.7) [‡]	
Current rural residence	385 (27.8)	11 (19.3)	339 (27.6)	57 (26.8)	335 (28.4)	41 (21.2) [‡]	
Exposures in the first year of life							
Rural residence	356 (24.7)	11 (19.0)	319 (24.9)	48 (21.8)	326 (25.1)	41 (20.4)	
Any paracetamol use	1220 (85.1)	52 (89.7)	1067 (84.1)	205 (92.3) [‡]	1094 (85.0)	178 (87.3)	
Any use of antibiotics	877 (62.4)	44 (77.2) [‡]	746 (60.0)	175 (80.3) [‡]	766 (60.8)	155 (76.4) [‡]	
Bronchiolitis	237 (16.7)	26 (49.1) [‡]	172 (13.7)	91 (42.9) [‡]	194 (15.3)	69 (34.3) [‡]	
Cat in the house	356 (24.6)	14 (24.6)	307 (23.9)	63 (28.5)	317 (24.4)	53 (26.1)	
Dog in the house	978 (67.9)	38 (66.7)	869 (68.1)	147 (66.5)	878 (67.8)	138 (68.0)	

Characteristic	Current asthma		Current wheeze		Allergic rhino-conjunctivitis	
	No (n=1,459)	Yes (n=58)	No (n=1,293)	Yes (n=224)	No (n=1,310)	Yes (n=207)
Consumption of unpasteurized milk	282 (20.0)	4 (7.1) [‡]	250 (20.0)	36 (16.8)	249 (19.7)	37 (18.8)
Contact with farm animals [/]	398 (27.8)	15 (25.9)	348 (27.4)	65 (29.7)	358 (27.8)	55 (27.1)
Contact with silos of cereal	230 (16.3)	14 (25.5)	198 (15.9)	46 (21.3) [‡]	198 (15.7)	46 (23.1) [‡]
Residence near dairy farm	253 (17.8)	7 (12.3)	225 (17.8)	35 (16.1)	227 (17.8)	33 (16.3)
Day care attendance	77 (5.4)	3 (5.3)	66 (5.2)	14 (6.4)	63 (4.9)	17 (8.5) [‡]
Maternal smoking	172 (12.1)	4 (7.1)	145 (11.5)	31 (14.4)	150 (11.8)	26 (13.1)
Contact with farm animals [/] during pregnancy	367 (25.5)	14 (24.1)	326 (25.6)	55 (24.8)	329 (25.5)	52 (25.5)

Data are presented as No. (%) for binary variables or mean (SD) for continuous variables. For some variables, percentages reflect missing data.

[‡] P<0.05;

[‡] P<0.01 for the comparison between cases and controls

[/] Farm animals include poultry, cows, lambs, pigs, and horses

Table 2

Multivariable analysis of antibiotic use in the first year of life and allergic diseases

	Model 1	Model 2 [*]
Outcome	Odds ratio, 95% confidence interval, P value	
Current asthma		
Antibiotic use, first year of life	1.8 (0.9 to 3.4), N.S.	1.3 (0.6 to 2.6), N.S.
Bronchiolitis, first year of life	--	3.1 (1.7 to 5.6), <0.01
Paracetamol use, first year of life	--	1.0 (0.4 to 2.7), N.S.
Current wheeze		
Antibiotic use, first year of life	2.4 (1.7 to 3.4), <0.01	1.8 (1.3 to 2.6), <0.01
Bronchiolitis, first year of life	--	3.0 (2.2 to 4.2), <0.01
Paracetamol use, first year of life	--	1.4 (0.8 to 2.4), N.S.
Allergic rhino-conjunctivitis		
Antibiotic use, first year of life	2.1 (1.5 to 2.9), <0.01	1.9 (1.3 to 2.7), <0.01
Bronchiolitis, first year of life	--	2.2 (1.6 to 3.1), <0.01
Paracetamol use, first year of life	--	0.8 (0.5 to 1.2), N.S.

Both models were adjusted for age, gender, parental history of allergy and rural residence in the first year in life.

^{*} Model 2 was additionally adjusted for use of paracetamol in the first year of life and bronchiolitis in the first year of life.