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Hormonal factors and incident asthma and allergic rhinitis during puberty in girls

Junxiang Wei, MSc^{*}; Jessica Gerlich, Dr, MSc^{*}; Jon Genuneit, MD, MSc[†]; Dennis Nowak, MD^{*}; Christian Vogelberg, MD[‡]; Erika von Mutius, MD, MSc[§]; and Katja Radon, Dr, MSc^{*}

^{*} Occupational and Environmental Epidemiology & Net Teaching Unit, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU), Munich, Germany

[†] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

[‡] Pediatric Department, University Hospital Carl Gustav Carus Dresden, TU Dresden, Dresden, Germany

[§] Dr v Haunersches Kinderspital, University Hospital Munich (LMU), Munich, Germany

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ABSTRACT

Background: Accumulating evidence is indicating that hormonal factors play a role in new-onset allergic rhinitis and asthma after puberty.

Objective: To determine whether age at menarche and use of hormonal contraceptives predict new-onset allergic rhinitis and asthma after puberty in young German women.

Methods: A prospective community-based cohort study followed 1,191 girls 9 to 11 years old to early adulthood (19–24 years old). Self-administrated questionnaires concerning age at menarche, use of hormonal contraceptives, and status and age at onset of physician-diagnosed allergic rhinitis and asthma were collected at 16 to 18 and 19 to 24 years of age. Logistic regression models were used to analyze the incidence of asthma and allergic rhinitis after puberty and pooled estimates were obtained from the final model.

Results: Eleven percent of girls developed allergic rhinitis after menarche and 3% reported new-onset asthma. Late menarche (>13 years of age) was statistically significantly inversely related to allergic rhinitis (adjusted odds ratio [OR] 0.32, 95% confidence interval [CI] 0.14–0.74) but did not reach the level of statistical significance for asthma (OR 0.32, 95% CI 0.07–1.42). Use of hormonal contraceptives was inversely associated with new-onset allergic rhinitis (OR 0.14, 95% CI 0.08–0.23) and asthma (OR 0.27, 95% CI 0.12–0.58) after puberty.

Conclusion: This study shows that girls with late onset of menarche are less likely to develop allergic rhinitis after puberty compared with those who have menarche at an average age. These findings also suggest that, in addition to endogenous hormones, hormonal contraceptives play a role and might protect young women from allergies and asthma.

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Introduction

A potential role of sex differences in the etiology of asthma and allergies has been suspected. This is because the lifetime prevalence or incidence of asthma and allergic rhinitis is higher in boys than in girls before puberty but switches to a female preponderance after puberty.^{1–5} As a possible cause of this phenomenon, the relative size of the lung, airways, and their smooth muscle and

vascular functions have been discussed.⁶ Nevertheless, the association between female hormones and the course of asthma and allergic rhinitis has gained much attention recently.⁷

Menarche and hormonal contraceptive use are 2 main hormone-related events in young women. As such, these events determine cumulative estrogen exposure⁸ and therefore influence the levels and stability of female hormones. Epidemiologic studies have shown that early cumulative endogenous hormones double the risk of developing asthma.^{9,10} However, analyses of the association between exogenous hormones, such as hormonal contraceptives, and asthma have found positive and negative effects on asthma symptoms.^{9,11} Animal studies have provided evidence that estrogen and progesterone have effects on humoral and cellular immunity and smooth muscle function.¹² Therefore, hormonal factors might be expected to be associated with the clinical occurrence of asthma in humans.

Reprints: Jessica Gerlich, Dr, MSc, Occupational and Environmental Epidemiology & Net Teaching Unit, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU), Ziemssenstr 1, 80336 Munich, Germany; E-mail: jessica.gerlich@med.lmu.de.

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Compared with asthma, the association between female hormones and allergic rhinitis has been studied even less. Some studies have mainly assessed the impact of maternal oral contraceptive use on rhinitis in offspring, whereas studies on how oral contraceptive intake influences the incidence of allergic rhinitis in women themselves are sparse. Only 1 Danish study has associated early menarche with a higher risk of allergic rhinitis, especially in nulliparous women,¹³ but the cross-sectional design did not allow the detection of a causal association.

Most studies on age at menarche and asthma to date have examined the persistence or severity but not the incidence of asthma.^{14,15} In addition, the association between hormonal factors and incidence of allergic rhinitis has never been explored longitudinally. Therefore, this study investigated whether there are associations among age at menarche, hormonal contraceptive use, and new-onset allergic rhinitis and asthma after puberty in young women in a German cohort who participated in the International Study of Asthma and Allergies in Childhood (ISAAC) Phase II and were prospectively followed until young adulthood.

Methods

Study Population and Design

Participants of this study were a subset of the cohort enrolled in Munich and Dresden in 1995 and 1996 as the German part of the multicenter ISAAC Phase II. Detailed information on the study protocol and methods of this study has been described previously.^{16,17} In brief, a community-based sample was recruited from grade 4 pupils (9–11 years old) in these 2 cities. Parental questionnaires included core questions on asthma and allergic rhinitis and on environmental risk factors.¹⁸ Of the 7,498 parents who were asked to complete the questionnaire, 85% filled them in. In addition, a random sample of these children was examined for lung function and allergic sensitization by spirometry and skin prick test (SPT). Bronchial hyperresponsiveness (BHR) was tested using nebulized hypertonic saline.

To study the course of asthma and allergic rhinitis during puberty, a first follow-up study was conducted in 2002 through 2003 (Study on Occupational Allergy Risks [SOLAR], 16–18 years old). Of the 4,893 respondents who could be re-contacted, 3,785 adolescents (77%) participated and gave informed consent to combine the baseline and follow-up data. A second follow-up was done in 2007 through 2009 (SOLAR II, 19–24 years old). The enrollment process and methods were described in detail in a previous article.¹⁹ Self-administered questionnaires were used for collecting information on age at menarche in SOLAR I and hormonal contraceptive use in SOLAR II. Age at first asthma and allergic rhinitis attacks and status of smoking were queried at the 2 follow-ups. Examinations of BHR and SPT also were offered to these participants. All study phases were approved by the ethical committees of the Medical Faculty of the University of Dresden (Dresden, Germany) and the Bavarian Chamber of Physicians (Munich, Germany).

Variable Definition

Hormonal factors were the independent variables of interest in this study.

Age at menarche was based on the answer to the question, “At what age did you have your first menstrual period?” and was assessed in years only. Age at menarche was divided into 3 groups: early (less than mean – 1 SD), normal (mean $\pm$ 1 SD), or late (greater than mean + 1 SD).^{20,21}

Exposure to hormonal contraceptives was defined as taking hormonal contraceptives for at least 1 year before the occurrence of outcomes or taking hormonal contraceptives but not developing allergic rhinitis or asthma by the time of SOLAR II.

Participants who reported pregnancies were excluded from the analyses. On the one hand, there was inadequate information on the age of pregnancy in the data; on the other hand, pregnancy causes hormonal level fluctuations and therefore would interfere with the investigation of the role of age at menarche and hormonal contraceptive use.

Based on previous literature search, socioeconomic status (SES), body mass index (BMI), and smoking have been associated with onset of menarche or contraceptive usage and asthma or allergic rhinitis and therefore were considered potential confounders. SES was collected at baseline and was defined based on parental education level (eg, a high SES meant that either parent had qualified for university entrance or a university diploma). Information on BMI was collected at the second follow-up and was categorized as underweight (BMI <18.50 kg/m²), normal (18.50–24.99 kg/m²), or overweight (BMI $\geq$ 25 kg/m²) according to the international classification for adults. Smoking was initially classified as never or irregular smoker, ex-smoker, and current smoker. Cumulative smoking exposure of ex- and current smokers was quantified in pack-years by multiplying the duration of years smoked with the number of packs per day.²² Subjects were classified as never or irregular smoker (0 pack-year), light smoker (<1.5 pack-years), moderate smoker (1.5–3.8 pack-years), or heavy smoker (>3.8 pack-years). The cutoff points of pack-years were based on tertiles, with the aim of dividing smokers into equal-size groups.

At baseline and the 2 follow-ups, asthma was defined based on parental or self-report of physician diagnosis of asthma according to the question, “Have you ever been diagnosed with asthma or asthmatic bronchitis by a physician?” Allergic rhinitis was defined as a reported nasal allergy ever diagnosed by a physician based on this question, “Have you been diagnosed with nasal allergies such as hay fever by a physician?”

For asthma and allergic rhinitis, participants also were asked when they had their first attack and the age was assessed in whole years. New onset was defined as developing the respective disease at least 1 year after menarche. Subjects whose age at menarche was equal to or older than the age at onset of the respective disease or who provided insufficient or implausible information regarding the exposures or outcomes were excluded from the analyses.

The spirometric parameters forced expiratory volume in 1 second and forced vital capacity were used to indicate airway obstruction. An obstructive pulmonary defect was defined by a decreased ratio of forced expiratory volume in 1 second to forced vital capacity below the fifth percentile of the lower limit of normal suggested by the Global Lung Function Initiative²³ and guidelines of the American Thoracic Society and European Respiratory Society.²⁴ New occurrence of an obstructive pulmonary defect or BHR was defined as the absence of an obstructive pulmonary defect or BHR at baseline but its presence at SOLAR II. Positive sensitization response to an allergen was defined as a wheal at least 3 mm larger than the negative control reaction. The definition of new allergic sensitization in SOLAR II was a negative SPT response at baseline but a positive response at second follow-up.

To maximize the sample size for analyses, complete case analysis was performed separately for each of the 2 outcomes of interest.

Statistical Methods

Bivariate logistic regression was used to evaluate associations between the 2 exposures (age at menarche and hormonal contraceptive use) and incidence of asthma and allergic rhinitis, in addition to the potential confounding factors BMI, SES, and smoking. In addition, the Jonckheere-Terpstra test²⁵ was applied to test for a possible trend of differential new-onset asthma and

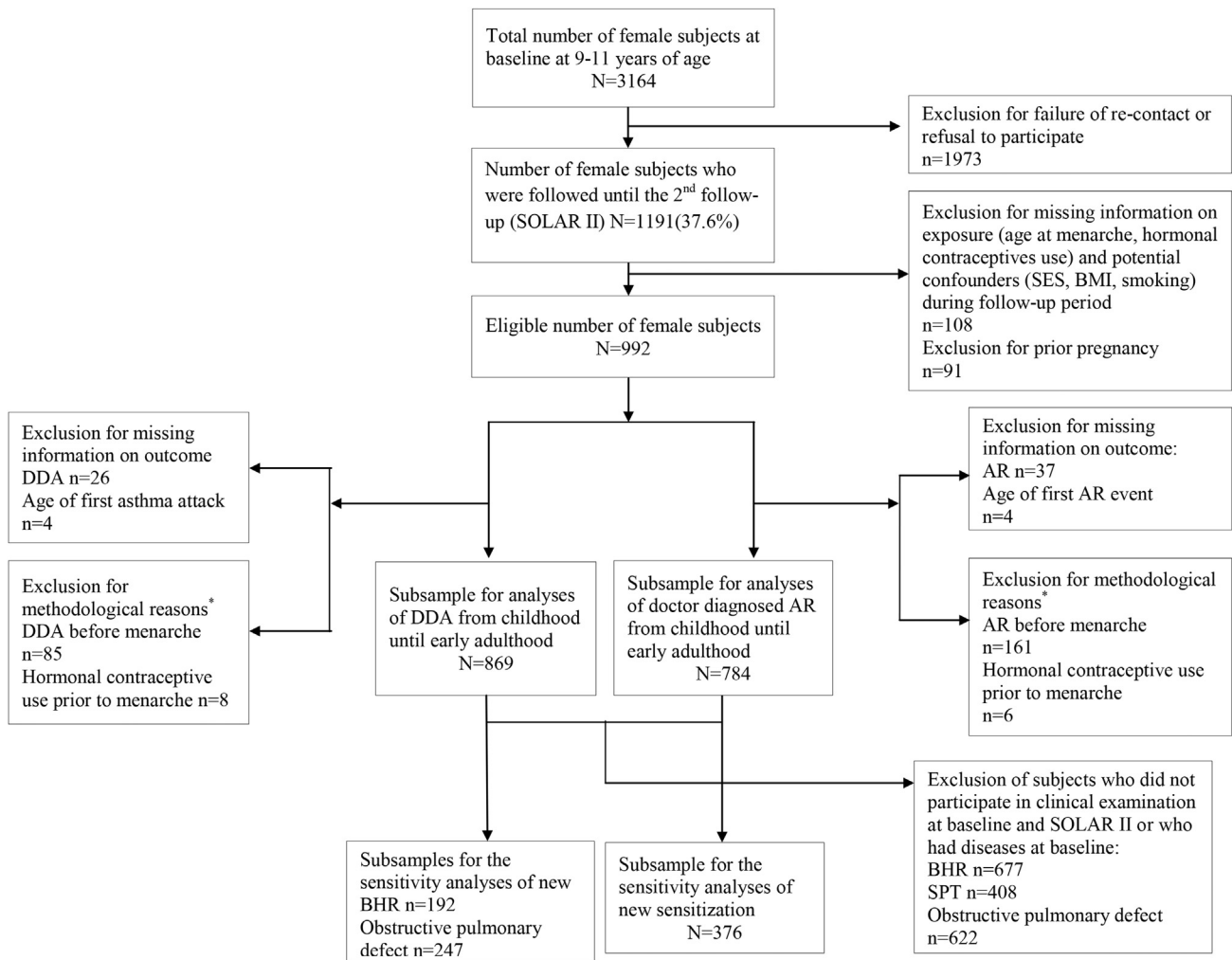


Figure 1. Subsamples for study population from baseline (1995–1996) until second follow-up (2007–2009). *Detailed information is presented in the Methods section. AR, allergic rhinitis; BHR, bronchial hyperresponsiveness; BMI, body mass index; DDA, physician-diagnosed asthma; SES, socioeconomic status; SOLAR II, Study on Occupational Allergy Risks II; SPT, skin prick test.

allergic rhinitis by age at menarche. Crude odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were evaluated. Any confounding factor with a statistically significant association in the preceding bivariate logistic regression models was included in the final multiple logistic regression models. Thereafter, adjusted ORs were calculated to assess the pooled effect of each exposure on asthma and allergic rhinitis incidences. Bivariate and multiple logistic regression models also were fitted using new occurrence of an obstructive pulmonary defect, BHR, and SPT as outcomes to assess the effect of these exposures on clinical measurements. The associations of incidence of physician-diagnosed asthma and allergic rhinitis with age at menarche and use of hormonal contraceptives also were analyzed in the subsets of the study population tested for pulmonary lung function, BHR, and SPT to assess the representativeness of the subset regarding these associations. Agreements between pulmonary function or BHR and physician-diagnosed asthma and between SPT and physician-diagnosed allergic rhinitis were evaluated by calculating the proportions of the overall agreement. Sensitivity and specificity of spirometry, BHR, and SPT also were assessed based on physician diagnosis of asthma and allergic rhinitis. All statistical analyses were performed using SPSS 21 for Windows (SPSS, Inc, Chicago, Illinois). All tests were 2-sided and a *P* value less than .05 was considered statistically significant.

Results

At baseline, 3,164 female participants completed the questionnaires and 1,191 (38%) were followed until SOLAR II. One hundred ninety-nine participants (17%) were excluded from analyses because of pregnancy (8%) or missing information (9%) on exposure or potential confounding variables. Moreover, some were excluded from the analyses because of premenarcheal asthma or allergic rhinitis, resulting in 869 and 748 complete cases for asthma and allergic rhinitis, respectively. The proportions for clinical measurements were 22% for lower pulmonary function and 51% for allergic sensitization (Fig 1).

The average age at menarche was 12.6 years (range 8–16 years, SD 1.2 years). According to the definition in the present study, 19% of participants had early (<12 years) and 23% had late menarche (>13 years). Of eligible female subjects, 73% had been taking an oral contraceptive or other hormonal contraceptives for at least 1 year by the end of the study. At follow-up, the cumulative incidences of allergic rhinitis and asthma at least 1 year after menarche were 83 (11%) and 27 (3%), respectively (Table 1).

In the bivariate analysis, early menarche was not associated with new-onset asthma or allergic rhinitis when using normal age at menarche as the reference. Late menarche was associated with a decreased incidence of allergic rhinitis (OR 0.35, 95% CI 0.15–0.78)

Table 1
Demographic and social characteristics of eligible study participants (n = 992)

	Values	Missing data, n (%)
Age baseline (y), mean (SD)	9.6 (0.5)	3 (<0.1)
Age at second follow-up (y), mean (SD)	21.7 (0.7)	0 (0)
Age at menarche (y), mean (SD)	12.6 (1.2)	0 (0)
Age at menarche in categories, n (%)		43 (3.6)
Early (<12 y)	190 (19)	
Normal (12–13 y)	576 (58)	
Late (>13 y)	226 (23)	
Hormonal contraceptive use, n (%)		17 (1.4)
Nonuser	271 (27)	
User	721 (73)	
SES at baseline, n (%) ^a		23 (1.9)
Low	398 (40)	
High	594 (60)	
BMI categories at second follow-up, n (%)		10 (0.8)
Underweight (<18.50 kg/m ²)	87 (9)	
Normal weight (18.50–24.99 kg/m ²)	769 (78)	
Overweight (≥25 kg/m ²)	136 (14)	
Smoking at second follow-up, n (%) ^b		30 (2.5)
Never or irregular smoker	550 (56.8)	
Light smoker	142 (14.7)	
Moderate smoker	139 (14)	
Heavy smoker	137 (14)	

Abbreviations: BMI, body mass index; SES, socioeconomic status.

^aBased on parental education level: high means either parent had qualified for university entrance or a university diploma.^bNever or irregular smoker was defined as smoking fewer than 20 packs of cigarettes in a lifetime or fewer than 1 cigarette per day or 1 cigar per week for a year. Based on pack-years of smoking for adolescents in this study, light, moderate, and heavy smokers were classified as less than 1.5, 1.5 to 3.8, and more than 3.8 pack-years, respectively.

but did not reach statistical significance for asthma (OR 0.33, 95% CI 0.08–1.44). However, trend values from the Jonckheere-Terpstra test indicated that a later menarche implied a lower likelihood of development of allergic rhinitis (*P* for trend = .001) or asthma (*P* for trend = .018). Likewise, use of hormonal contraceptives was associated with decreased incidence of allergic rhinitis (OR 0.14, 95% CI 0.08–0.24) and asthma (OR 0.27, 95% CI 0.12–0.58). Because no statistically significant association was observed between the potential confounders and new-onset asthma and allergic rhinitis,

only age at menarche and use of hormonal contraceptives were included in the final logistic regression models. In the final models, the adjusted estimates remained unchanged (Table 2).

Clinical data showed that use of hormonal contraceptives was a protective factor against developing new-onset BHR (OR 0.7, 95% CI 0.3–1.7) but a risk factor for an obstructive pulmonary defect (OR 4.4, 95% CI 0.5–34.1), although the associations were not statistically significant. There were statistically significant associations between decreased new allergic sensitization and late menarche (OR 0.42, 95% CI 0.23–0.79) and hormonal contraceptive use (OR 0.52, 95% CI 0.33–0.83). A trend toward a lower risk of incident BHR or new sensitization from early to late menarche was observed for an obstructive pulmonary defect but not for BHR and SPT. The estimates did not change after mutual adjustment of exposures (Table 3). Further analyses of the associations of incident physician-diagnosed asthma and allergic rhinitis with age at menarche and hormonal contraceptive use within this subsample are presented in the supplementary material (eTable 1).

The overall agreement between lung function and physician-diagnosed asthma was 93% at baseline and 87% at SOLAR II compared with 84% and 77% for the agreement of BHR and physician-diagnosed asthma at each study point. For SPT and physician-diagnosed allergic rhinitis, the overall agreements at baseline and SOLAR II were 86% and 75%, respectively. The sensitivity and specificity for spirometry, BHR, and SPT concerning physician diagnosis of asthma and allergic rhinitis are presented in eTable 2.

Discussion

This study showed that late menarche was a protective factor against new-onset allergic rhinitis. Moreover, there was a trend showing that a later menarche indicated a lower likelihood of developing allergic rhinitis or asthma, although the association for asthma was not statistically significant. In addition, hormonal contraceptive use was inversely related to new-onset asthma and allergic rhinitis after puberty independent of age at menarche.

This study sought to observe the effects of hormonal factors on new-onset asthma and for the first time addressed the association between hormonal contraceptive use and incidence of allergic

Table 2
Proportions of exposures and variables of interest and their crude and adjusted associations with new-onset asthma and allergic rhinitis after puberty

	New-onset asthma after puberty					New-onset allergic rhinitis after puberty				
	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age at menarche in categories										
Early (<12 y)	154	9	6	1.82 (0.79–4.20)	1.87 (0.80–4.37)	128	23	15	1.41 (0.83–2.39)	1.50 (0.85–2.63)
Normal (12–13 y)	498	16	3	1	1	415	53	11	1	1
Late (>13 y)	190	2	1	0.33 (0.08–1.44)	0.32 (0.07–1.42)	158	7	4	0.35 (0.15–0.78)	0.32 (0.14–0.74)
Hormonal contraceptives										
Nonuser	238	16	6	1	1	199	61	24	1	1
User	604	11	2	0.27 (0.12–0.59)	0.27 (0.12–0.58)	502	22	4	0.14 (0.08–0.24)	0.14 (0.08–0.23)
SES at baseline ^a										
Low	327	13	4	1		277	35	11	1	
High	515	14	3	0.68 (0.32–1.47)		424	48	10	0.90 (0.56–1.42)	
BMI in categories at second follow-up										
Underweight (<18.50 kg/m ²)	71	4	5	2.05 (0.68–6.24)		69	4	6	0.48 (0.17–1.38)	
Normal weight (18.50–24.99 kg/m ²)	656	18	3	1		533	64	11	1	
Overweight (≥25 kg/m ²)	115	5	4	1.58 (0.58–4.35)		99	15	13	1.26 (0.69–2.30)	
Smoking at second follow-up ^b										
Never or irregular smoker	476	12	3	1		393	41	9	1	
Light smoker	120	4	3	1.32 (0.42–1.17)		98	10	9	0.98 (0.47–2.02)	
Moderate smoker	119	3	3	1.00 (0.28–3.60)		96	15	14	1.50 (0.80–2.82)	
Heavy smoker	109	7	6	2.55 (0.98–6.62)		99	16	14	1.55 (0.84–2.88)	

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; SES, socioeconomic status.

^aBased on parental education level: High means either parent had qualified for university entrance or university diploma.^bNever or irregular smoker was defined as smoking fewer than 20 packs of cigarettes in a lifetime or fewer than 1 cigarette per day or 1 cigar per week for a year. Cumulative smoking exposure was determined in terms of pack-years based on duration of years smoked and number of packs smoked per day. Based on pack-years of smoking for adolescents in this study, light, moderate, and heavy smokers were classified as less than 1.5, 1.5 to 3.8, and more than 3.8 pack-years, respectively. Nineteen smokers for new-onset asthma and 16 smokers for new-onset AR were excluded due to lack of information on pack-years of smoking.

Table 3
Proportions of exposures and variables of interest and crude and adjusted associations with new obstructive pulmonary defect, new bronchial hyperresponsiveness, and new sensitization

	Obstructive pulmonary defect (n = 247)					Bronchial hyperresponsiveness (n = 192)					Skin prick test (n = 376)				
	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age at menarche in categories															
Early (<12 y)	42	3	7	1.9 (0.4–8.8)	1.9 (0.4–8.9)	31	4	11	0.5 (0.2–1.7)	0.5 (0.2–1.7)	51	21	29	0.7 (0.4–1.3)	0.7 (0.4–1.3)
Normal (12–13 y)	140	4	3	1	1	95	23	20	1	1	144	84	37	1	1
Late (>13 y)	55	3	5	2.5 (0.5–11.6)	2.4 (0.5–11.4)	32	7	18	0.9 (0.4–2.3)	0.9 (0.4–2.4)	61	15	20	0.4 (0.2–0.8)	0.4 (0.2–0.8)
Hormonal contraceptives															
Nonuser	61	1	2	1	1	37	10	21	1	1	68	49	42	1	1
User	176	9	5	3.1 (0.4–25.1)	3.1 (0.4–24.8)	121	24	17	0.7 (0.3–1.7)	0.7 (0.3–1.7)	188	71	27	0.5 (0.3–0.8)	0.5 (0.3–0.8)
SES at baseline ^a															
Low	93	5	5	1	1	56	13	19	1	1	98	49	33	1	1
High	144	5	3	0.6 (0.2–2.3)		102	21	17	0.9 (0.4–1.9)		158	71	31	0.9 (0.6–1.4)	
BMI in categories at second follow-up															
Underweight (<18.50 kg/m ²)	13	1	7	1.9 (0.2–16.2)		5	4	44	3.9 (1.0–15.7)		28	8	22	0.6 (0.3–1.4)	
Normal weight (18.50–24.99 kg/m ²)	195	8	4	1	1	134	27	17	1	1	198	95	32	1	1
Overweight (≥25 kg/m ²)	29	1	3	0.8 (0.1–6.9)		19	3	14	0.8 (0.2–2.8)		30	17	36	1.2 (0.6–2.3)	
Smoking at second follow-up ^b															
Never or irregular smoker	148	4	3	1	1	99	19	16	1	1	149	72	33	1	1
Light smoker	34	3	8	3.3 (0.7–15.3)		26	6	19	1.2 (0.4–3.3)		34	17	33	1.0 (0.5–1.9)	
Moderate smoker	31	1	3	1.2 (0.1–11.0)		18	3	14	0.9 (0.2–3.2)		36	16	31	0.9 (0.5–1.8)	
Heavy smoker	24	2	8	3.1 (0.5–17.8)		14	4	22	1.5 (0.4–5.0)		31	15	33	1.0 (0.5–1.9)	

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; SES, socioeconomic status.

^aBased on parental education level: High means either parent had qualified for university entrance or university diploma.^bNever or irregular smoker was defined as smoking fewer than 20 packs of cigarettes in a lifetime or fewer than 1 cigarette per day or 1 cigar per week for a year. Based on pack-years of smoking for adolescents in this study, light, moderate, and heavy smokers were classified as less than 1.5, 1.5 to 3.8, and more than 3.8 pack-years, respectively. Five, 3, and 6 smokers for obstructive pulmonary defect, bronchial hyperresponsiveness, and skin prick test, respectively, were excluded due to lack of information on pack-years of smoking.

rhinitis. Menarche is prominent in the puberty transition and is a surrogate of maturation and the starting point of reproductive life for women. Hormones are changing substantially at menarche, especially endogenous sex steroid hormones. Furthermore, early menarche has been involved in several health issues, including breast cancer²⁶ and cardiovascular disease,²⁷ indicating that changes of hormone levels have effects on health outcomes. Aside from menarche, which interferes with hormonal levels in early adolescence, hormonal contraceptive use is a behavior that is observed commonly from puberty onward. It interacts with the endocrine system directly and then alters the overall hormonal conditions.

This study suggests that late menarche is a strong protective factor against allergic rhinitis. This finding is in line with the result from a cross-sectional Danish study conducted in 31,145 participants.¹³ This study showed an increasing likelihood of allergic rhinitis with decreasing age at menarche ($P = .003$).

Evidence of an inverse association between hormonal contraceptive use and asthma or allergic rhinitis in this study confirmed results from some previous studies. Salam et al⁹ tried to shed light on the association between oral contraceptive use and current wheeze and found that this inverse association held true only in women with a history of asthma (OR 0.18, 95% CI 0.06–0.56). Findings from Jenkins et al²⁸ reported a decreased asthma prevalence with an increasing number of years of oral contraceptive use. However, the present findings conflict with analyses from a Nordic-Baltic population survey that suggested that use of oral contraceptives was associated with an increased risk for asthma in normal-weight and overweight women.²⁹ Nevertheless, the different study design and analysis and differences in measurements of outcomes impede a comparison of the results. In particular, different inclusion and exclusion criteria and different definitions of asthma outcome might lead to recruitment of subjects with distinct pathophysiology.³⁰ For instance, the present participants ranged from adolescent girls to young women, whereas heavier and older (25–44 years) adults were included in a study by Macsali et al,²⁹ which might indicate different asthma endotypes.³⁰ To the authors' knowledge, there are no other studies published that have investigated the influence of hormonal contraceptives on allergic rhinitis.

Based on the present results, there seemed to be an inverse dose–response relation between age at menarche and incidence of asthma, with earlier menarche being associated with a higher risk of developing asthma after puberty. This is consistent with some previous studies with respect to the influence of early menarche on asthma. For example, a national longitudinal study of 1,176 young Canadian women 18 to 21 years old showed that girls who matured very young had more than twice the risk of developing asthma than those who matured late (OR 2.34, 95% CI 1.19–4.59).¹⁰ A previous study indicated that compared with girls who had menarche after 12 years of age, those who had their menarche before 12 years had a more than 2-fold higher risk of asthma after puberty (OR 2.08, 95% CI 1.05–4.12).⁹

The underlying mechanisms of associations between hormonal factors and allergic rhinitis or asthma are largely unknown, but plausible explanations have implied a role for gonadotropin-releasing hormone and the estradiol indices. Early menarche is associated with an increased serum concentration of follicle-stimulating hormone, a higher circulating estradiol concentration, and a lower serum sex hormone-binding globulin level.^{31,32} In addition, gonadotropin-releasing hormone agonist, which is a treatment for controlling premature activation of the hypothalamic–pituitary–ovarian axis, could bring the age of menarche in girls with central precocious puberty close to that of the general population.³³ Thus, girls who had late menarche might have had less exposure to gonadotropins compared with girls with

early-onset menarche. A case study has shown that suppression of gonadotropin secretion results in improvement in respiratory symptoms.³⁴ In addition, an animal study has shown that estrogen can promote the release of histamine and serotonin from rat mast cells.³⁵ Moreover, estrogen has a proinflammatory effect³⁶ and enhances eosinophil to human mucosal endothelial cells.³⁷ These pathophysiologic findings could account for the association and dose–response relation between age at menarche and incidence of allergic rhinitis and asthma after puberty.

The inverse association between hormonal contraceptive use and new-onset allergic rhinitis and asthma can be attributed in part to the fact that hormonal contraceptives influence pituitary and ovarian functions and therefore affect airway activities.³⁸ One study has shown that basal luteinizing hormone, follicle-stimulating hormone, and gonadotropin response to gonadotropin-releasing hormone are significantly suppressed in women receiving 3 months of hormonal contraception.³⁹ Further, oral contraceptives have been found to suppress the luteal phase increase in sex hormones and to attenuate airway reactivity.³⁸ However, why are findings from existing studies about the effects of oral contraceptives on the incidence of asthma inconsistent?^{9,28,29,40–42} The authors speculate that this might be due to the different compositions of the hormonal contraceptives, ie, combinations of estrogen and progesterone or progesterone only.⁴³ A hormone replacement therapy study has found that the use of estrogen alone as a treatment is statistically significantly associated with an increased risk of asthma onset in postmenopausal women compared with the use of combined estrogen-and-progesterone treatment.⁴⁴ Unfortunately, the comparison of the content of this hormone replacement therapy with that of the contraceptives used in the present study population was not feasible because no information about the composition of the hormonal contraceptives was available.

Analyses of the clinical data showed the same directionality of the associations of late menarche and use of hormonal contraceptives with pulmonary lung function, BHR, and sensitization compared with the primary analyses, except for the association between hormonal contraceptive use and an obstructive pulmonary defect (not statistically significant). In addition, the trend effects of age at menarche disappeared when using BHR and SPT as outcomes and girls who had had early menarche seemed to have a lower risk of developing airway responsiveness and sensitization compared with those who had normal onset of menarche. Nonetheless, analyses of the correlations of incidence of physician-diagnosed asthma and allergic rhinitis with age at menarche and use of hormonal contraceptives in the subsets tested for pulmonary lung function, BHR, and SPT showed that the trends in effect remained the same except between late menarche and physician diagnosis of asthma (eTable 1). Therefore, the subsets with clinical data were overall representative of the primary study sample with regard to these associations of the primary outcomes. From this point of view, the discrepant associations of hormonal contraceptive use and an obstructive pulmonary defect in the primary samples and clinical subsamples in the present study seem in line with findings from Salam et al⁹ that hormonal contraceptive use was associated with a high risk of current wheezing in women without asthma, which might imply a different biological response of existing asthma status to the exogenous hormones. Moreover, airway obstruction, BHR, and SPT were basically point prevalences at the time of examination during 2 visits, and their exact time of onset is unknown. Thus, new onset of an obstructive pulmonary defect or BHR and new SPT are not concordant with new-onset asthma and allergic rhinitis, and the estimates from the 2 analyses are not necessarily comparable.

The overall agreement between airway obstruction and physician-diagnosed asthma is relatively high and therefore supports the diagnosis of asthma. The agreement between BHR and

physician-diagnosed asthma is characterized by a low sensitivity and high specificity for BHR (eTable 2). This also might account for the difference of the results between the main analyses and the analyses of using clinical measurements and implies that BHR might be a necessary but insufficient condition for asthma. Asthma can be variably defined, but physician diagnosis of asthma and allergic rhinitis are frequently used in large-scale epidemiologic studies.¹⁶ As a result, the findings of the present study rely on the main analyses to evaluate the incidence of asthma and allergic rhinitis, and results from clinical measurements should be interpreted with caution.

Limitations and Strengths

In this study, age at menarche and years of hormonal contraceptive use were the key exposure variables that were collected retrospectively from self-administrated questionnaires completed by the study participants. One might argue that this could have introduced recall bias and resulted in misclassification for the exposures. However, women are very likely to remember their first period and when they first used hormone contraception. In addition, self-reported age at menarche has been shown to be reliable within the first 5 years after menarche,^{45,46} indicating that it is a suitable measurement for the present study. Moreover, it is very likely that misclassification of this exposure would have been nondifferential, resulting in a bias toward the null. Similarly, the 2 primary outcomes were assessed based on self-reported age at the first attack of asthma and allergic rhinitis and physician diagnosis of asthma and allergic rhinitis at each of 2 follow-up studies. Symptoms of asthma and allergic rhinitis, such as wheezing and rhinoconjunctivitis, usually precede actual attacks of asthma and allergic rhinitis. Some girls might have had asthma or allergic rhinitis symptoms before the onset of menarche and before beginning hormonal contraceptive use but had their first attack of disease afterward, which might have led to some misclassification of disease onset. However, participants were more likely to correctly remember the age at their first attack of disease than the age when they had the first less specific symptoms. Therefore, a combination of age at first attack and physician's diagnoses was deliberately chosen to define the outcomes because it is more specific than a definition based on symptoms and thus lowers the risk of overestimation by avoiding false-positive reporting. In addition, subjects with asthma or allergic rhinitis commonly are more careful with answers to questions regarding their problems than those without those conditions. Furthermore, the additional cues and probing in the questionnaire would be expected to minimize recall errors, and agreement between the first and second follow-ups was good for age at asthma onset (82%), indicating that the information is reasonably reliable.

The number of incident cases in the present study was small, particularly for asthma onset (3%) and for an obstructive pulmonary defect (5%), which led to a lower statistical power and very wide CIs. Therefore, it cannot be excluded that the lack of statistical significance for the association between the exposures under study and new onset of asthma might be attributed to the small number of cases in this study population. Therefore, these results should be interpreted cautiously; further studies on this aspect with larger numbers and greater statistical power are needed.

A large portion of the initial sample was lost to follow-up for various reasons. Selection bias has been considered in a nonresponder analysis in a previous publication.²⁸ Children whose parents had a higher SES or who themselves had atopy or respiratory symptoms at baseline were more likely to participate in the follow-up studies. However, SES did not confound the present results and the authors do not believe that this self-selection was associated with age at menarche or oral contraceptive use.

Strengths of this study include its community-based prospective design, the study sample size, and the low likelihood of recall bias.

In addition, 3 variables were selected as potential confounders based on a review of the previous literature^{47–50} to increase statistical power by using parsimonious final models. None of them was associated with either outcome.

In conclusion, this study adds to the growing evidence that hormonal factors are associated with asthma and allergic rhinitis and even contribute to the incidence of these diseases. This first attempt of investigating the effects of hormonal contraceptives on the incidence of asthma and allergic rhinitis suggests that exogenous hormones protect young women against new-onset allergic rhinitis or asthma after puberty.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anaai.2015.04.019>.

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eTable 1

Simple and multiple logistic regressions for incident asthma and allergic rhinitis within the subsample of subjects who participated in the clinical examination

	New-onset asthma after puberty in subset tested for obstructive pulmonary defect (n = 247)					New-onset asthma after puberty in subset tested for BHR (n = 192)					New-onset allergic rhinitis after puberty in subset tested for SPT (n = 376)				
	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	No	Yes	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age at menarche in categories															
Early (<12 y)	43	2	4	1.3 (0.2–6.9)	1.4 (0.3–7.4)	33	2	6	3.5 (0.5–25.9)	3.9 (0.5–19.8)	61	11	15	1.5 (0.7–3.3)	1.8 (0.8–4.2)
Normal (12–13 y)	139	5	4	1	1	116	2	2	1	1	204	24	11	1	1
Late (>13 y)	57	1	2	0.5 (0.1–4.3)	0.5 (0.1–4.3)	38	1	3	1.5 (0.1–17.3)	1.7 (0.2–20.3)	75	1	1	0.1 (0.1–0.9)	0.1 (0.1–0.9)
Hormonal contraceptives															
Nonuser	58	4	7	1	1	44	3	6	1	1	91	26	22	1	1
User	181	4	2	0.3 (0.1–1.3)	0.3 (0.1–1.3)	143	2	1	0.2 (0.1–1.3)	0.2 (0.1–1.2)	249	10	4	0.1 (0.1–0.3)	0.1 (0.1–0.3)
SES at baseline ^a															
Low	93	5	5	1		66	3	4	1		132	15	10	1	
High	146	3	2	0.4 (0.1–1.6)		121	2	2	0.4 (0.1–2.2)		208	21	9	0.9 (0.4–1.8)	
BMI in categories at second follow-up															
Underweight (<18.50 kg/m ²)	11	3	21	— ^c		6	3	33	— ^c		35	1	3	0.3 (0.1–2.1)	
Normal weight (18.50–24.99 kg/m ²)	201	2	1	—		160	1	1	—		266	27	9	1	
Overweight (≥25 kg/m ²)	27	3	10			21	1	5	—		39	8	17	2.0 (0.9–4.8)	
Smoking at second follow-up ^b															
Never/irregular smoker	147	5	3	—		117	1	1	—		200	21	10	1	
Light smoker	35	2	5	—		30	2	6	—		47	4	8	0.8 (0.3–2.5)	
Moderate smoker	31	1	3	—		20	1	5	—		47	5	10	1.0 (0.4–2.8)	
Heavy smoker	26	0	0	—		18	0	0	—		41	5	11	1.2 (0.4–3.3)	

Abbreviations: AR, allergic rhinitis; BHR, bronchial hyperresponsiveness; BMI, body mass index; CI, confidence interval; OR, odds ratio; SES, socioeconomic status; SPT, skin prick test.

^aBased on parental education level: High means either parent had qualified for university entrance or university diploma.^bNever or irregular smoker was defined as smoking fewer than 20 packs of cigarettes in a lifetime or fewer than 1 cigarette per day or 1 cigar per week for a year. Based on pack-years of smoking for adolescents in this study, light, moderate, and heavy smokers were classified as less than 1.5, 1.5 to 3.8, and more than 3.8 pack-years, respectively. Three and 6 smokers for new onset of asthma and allergic rhinitis, respectively, were excluded due to lack of information on pack-years of smoking.^cThe OR and 95% CI are missing due to the small number of incident cases in each category.

eTable 2

Prevalences of BHR and SPT in a subsample of subjects who underwent clinical examinations and prevalence of self-reported physician-diagnosed asthma and allergic rhinitis at baseline and second follow-up

	PDA				Physician-diagnosed AR							
	Yes		No		Yes				No			
	n	%	n	%	n	%	n	%	n	%		
BHR												
Baseline	SPT											
Yes	1	8 ^a	21	11	Yes	33	80 ^c	69	13			
No	11	92	173	89 ^a	No	8	20	458	87 ^c			
Total	12	100	194	100	Total	41	100	527	100			
Second follow-up												
Yes	6	40 ^a	38	20	Yes	121	92 ^c	133	31			
No	9	60	153	80 ^a	No	11	8	303	69 ^c			
Total	15	100	191	100	Total	132	100	436	100			
Obstructive pulmonary defect												
Baseline												
Yes	4	9 ^b	2	1								
No	17	81	259	99 ^b								
Total	21	100	261	100								
Second follow-up												
Yes	6	21 ^b	13	5								
No	23	79	245	95 ^b								
Total	29	100	258	100								

Abbreviations: AR, allergic rhinitis; BHR, bronchial hyperresponsiveness; PDA, physician-diagnosed asthma; SPT, skin prick test.

^aAgreement between BHR and PDA.

^bAgreement between obstructive pulmonary defect and PDA.

^cAgreement between SPT and physician-diagnosed AR.