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GESTATIONAL AGE AT BIRTH AND RISK OF ALLERGIC RHINITIS IN YOUNG ADULTHOOD

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Abstract

Background—Previous studies of the association between gestational age or birth weight and allergic rhinitis in later life have had various limitations, including inability to estimate risk among individuals born extremely preterm and/or to examine specific contributions of gestational age and fetal growth.

Objective—To determine whether gestational age at birth, independent of fetal growth, is associated with allergic rhinitis medication prescription in a national cohort of young adults.

Methods—We conducted a national cohort study of 630,090 infants born in Sweden from 1973 through 1979 (including 27,953 born preterm, <37 weeks), followed for prescription of nasal corticosteroids and oral antihistamines in 2005–2009 (ages 25.5–37.0 years). Medication data were obtained from all outpatient and inpatient pharmacies throughout Sweden.

Results—The overall prevalence of nasal corticosteroid and oral antihistamine prescription was 16.3% and 16.8%, respectively, similar to the reported prevalence of allergic rhinitis in this population. Low gestational age at birth was associated with a decreased risk of nasal corticosteroid and/or oral antihistamine prescription in young adulthood, after adjusting for fetal growth and other potential confounders. For individuals born extremely preterm (23–28 weeks), adjusted odds ratios were 0.70 (95% CI, 0.51–0.96) for nasal corticosteroid prescription, and 0.45 (95% CI, 0.27–0.76) for both nasal corticosteroid and oral antihistamine prescription, relative to full-term births.

Conclusion—These findings suggest that low gestational age at birth, independent of fetal growth, is associated with a decreased risk of allergic rhinitis in young adulthood, possibly due to a protective effect of earlier exposure to pathogens.

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Key messages

- This national cohort study found that low gestational age at birth, independent of fetal growth, was associated with a decreased risk of nasal corticosteroid and/or oral antihistamine prescription in young adulthood.
- These findings suggest that low gestational age at birth is associated with a decreased risk of allergic rhinitis in later life, possibly due to a protective effect of earlier exposure to environmental pathogens.

Keywords

anti-allergic agents; gestational age; rhinitis; allergic; perennial; rhinitis; allergic; seasonal; premature birth

INTRODUCTION

A growing body of evidence has suggested perinatal origins for atopic disease in later life. Relatively few studies have examined the association between perinatal risk factors and allergic rhinitis, however, and these have yielded conflicting results. One study reported an association between preterm birth and a decreased risk of physician-diagnosed allergic rhinitis in 149,398 Swedish military conscripts (ages 17-20 years).¹ A U.K. study of 10,809 adolescents² and a Finnish study of 4,722 adolescents³ also reported an association between high birth weight or high gestational age and an increased risk of parental-reported allergic rhinitis. Other studies, however, have failed to confirm these findings. No association was found between fetal growth or gestational age at birth and parental-reported hay fever in 10,896 Swedish children (ages 9 and 12 years).⁴ Two U.K. studies reported no association between birth weight and parental-reported hay fever in 15,564 adolescents,⁵ or between preterm birth and hay fever ascertained from medical chart review in 567 young adults (ages 18-25 years).⁶ A German study found no association between preterm birth and parental-reported hay fever in 1,138 children (ages 5-7 years).⁷ A New Zealand study of 1,265 adolescents also found no association between gestational age or birth weight and medical consultation for any atopic conditions.⁸ These studies have had various limitations, including the use of self- or parental-reported diagnoses,^{2-5, 7} or the inability to examine the specific effects of gestational age and fetal growth.^{2-3, 5-7} In addition, most studies have had insufficient statistical power, and none has had the ability to examine the risk of allergic rhinitis among individuals born extremely preterm.

To address these gaps in the current knowledge, we conducted a national cohort study which is the largest to date of perinatal factors and the risk of allergic rhinitis in later life. We used nationwide pharmacy data to assess whether low gestational age at birth, independent of fetal growth, is associated with prescription of allergic rhinitis medications (nasal corticosteroids and oral antihistamines) in young adulthood (ages 25.5-37.0 years). Medication data were obtained from 4.5 years of outpatient and inpatient pharmacy records from all health care settings throughout Sweden. We hypothesized that individuals born preterm would have lower odds of allergic rhinitis medication prescription in young adulthood relative to those born full-term, since earlier exposure to environmental pathogens may protect against atopy in later life.¹⁻³

METHODS

Study population

We identified 648,276 individuals in the Swedish Medical Birth Register who were born from 1973 through 1979. Of this total, we excluded 6,553 (1.0%) individuals who were no longer living in Sweden at the time of follow-up (2005-2009); 7,926 (1.2%) who had significant congenital anomalies (i.e., other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation); and 1,882 (0.3%) who had missing information on birth weight. In order to remove possible coding errors, we also excluded 6 (<0.01%) individuals who had a reported gestational age <23 weeks, and 1,819 (0.3%) who had a reported birth weight more than four standard deviations above or below the mean birth weight for gestational age and sex from a Swedish reference growth curve.⁹ A total of 630,090 individuals (97.2% of the original cohort) remained for inclusion in the study.

This study was approved by the Ethics Committee of Lund University in Malmö, Sweden.

Study period

Study participants were followed for medication prescriptions from July 1, 2005 through December 31, 2009, the first 4.5 years that the national pharmacy register was kept. These individuals were between 25.5 and 37.0 years of age during the period of follow-up.

Outcome measurement

Medication prescription data were obtained using a national pharmacy register maintained by the Swedish National Board of Health and Welfare.¹⁰ This register contains a record of each medication prescribed by a health care provider and dispensed to a patient by any outpatient or inpatient pharmacy in Sweden. For inpatients, the register includes all medications prescribed and dispensed to a patient upon discharge from the hospital. All medication data are categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System developed by the WHO Collaborating Centre for Drug Statistics Methodology.¹¹ We obtained records of all outpatient and inpatient prescriptions for nasal corticosteroids (ATC code R01AD) and oral antihistamines (ATC code R06). These data were linked to the national Medical Birth Register using an anonymous identification number. Other nasal antiallergic agents (ATC code R01AC, which includes nasal antihistamines, cromolyn, and olopatadine) were not prescribed in large enough numbers for meaningful analysis and therefore were not included.

The primary outcome was defined as at least one nasal corticosteroid prescription (ATC code R01AD) during the follow-up period. Secondary outcomes were defined alternatively as at least one oral antihistamine prescription (ATC code R06), or at least one nasal corticosteroid and oral antihistamine prescription, during the follow-up period. Oral antihistamines are commonly prescribed for allergic rhinitis but also for other conditions, hence they are expected to have a lower positive predictive value for allergic rhinitis than nasal corticosteroids.

Exposure measurement

Information on gestational age at birth and birth weight was obtained from prenatal and birth records in a national research database, WomMed, located at the Center for Primary Health Care Research, Lund University, Sweden. Gestational age at birth was based on maternal report of last menstrual period, and was categorized into five groups in the current analyses to allow for a non-linear response (23-28 weeks, 29-34 weeks, 35-36 weeks, 37-42 weeks, ≥ 43 weeks). Fetal growth was measured as birth weight for gestational age and sex, and was categorized into six groups according to the number of standard deviations from the mean birth weight for gestational age and sex from a Swedish reference growth curve (< -2 SD; -2 SD to < -1 SD; -1 SD to < 0 SD; 0 SD to < 1 SD; 1 SD to < 2 SD; ≥ 2 SD).⁹ Longitudinal growth data were not available and therefore it was not possible to examine other specific patterns of fetal growth.

Adjustment variables

The WomMed database also contains sociodemographic information for the parents, including age, marital status, and socioeconomic indicators, collected annually starting in 1990. For the current study, sociodemographic characteristics were obtained using the Swedish Population and Housing Census of 1990, the most recent census when the young adults in this study (who were then 11 to 17 years of age) were still likely to be residing in the same household as their mothers. This information was used to identify maternal characteristics that would reflect the social conditions of these individuals during their

upbringing that may be associated with subsequent risk of allergic rhinitis.¹² An anonymous, serial-number version of the personal identification number (similar to the U.S. social security number but nearly 100% complete) was used to link the mothers to their children. The following variables were included as potential confounders:

Age—Modeled as a continuous variable by infant's date of birth.

Gender—Female or male.

Multiple gestation status—Singleton or twin; included because multiple gestation is associated with poor fetal growth and preterm delivery, and may be associated with a decreased risk of allergic rhinitis in the offspring.¹

Maternal age at delivery—<20 years, 20-24 years, 25-29 years, 30-34 years, or ≥35 years; included because very early or advanced maternal age is associated with preterm delivery, and increasing maternal age may be associated with an increased risk of allergic rhinitis in the offspring.¹

Maternal parity—0, 1, or ≥2; included as a proxy for number of older siblings. Nulliparity is associated with increased risk of low birth weight or small for gestational age,¹³ and high parity (or the presence of older siblings) is associated with decreased risk of allergic sensitization.^{1, 12, 14}

Maternal marital status in 1990—Married/cohabiting, never married, divorced, or widowed.

Maternal education in 1990—Compulsory high school or less (≤9 years), practical high school or some theoretical high school (10-11 years), or theoretical high school and/or college (≥12 years).

Family income in 1990—Calculated as the annual family income divided by the number of people in the family, or family income per capita, using a weighted system whereby small children were given lower weights than adolescents and adults. The final variable was categorized in quartiles.

Total number of all medication prescriptions during the follow-up period—Modeled as a continuous variable after logarithmic transformation to correct for positive skewness. This was included as a proxy for health care resource use, a potentially important confounder because preterm birth is associated with neurodevelopmental morbidities which may result in differential ascertainment and treatment of allergic rhinitis due to increased health care utilization.

Maternal prescription of allergic rhinitis medications during the follow-up period—Prescription of nasal corticosteroids (ATC code R01AD) or oral antihistamines (ATC code R06) to the mothers of the study participants during the follow-up period, dichotomized as 0 or ≥1 and entered into the model separately.

Statistical analysis

Generalized estimating equations were used to estimate odds ratios and 95% confidence intervals for the association between gestational age at birth or fetal growth and allergic rhinitis medication prescription (as defined above) in young adulthood. Analyses were conducted unadjusted and adjusted. The adjusted model included the following variables:

gestational age at birth, fetal growth, age, gender, multiple gestation status, maternal age at delivery, maternal parity at delivery, maternal marital status, maternal education, family income, total number of all medication prescriptions, and maternal prescription of nasal corticosteroids or oral antihistamines during the follow-up period (see variable definitions above). In the adjusted model, a likelihood ratio test was performed for departure from linear trend across ordinal categories of gestational age at birth or fetal growth. All models used robust standard errors to account for correlation among siblings. An α -level of 0.05 was used for all significance tests. Pearson chi-square goodness-of-fit tests were used to confirm that the final models were an appropriate fit for these data.

We also explored first-order interactions between gestational age at birth or fetal growth and each of the covariates with respect to allergic rhinitis medications in young adulthood, using a likelihood ratio test to evaluate for statistical significance. All analyses were conducted using Stata statistical software, version 11.0.¹⁵

RESULTS

Of the 630,090 individuals who were identified, 27,953 (4.4%) were born prematurely (<37 weeks), including 419 (0.1%) born at 23-28 weeks; 8,509 (1.4%) born at 29-34 weeks; and 19,025 (3.0%) born at 35-36 weeks. Compared to individuals who were born full-term, those born prematurely were more likely to be male, a twin, and/or to have ≥ 50 prescriptions of any medications during the follow-up period; and their mothers were more likely to be <20 or ≥ 35 years old at the time of delivery, have parity of 1 or ≥ 3 , be divorced or never married, have the lowest educational attainment and/or the lowest family incomes (Table 1).

A total of 102,934 (16.3%) young adults from the entire cohort were prescribed a nasal corticosteroid, and 105,789 (16.8%) were prescribed an oral antihistamine (Table 2). A lower prevalence of nasal corticosteroid prescription was observed across the full range of preterm gestational ages (<37 weeks), including 14.6% of those born at 23-28 weeks, 14.3% of those born at 29-34 weeks, and 15.6% of those born at 35-36 weeks, compared to 16.4% of those born full-term (37-42 weeks). For oral antihistamine prescription, a lower prevalence was observed only among individuals born at gestational ages <35 weeks, including 15.3% of those born at 23-28 weeks and 16.0% of those born at 29-34 weeks, compared to 16.8% of those born full-term (37-42 weeks).

Young adults who were born preterm had decreased relative odds of nasal corticosteroid and/or oral antihistamine prescription in young adulthood, after adjusting for fetal growth and other potential confounders. For nasal corticosteroids, decreased relative odds were observed across the full range of preterm gestational ages, including late preterm births (Table 3). Individuals born extremely preterm had the lowest relative odds (adjusted OR 0.70; 95% CI, 0.51-0.96). The effect across gestational age groups was not linear ($P < 0.0001$ for departure from linear trend). Individuals born post-term (≥ 43 weeks) also had a small but statistically significant decreased odds of nasal corticosteroid prescription relative to full-term births. For oral antihistamines, similar results were observed except that among individuals born preterm, a decreased relative odds were observed only at gestational ages <35 weeks, and not for late preterm births (35-36 weeks). The only significant confounder among the model covariates was the total number of all medication prescriptions. Adjustment for any combination of other variables had negligible effects on the odds ratios.

Compared to gestational age at birth, fetal growth had a much weaker but significant association with nasal corticosteroid prescription in the adjusted model. Individuals with either the highest or lowest fetal growth had very slightly decreased odds of nasal corticosteroid prescription relative to the reference group (Table 3). High fetal growth was

also associated with slightly decreased relative odds of oral antihistamine prescription after adjusting for gestational age and the other covariates.

Table 4 presents odds ratios for the association between the model covariates and nasal corticosteroid prescription in young adulthood. After adjusting for the other variables included in the model, the following were associated with increased nasal corticosteroid prescription: males, singletons, increasing maternal age at delivery, decreasing parity, married/cohabiting status, increasing educational attainment, increasing income, and maternal prescription of nasal corticosteroids or oral antihistamines during the follow-up period. The strongest of these risk factors was maternal prescription of nasal corticosteroids (adjusted OR 1.31; 95% CI, 1.29-1.34). Odds ratios for the association between model covariates and oral antihistamine prescription (a secondary outcome) were very similar, except that the strongest risk factor was maternal prescription of oral antihistamines (adjusted OR 1.28; 95% CI, 1.26-1.31; data not shown). Compared to twins, singletons had a higher prevalence of nasal corticosteroid prescription (16.4% vs. 13.9%, $P<0.0001$) or oral antihistamine prescription (16.8% vs. 14.7%, $P<0.0001$; data not shown), although multiple gestation status was not a significant confounder in the models.

The only first-order interaction that was significant at the $P<0.01$ level was that between gestational age at birth and the total number of all medication prescriptions with respect to nasal corticosteroid prescription ($P=0.0001$). The association between increasing gestational age at birth and nasal corticosteroid prescription was stronger among individuals with a greater number of all medication prescriptions (used as a proxy for health care resource use).

DISCUSSION

These findings from a large national cohort suggest that low gestational age at birth is associated with a decreased risk of allergic rhinitis in young Swedish adults. The relative odds of nasal corticosteroid prescription decreased monotonically by earlier preterm gestational ages, including a small decreased risk for late preterm births (35-36 weeks). Individuals born post-term (≥ 43 weeks) also had slightly decreased odds of nasal corticosteroid and/or oral antihistamine prescription, relative to full-term births. These associations were independent of fetal growth and other broadly measured potential confounders. An independent but much weaker association was observed between highest or lowest fetal growth and nasal corticosteroid prescription, and between highest fetal growth and oral antihistamine prescription. These findings are consistent with some but not all previous smaller studies, and extend them by having much greater statistical power as well as the ability to estimate risk among individuals born extremely preterm.

Atopic conditions including allergic rhinitis are believed to reflect a predominant T helper cell type 2 (TH2) lymphocyte response to environmental antigens.¹⁶ The “hygiene hypothesis”¹⁷⁻¹⁸ postulates that early exposure to pathogens protects against atopy in later life by promoting a shift from a TH2 to a T helper cell type 1 (TH1) preponderance, leading to greater immune tolerance to a broad spectrum of environmental allergens.¹⁹ The current study's findings for preterm birth, but not necessarily for post-term birth, are consistent with this hypothesis. Individuals who are born preterm have earlier exposure to pathogens which may further promote the shift to a TH1 type response, which in turn may protect against the development of atopic conditions in later life. Alternatively, murine models have suggested that a mother's immune system is predominantly the TH2 type, because TH1 cytokines may be harmful to the maintenance of pregnancy.^{14, 20} Longer exposure to TH2 cytokines during pregnancy could modify the fetal immune system toward the TH2 type and increase the risk of atopy in later life.¹⁴ Further research is needed to identify the specific etiologic pathways, including the possibility of different mechanisms for post-term births.

A limitation of the current study is the use of medication prescriptions as a surrogate measure for allergic rhinitis. This approach fails to identify individuals with allergic rhinitis who are untreated or self-treated. Nasal corticosteroids and oral antihistamines are available over-the-counter as well as by prescription in Sweden. The prevalence of either nasal corticosteroid (16.3%) or oral antihistamine (16.8%) prescription in this cohort, however, was comparable to a previously reported prevalence of allergic rhinitis in southern Sweden (15.0%), based on the combination of self-reported history of hay fever and permanent or recurrent nasal symptoms in 4,280 adults aged 28 to 67 years.²¹ Preterm birth is associated with an increased use of health care resources due to co-morbidities, and therefore individuals who are born preterm may be differentially more likely to be prescribed nasal corticosteroids or oral antihistamines due to a greater opportunity for ascertainment and treatment. We controlled for this potentially confounding effect by adjusting for the total number of medication prescriptions as a proxy for health care resource use. Residual confounding by this factor is possible, but if it exists, it would be expected to bias the results in the opposite direction of the association we observed, in which case the reported results are conservative estimates of the true effect size.

Information on maternal smoking and postnatal growth patterns was unavailable for this cohort, thus we were unable to examine the potential effects of these factors. A final limitation is the estimation of gestational age by maternal report of last menstrual period rather than by ultrasound, which was not yet widely used at the time these study participants were born (1973-1979). In order to reduce misclassification, we excluded individuals whose birth weight deviated more than four standard deviations from the mean reference birth weight.

The most important strength of this study is its ability to examine the association between gestational age and allergic rhinitis in a large national cohort using nationwide medication data. These data were obtained from all outpatient and inpatient pharmacies from all health care settings throughout Sweden, thus avoiding bias that may result from self-reporting. Information on the total number of all medication prescriptions enabled adjustment for the potentially important confounding effect of health care resource use.

In summary, this national cohort study is the largest to date of perinatal risk factors and allergic rhinitis in later life. The findings suggest that low gestational age at birth, independent of fetal growth, is associated with a decreased risk of allergic rhinitis in young adulthood. Further research is needed to clarify the specific biologic mechanisms as well as the relationship between perinatal risk factors and other atopic conditions.

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Abbreviations

ATC	Anatomical Therapeutic Chemical
CI	confidence interval
OR	odds ratio
SD	standard deviation

TH1	T helper cell type 1
TH2	T helper cell type 2
WHO	World Health Organization

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Table 1

Infant and maternal characteristics by gestational age at birth (1973-1979)

	Gestational Age, %				
	23-28 weeks (N=419)	29-34 weeks (N=8,509)	35-36 weeks (N=19,025)	37-42 weeks (N=583,571)	≥43 weeks (N=18,566)
Gender					
Female	46.3	44.0	44.8	48.8	49.9
Male	53.7	56.0	55.2	51.2	50.1
Multiple gestation status					
Singleton	90.0	83.6	90.2	98.8	99.4
Twin	10.0	16.4	9.8	1.2	0.6
Maternal age (years)					
<20	8.6	9.6	8.7	6.3	8.4
20-24	29.1	29.3	28.9	30.0	34.9
25-29	35.6	32.9	34.3	38.3	37.4
30-34	20.3	19.8	20.1	19.4	15.8
≥35	6.4	8.4	8.0	6.0	3.5
Maternal parity					
1	47.3	44.5	45.2	43.2	47.6
2	33.9	32.7	33.3	38.1	34.0
≥3	18.8	22.8	21.5	18.7	18.4
Maternal marital status in 1990					
Married/cohabiting	74.3	70.2	72.0	76.3	72.9
Never married	12.9	13.0	11.7	9.5	11.5
Divorced	12.4	15.8	14.8	13.0	14.6
Widowed	0.5	1.0	1.5	1.2	1.0
Maternal education in 1990 (years)					
Compulsory high school or less (≤9)	26.0	32.0	31.0	27.0	29.5
Practical high school or some theoretical high school (10-11)	48.9	46.8	46.5	47.2	47.5
Theoretical high school and/or college (≥12)	25.1	21.2	22.5	25.8	23.0
Family income in 1990					
Lowest quartile	29.1	27.8	26.1	23.0	24.1
Second quartile	24.6	24.9	25.8	25.8	25.3

	Gestational Age, %					
	23-28 weeks (N=419)	29-34 weeks (N=8,509)	35-36 weeks (N=19,025)	37-42 weeks (N=583,571)	≥43 weeks (N=18,566)	
Third quartile	23.9	24.9	25.0	25.7	25.8	
Highest quartile	22.4	22.5	23.1	25.5	24.8	
Total number of all medication prescriptions during follow-up period						
0	9.3	12.2	11.9	11.5	11.3	
1-9	43.9	42.2	45.1	45.8	44.9	
10-49	34.1	35.1	35.5	36.1	36.4	
≥50	12.7	8.5	7.5	6.6	7.4	
Maternal prescription of nasal corticosteroids during follow-up period						
	17.4	17.1	18.0	18.4	18.2	
Maternal prescription of oral antihistamines during follow-up period						
	18.9	17.0	17.3	16.5	17.2	

Table 2

Prescription of allergic rhinitis medications in young adulthood (ages 25.5-37.0 years) by gestational age at birth (1973-1979)

Medications [ATC code]	Gestational Age, n (%)						
	<37 weeks (N=27,953)	23-28 weeks (N=419)	29-34 weeks (N=8,509)	35-36 weeks (N=19,025)	37-42 weeks (N=583,571)	≥43 weeks (N=18,566)	All (N=630,090)
Any nasal corticosteroids [R01AD]	4,243 (15.2)	61 (14.6)	1,213 (14.3)	2,969 (15.6)	95,736 (16.4)	2,955 (15.9)	102,934 (16.3)
Any oral antihistamines [R06]	4,665 (16.7)	64 (15.3)	1,365 (16.0)	3,236 (17.0)	98,028 (16.8)	3,096 (16.7)	105,789 (16.8)
Both nasal corticosteroids and oral antihistamines [R01AD and R06]	1,804 (6.4)	20 (4.8)	509 (6.0)	1,275 (6.7)	39,660 (6.8)	1,263 (6.8)	42,727 (6.8)

Odds ratios for association between gestational age at birth or fetal growth (1973-1979) and allergic rhinitis medication prescription in young adulthood (ages 25.5-37.0 years)

Table 3

Outcome variable	Predictor variable	Unadjusted		Adjusted Model*		
		OR [†]	95% CI	OR [†]	P value	
Any nasal corticosteroids	Gestational age					
	<37 wks	0.91	0.88, 0.94	0.90	0.87, 0.93	<0.0001
	23-28 wks	0.87	0.66, 1.14	0.70	0.51, 0.96	<0.0001 ^{††}
	29-34 wks	0.85	0.80, 0.90	0.82	0.76, 0.88	
	35-36 wks	0.94	0.91, 0.98	0.94	0.90, 0.98	
	37-42 wks	1.00		1.00		
	≥43 wks	0.96	0.93, 1.00	0.93	0.89, 0.97	
	Fetal growth					
	<-2 SD	1.03	0.99, 1.07	0.95	0.91, 1.00	0.02 ^{††}
	-2 to <-1 SD	1.03	1.01, 1.06	0.98	0.96, 1.01	
Any oral antihistamines	-1 to <0 SD	1.02	1.01, 1.04	1.00	0.98, 1.02	
	0 to <1 SD	1.00		1.00		
	1 to <2 SD	0.97	0.95, 0.99	0.98	0.96, 1.00	
	≥2 SD	0.93	0.90, 0.96	0.96	0.92, 1.00	
	Gestational age					
	<37 wks	0.99	0.96, 1.02	0.96	0.93, 1.00	0.03
	23-28 wks	0.89	0.68, 1.17	0.66	0.48, 0.89	<0.0001 ^{††}
	29-34 wks	0.94	0.89, 1.00	0.89	0.83, 0.95	
	35-36 wks	1.01	0.98, 1.05	1.00	0.96, 1.05	
	37-42 wks	1.00		1.00		
Fetal growth						
<-2 SD	1.11	1.07, 1.15	0.99	0.95, 1.04	0.19 ^{††}	

Outcome variable	Predictor variable	Unadjusted			Adjusted Model*		
		OR [†]	95% CI	OR [†]	95% CI	P value	
Both nasal corticosteroids and oral antihistamines	-2 to <1 SD	1.09	1.06, 1.11	1.01	0.99, 1.04		
	-1 to <0 SD	1.05	1.03, 1.06	1.01	1.00, 1.03		
	0 to <1 SD	1.00		1.00			
	1 to <2 SD	0.96	0.94, 0.98	0.98	0.95, 1.00		
	≥2 SD	0.93	0.90, 0.96	0.96	0.92, 1.00		
Gestational age	<37 wks	0.95	0.90, 0.99	0.91	0.86, 0.96	0.0005	
	23-28 wks	0.68	0.43, 1.09	0.45	0.27, 0.76	0.0001 ^{††}	
	29-34 wks	0.87	0.80, 0.96	0.81	0.73, 0.89		
	35-36 wks	0.99	0.93, 1.04	0.97	0.91, 1.03		
	37-42 wks	1.00		1.00			
	≥43 wks	1.00	0.95, 1.06	0.96	0.90, 1.03		
Fetal growth	<2 SD	1.06	1.00, 1.13	0.94	0.88, 1.01	0.02 ^{††}	
	-2 to <1 SD	1.07	1.04, 1.10	1.00	0.97, 1.03		
	-1 to <0 SD	1.03	1.01, 1.06	1.00	0.97, 1.03		
	0 to <1 SD	1.00		1.00			
	1 to <2 SD	0.96	0.93, 0.99	0.97	0.94, 1.01		
	>2 SD	0.89	0.85, 0.94	0.92	0.87, 0.97		

* Adjusted model included gestational age at birth, fetal growth, age, gender, multiple gestation status, maternal age at delivery, maternal parity at delivery, maternal marital status, maternal education, family income, total number of all medication prescriptions, and maternal prescription of nasal corticosteroids or oral antihistamines during the follow-up period.

[†] All odds ratios for gestational age groups are relative to 37-42 weeks (full-term), and for fetal growth groups are relative to ≥0 and <1 SD from the reference birth weight for gestational age and sex.

^{††} Likelihood ratio test for departure from linear trend across ordinal categories.

Table 4

Adjusted odds ratios* for association between categorical model covariates and nasal corticosteroid prescription in young adulthood (ages 25.5-37.0 years)

	OR	95% CI	P value
Gender			
Female	1.00		
Male	1.16	1.14, 1.18	<0.001
Multiple gestation status			
Singleton	1.00		
Twin	0.89	0.83, 0.95	<0.001
Maternal age (years)			
<20	1.00		
20-24	1.13	1.09, 1.17	<0.001
25-29	1.20	1.16, 1.24	<0.001
30-34	1.21	1.17, 1.25	<0.001
≥35	1.21	1.16, 1.26	<0.001
Maternal parity			
1	1.00		
2	0.95	0.94, 0.97	<0.001
≥3	0.90	0.88, 0.92	<0.001
Maternal marital status in 1990			
Married/cohabiting	1.00		
Never married	0.84	0.82, 0.87	<0.001
Divorced	0.89	0.87, 0.91	<0.001
Widowed	0.94	0.88, 1.01	0.09
Maternal education in 1990 (years)			
Compulsory high school or less (≤9)	1.00		
Practical high school or some theoretical high school (10-11)	1.05	1.03, 1.07	<0.001
Theoretical high school and/or college (≥12)	1.05	1.02, 1.07	<0.001
Family income in 1990			
Lowest quartile	1.00		
Second quartile	1.04	1.02, 1.07	<0.001
Third quartile	1.07	1.05, 1.10	<0.001
Highest quartile	1.09	1.07, 1.12	<0.001
Maternal prescription of nasal corticosteroids during follow-up period			
0	1.00		
≥1	1.31	1.29, 1.34	<0.001
Maternal prescription of oral antihistamines during follow-up period			
0	1.00		
≥1	1.10	1.08, 1.12	<0.001

* The model included gestational age at birth, fetal growth, age, gender, multiple gestation status, maternal age at delivery, maternal parity at delivery, maternal marital status, maternal education, family income, total number of all medication prescriptions, and maternal prescription of nasal