Endogenous and exogenous sex steroid hormones and asthma and wheeze in young women

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Background: Emerging evidence suggests that both endogenous and exogenous sex steroid hormones may influence the occurrence of asthma and wheeze among women.

Objective: We investigated the associations between exogenous sex hormone (oral contraceptive [OC]) use and wheezing in young women with and without asthma history. To investigate the role of endogenous sex hormones, we examined the association between age at menarche and the development of asthma after puberty.

Methods: We conducted a study among 905 women who had undergone menarche. Subjects were between 13 and 28 years of age and had participated in the Children's Health Study.

Results: In women without asthma, OC use was associated with higher risk of current wheeze (odds ratio [OR], 1.75; 95% CI, 1.15-2.65). In contrast, OC use was associated with a markedly reduced prevalence of current wheeze in women with a history of asthma (OR, 0.18; 95% CI, 0.06-0.56; *P* value for interaction = .003). These associations showed significant trends with duration of OC use. Age at menarche was associated with new-onset asthma after puberty. Compared with women who had menarche after age 12 years, women with menarche before age 12 years had a 2.08-fold (95% CI, 1.05-4.12) higher risk of asthma after puberty.

Conclusion: Both endogenous and exogenous sex steroid hormones affect asthma and wheeze occurrences in young women.

Clinical implications: Because women have higher asthma risk after puberty, and OC use is common among young women, clinicians may inform women with asthma about the potential effects of OC on asthma-related respiratory symptoms. (J Allergy Clin Immunol 2006;117:1001-7.)

Key words: *Oral contraceptives, sex hormones, estrogen, progesterone, puberty, menarche, wheeze, asthma*

Abbreviations used

AHR: Airway hyperresponsiveness
BMI: Body mass index
CHS: Children's Health Study
HR: Hazard ratio
OC: Oral contraceptive
OR: Odds ratio
PEFR: Peak expiratory flow rate
SES: Socioeconomic status

Accumulating evidence indicates that both endogenous and exogenous sex steroid hormones can modulate pulmonary inflammatory processes and smooth muscle function, and thereby play a role in the occurrence of asthma and wheeze in women.[1-3] Studies have shown that young women after puberty are at higher risk of asthma than young men,[4-6] and asthma incidence decreases after menopause.[7] These findings are consistent with estrogens and progestins playing a role in asthma incidence after puberty. Although early age at puberty has been associated with asthma persistence in women independent of body mass index (BMI)[8] and asthma symptoms in obese women,[9] to our knowledge, the effect of early puberty on asthma occurrence in young women has not been examined in detail.

Beyond the potential role of endogenous sex hormones in asthma occurrence among young women after puberty, existing evidence also suggests that oral contraceptive (OC), an exogenous sex hormone preparation that young women use commonly, can affect asthma or atopic phenotypes, and the effects may differ in women with and without pre-existing asthma. In women using OC, Siroux et al[10] observed elevated serum IgE levels and greater numbers of positive skin prick tests in women without asthma; however, no significant change was detected in women with asthma. In another study conducted in women with asthma, Tan et al[11] observed increased airway hyperresponsiveness (AHR) to adenosine monophosphate with significant diurnal variation in peak expiratory flow rates (PEFRs) with lower PEFR in the morning compared with levels in the evening in women not using OC; however, in women who were using OC, there was no change in AHR and diurnal PEFR variability.

On the basis of this existing evidence, we aimed to test 2 hypotheses in a prospective study conducted among young women who had participated in the Children's

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Health Study (CHS): (1) early age at menarche (a surrogate for early puberty) is associated with asthma occurrence after puberty, and (2) the association between OC use and current wheeze and current exercise-induced wheeze (important symptoms of asthma) differs by preexisting asthma status.

METHODS

Study design and subject enrollment

Details of the CHS have been described previously.[12,13] In brief, the CHS was a population-based study that examined the determinants of respiratory health in 6259 school age children (3245 girls and 3014 boys) who were recruited from public school classrooms located in 12 Southern California communities. We recruited 4th grade (n = 2192), 7th grade (n = 1048), and 10th grade (n = 938) students during 1993 and 1994 and another cohort of 4th grade students (n = 2081) during 1995 and 1996. The University of Southern California Institutional Review Board reviewed and approved the study. Written informed consent by parent or guardian was obtained at the onset of the CHS. By 1997, 3489 children (ie, 55.7% of the original CHS cohort; 1792 girls and 1697 boys) graduated or left their schools; we planned to follow up these children to obtain information on their respiratory health outcomes. The remaining 44.3% of the original CHS cohort (n = 2770; 1453 girls and 1317 boys) were actively followed annually at their respective schools.

We collected information on age at menarche, oral contraceptive use, and marital status from children who moved or graduated, because these data were collected either from mail-out questionnaire or from personal interview with the study subject. However, we did not collect such information from children followed annually at their schools for privacy concerns. Therefore, we tested our hypotheses by using data collected from women who moved or graduated from school. Of the 1792 women who moved/graduated from schools, we were unable to contact 697 subjects (38.9%) because they either moved from their residences or changed family names after marriage. Among those contacted, 171 women (9.5%) declined to participate. We mailed a self-administered questionnaire to 924 women who agreed to participate. Of them, 539 women returned the questionnaires. For the remaining 385 women, trained interviewers collected information by telephone interviews using the same questionnaire. Subjects who had not undergone menarche at follow-up (n = 19) were excluded from the analysis, which resulted in a final sample size of 905 young adult women. The mean duration between the enrollment and the follow-up was 7.7 years (SD, 1.5 years).

Variable definition

Categories of current wheeze, current exercise-induced wheeze, current use of asthma medications, and OC use were based on self-reports. Current wheeze was defined as presence of any wheezing, including wheezing that impaired sleep or speech and wheezing during exercise or play in the previous 12 months. The last of these criteria was used to define current exercise-induced wheeze. Current use of asthma medication was defined as any medication for asthma in the past 12 months. Asthma was defined on self-report of physician diagnosis of asthma during the subject's lifetime. New-onset asthma after puberty was determined when a subject developed asthma 1 or more years after her menarche.

The questionnaire also included items regarding age at menarche, personal and secondhand smoke exposures, and history of OC use including age at first use and duration of use. Age at menarche was grouped into 3 categories: <12 years, 12 years, and >12 years. Depending on the duration of OC use, subjects were categorized into nonusers, users for less than 1 year, and users for 1 or more years. Among OC users, we defined current OC use if a woman took OC in the year previous to the interview. The remaining OC users were categorized as past users.

Information on height and body weight was obtained from annual follow-up conducted at the schools from the year at cohort entry to the year the subjects left their schools using standard protocols. We categorized BMI at the cohort entry and follow-up (if <20 years) into normal, overweight, and obese using age-specific and sex-specific percentiles based on the Centers for Disease Control and Prevention BMI growth charts using 1-month age intervals (available at http://www.cdc.gov/nccdphp/dnpa/growthcharts/sas.htm). For those older than 20 years at follow-up, we defined overweight and obese on the basis of cutpoints of BMI of 25 and 30 kg/m^2, respectively. We did not have information on BMI at the year of menarche on 359 women (41 with asthma after puberty) among the 787 subjects available for the analysis that examined the association between age at menarche and asthma occurrence after puberty. However, BMI over an 8-year period was highly correlated (correlation coefficient, 0.62-0.97), and BMI categories changed little in subjects with available BMI over the 8-year period. Therefore, we used the BMI categories at cohort entry and last follow-up for the association between the age at menarche and asthma occurrence after puberty, and the association between OC use and current wheeze outcomes, respectively.

Because participants were lost to follow-up, we assessed the potential for bias from this loss by comparing the baseline distribution of demographic (ie, age, race) and socioeconomic (ie, annual family income, parental education, and health insurance coverage) factors and prevalence of wheeze and parental history of asthma in participants, nonparticipants, and overall female cohort of the CHS not included in the current study (see this article's Table E1 in the Online Repository at www.jacionline.org). Although participants in the follow-up differed on race and socioeconomic status (SES) factors from the nonparticipants, they were representative of the overall nonparticipating female cohort on these factors except age. The difference in age between participants and the entire CHS female cohort that was not included in the present study was a result of the study design, because we sought to recruit women who graduated or moved from schools.

Statistical analysis

We determined the adjusted hazard ratio (HR) and 95% CI for the association between age at menarche and asthma occurrence after puberty using Cox proportional hazard models. We used age in years as the time scale. Follow-up time was calculated in years with left-truncation at the age at baseline and right censoring at the age at last interview for the current study. We adjusted for age by stratifying on age at cohort entry.

To examine the association between OC use and current wheeze and current exercise-induced wheeze in the past 12 months in subjects with and without asthma, unconditional logistic regression models were fitted to compute odds ratio (OR) and 95% CI. Likelihood ratio tests were used to determine whether subjects' asthma status modified the associations between OC use and current wheeze and current exercise-induced wheeze. Selection of potential confounders was based on a review of the literature or a 10% change in effect estimates in multivariate analyses. In stratified models that included women with asthma, further adjustment was made for current asthma medication use.

We were unable to examine prospectively the association between OC use and new-onset physician-diagnosed asthma in this study because 61.5% (ie, 118/192) women with asthma were diagnosed before puberty and 75% (ie, 33/44) of the women with asthma after puberty who used OC were diagnosed before they had used OC. All

TABLE I. Selected characteristics of the female participants in the Children's Health Study who participated in the follow-up study (n = 905) and their association with current wheeze

	N*	(%)	OR† (95% CI)
Age group, y			
13-17	226	(25.0)	1.0
18-19	237	(26.2)	1.10 (0.76-1.59)
20-22	224	(24.7)	0.83 (0.57-1.21)
23-28	218	(24.1)	0.75 (0.51-1.11)
Race/ethnicity			
Non-Hispanic white	552	(61.0)	1.0
Hispanic white	215	(23.7)	0.69 (0.50-0.96)
African American	56	(6.2)	1.21 (0.70-2.11)
Other	82	(9.1)	0.99 (0.62-1.59)
Education of the subjects			
≤10th grade	182	(20.1)	1.0
11th-12th grade	317	(35.0)	1.13 (0.78-1.63)
Some college	336	(37.1)	0.82 (0.57-1.19)
Graduate	70	(7.7)	0.70 (0.39-1.25)
Married or living with a partner	169	(18.7)	0.88 (0.62-1.24)
BMI (kg/m^2)‡ at cohort entry			
Normal	653	(74.3)	1.0
Overweight	140	(15.9)	1.07 (0.74-1.55)
Obese	86	(9.8)	1.14 (0.72-1.80)
BMI (kg/m^2)§ at follow-up			
Normal	650	(73.9)	1.0
Overweight	138	(15.7)	1.10 (0.76-1.61)
Obese	91	(10.4)	1.54 (0.99-2.38)
Age at menarche, y			
<12	220	(24.3)	1.0
12	291	(32.1)	1.32 (0.92-1.89)
13	237	(26.2)	1.01 (0.69-1.48)
≥14	157	(17.4)	1.10 (0.72-1.67)
Personal smoking status			
Never smoker	651	(71.9)	1.0
Exsmoker	83	(9.2)	1.15 (0.72-1.84)
Current smoker	171	(18.9)	2.52 (1.79-3.55)
Any secondhand smoke	525	(58.0)	1.67 (1.27-2.19)
Health insurance	735	(81.2)	0.99 (0.71-1.40)

*Numbers do not always add up because of missing data.
†Unadjusted ORs and 95% CIs for current wheeze.
‡Normal, overweight, and obese at cohort entry were based on age-specific and sex-specific percentiles of <85th, 85th-94th, and ≥95th percentiles, respectively, because all subjects were younger than 18 years.
§Normal, overweight, and obese at follow-up were based on age-specific and sex-specific percentiles of <85th, 85th-94th, and ≥95th percentiles for subjects at or below 20 years of age. For subjects older than 20 years, normal, overweight, and obese were defined on BMI <25, 25-29.9, and ≥30, respectively.

tests were 2-sided at a 5% significance level. We used the statistical software package SAS (version 9.1; SAS Institute Inc, Cary, NC) for all analyses.

RESULTS

Subjects were between 13 and 28 years of age at the time of follow-up, and their mean age was 19.9 years (SD, 3.2 years). The majority of the study participants were non-Hispanic white, more than 50% were exposed to secondhand smoke, and 18.9% were current smokers (Table I). Hispanic-white women were at reduced risk of current wheeze (OR, 0.69; 95% CI, 0.50-0.96). Most of the participants (81%) had some form of health insurance. Exposure to secondhand smoke and personal smoking were significantly associated with current wheeze.

TABLE II. Current wheeze by asthma status and asthma onset and current medication

	N	(%)*
Women with asthma (n = 192)		
Current wheeze	147	(76.6)
Current exercise-induced wheeze	119	(62.0)
Asthma before or within 1 year of menarche	137	(71.4)
Asthma ≥1 year after menarche	55	(28.6)
Asthma medication use in previous 12 months	100	(52.1)
Women without asthma (n = 713)		
Current wheeze	214	(30.0)
Current exercise-induced wheeze	108	(15.1)

*Percentages for women with asthma were based on 192 women with asthma, and those for women without asthma were based on 713 women without asthma.

TABLE III. Association between age at menarche and asthma occurrence after puberty

Age at menarche (y)	Asthma after puberty		HR* (95% CI)	HR† (95% CI)
	Yes	No		
>12	21	309	1.0	1.0
12	18	230	1.55 (0.79-3.05)	1.41 (0.70-2.81)
<12	16	174	2.37 (1.22-4.59)	2.08 (1.05-4.12)
P for trend			.01	.04

*Unadjusted HRs and 95% CIs.
†HRs adjusted for age, race, BMI at cohort entry, subject's education, living with spouse/partner, personal smoking status, exposure to secondhand smoke, oral contraceptive use, health insurance coverage, and mode of data collection.

One hundred ninety-two study participants (21.2%) had physician-diagnosed asthma, and 55 of them had asthma 1 or more years after menarche (Table II). About 52% of the subjects with asthma used asthma medications in the previous 12 months. Prevalence of current wheeze and current exercise-induced wheeze in subjects with no asthma history were 30.0% and 15.1%, respectively, whereas prevalence estimates for these 2 wheeze outcomes in women with asthma history were 76.6% and 62.0%, respectively. Mean age at starting OC was 17.5 years (SD, 2.3 years), and asthma at baseline was not associated with subsequent OC use or age at first OC use (data not shown).

Endogenous sex hormone exposure, as measured by age at menarche, was associated with asthma occurrence after puberty (Table III). Women who had menarche

TABLE IV. Associations between OC use and wheezing conditions by asthma status

	Current wheeze			Current exercise-induced wheeze		
OC use	**Cases/controls***	**OR† (95% CI)**	**OR‡ (95% CI)**	**Cases/controls***	**OR† (95% CI)**	**OR‡ (95% CI)**
In women with no history of asthma						
Nonuser	90/254	1.0	1.0	45/299	1.0	1.0
User	124/245	1.43 (1.03-1.97)	1.75 (1.15-2.65)	63/306	1.37 (0.90-2.07)	2.04 (1.17-3.53)
User for <1 year	43/94	1.29 (0.84-1.99)	1.50 (0.92-2.45)	22/115	1.27 (0.73-2.21)	1.82 (0.96-3.44)
User for ≥1 year	81/151	1.51 (1.06-2.17)	2.05 (1.25-3.36)	41/191	1.43 (0.90-2.26)	2.30 (1.21-4.39)
P for trend		.04	.01		.17	.03
Current user	90/183	1.37 (0.97-1.94)	1.61 (1.05-2.47)	51/222	1.53 (0.99-2.37)	2.14 (1.23-3.74)
Past user	32/58	1.54 (0.94-2.52)	2.07 (1.12-3.86)	12/78	1.03 (0.52-2.03)	1.76 (0.75-4.13)
In women with a history of asthma						
Nonuser	71/15	1.0	1.0	59/27	1.0	1.0
User	76/30	0.54 (0.27-1.08)	0.18 (0.06-0.56)	60/46	0.60 (0.33-1.08)	0.32 (0.12-0.85)
User for <1 year	30/13	0.49 (0.21-1.15)	0.21 (0.06-0.75)	25/18	0.64 (0.30-1.36)	0.34 (0.12-1.02)
User for ≥1 year	46/17	0.57 (0.26-1.26)	0.15 (0.04-0.57)	35/28	0.57 (0.29-1.12)	0.30 (0.09-0.96)
P for trend		.33	.03		.16	.13
Current user	54/24	0.47 (0.23-0.98)	0.15 (0.05-0.49)	42/36	0.55 (0.29-1.04)	0.30 (0.11-0.81)
Past user	20/6	0.69 (0.24-2.02)	0.24 (0.05-1.16)	17/9	0.90 (0.36-2.26)	0.57 (0.15-2.24)
P values for asthma history by OC use interaction						
For OC nonuser vs user		.01	.003		.02	.01
For OC nonuser, user for <1 or ≥1 year		.04	.01		.07	.04
For OC nonuser, current or past user		.03	.01		.02	.01

*Numbers of cases/controls do not always add up because of missing data on duration of OC use.
†Unadjusted ORs and 95% CIs. Separate stratified models were run for ever/never OC use, duration of OC use, and nonusers, current users, and past users. The *P* values for asthma history by OC use interaction were obtained from likelihood ratio tests from nonstratified models with appropriate interaction terms. The *P* values for interaction for OC nonuser vs user were based on 1 *df*, and the *P* values for interaction for OC nonuser, user for <1 or ≥1 year, and OC nonuser, current user, or past user were based on 2 *df*.
‡ORs adjusted for age, race, BMI at follow-up, age at first menstrual period, subject's education, living with spouse/partner, personal smoking status, exposure to secondhand smoke, health insurance coverage, and mode of data collection. The ORs in women with asthma were further adjusted for current asthma medication use.

before 12 years of age were at 2.08 times higher risk (95% CI, 1.05-4.12) of developing asthma 1 or more years after puberty compared with women who had menarche after age 12 years. Although BMI was inversely associated with age at menarche (correlation coefficient = −0.18), the inverse association between age at menarche and asthma remained statistically significant after adjustment for BMI and other covariates. African Americans (P = .06) and Hispanic whites (P = .11) tended to have earlier menarche than non-Hispanic whites; however, we did not observe any significant associations between age at menarche and SES factors. The association between age at menarche and incident asthma after puberty was not modified by BMI.

We observed markedly contrasting associations between OC use and current wheeze or current exercise-induced wheeze in women with and without asthma (Table IV). In women with a history of asthma, OC use was inversely associated with current wheeze and current exercise-induced wheeze; however, in subjects with no history of asthma, OC use was positively associated with both forms of wheezing (P value for asthma history by OC use interaction = .003 and .01 for current wheeze and current exercise-induced wheeze, respectively). In asthma-free women, OC users were 75% more likely to have current wheeze (adjusted OR, 1.75; 95% CI, 1.15-2.65), and there was an increase in the ORs with increasing duration of OC use (P value for trend = .01). In contrast, in subjects with a history of asthma, OC users were 82% less likely to have current wheeze (adjusted OR, 0.18; 95% CI, 0.06-0.56) compared with OC nonusers. We also observed that OC use was inversely associated with current exercise-induced wheeze among women with asthma, but increased exercise-induced wheeze risk among women without asthma. Overall, these contrasting associations were stronger for current OC users than past OC users; however, in women without a history of asthma, both current and past OC users were at significantly higher risk of current wheeze.

We observed no association between current asthma medication use in the previous 12 months and OC use or duration of OC use (see this article's Table E2 in the Online Repository at www.jacionline.org). Because women using OC visit physicians regularly for their prescriptions, they may have a greater chance for asthma diagnosis and subsequent treatment for wheeze. Thus, the protective effect of OC use could arise from concurrent use of asthma medications. However, inclusion of asthma medication use in the models did not account for the protective effect of OC use among women with asthma. Personal smoking status or exposure to secondhand tobacco smoke did not modify the association between

OC use and current wheeze and current exercise-induced wheeze (all *P* values > .40; data not shown).

DISCUSSION

Our study supports a role for endogenous and exogenous sex hormones in asthma occurrence. We observed that early menarche was associated with increased asthma risk after puberty independent of BMI. We also observed that OC use was associated with increased occurrence of current wheeze among young women with no history of asthma. In marked contrast, women with a history of asthma who used OC had a reduced risk of wheezing. The associations showed significant trends with duration of OC use. These differences were not accounted for by access to health care (measured by health insurance, education, and income), BMI, or concurrent use of asthma medication.

Endogenous sex hormone levels increase markedly after puberty, and women with early age at menarche have higher estrogen levels and lower serum hormone binding globulin[14] and are exposed to a greater cumulative estrogen and progesterone doses than women with later onset of menarche. To date, few studies have examined the role of early menarche in atopy and allergic rhinitis in young women.[15,16] In a large Danish birth cohort study, Westergaard et al[16] observed significant increasing trend in the risk of allergic rhinitis with decreasing age at menarche. In a study by Xu et al,[15] the data suggested inverse association between age at menarche and atopy independent of BMI. Data from the Tucson Children's Respiratory Study showed a statistically significant positive association between obesity and wheezing in women who reached puberty before 11 years, but obesity was not associated with wheezing in women who attained puberty $\geq$11 years and in men irrespective of puberty.[9] Although we observed borderline statistically significant associations between obesity and current wheeze in bivariate analysis (Table I), BMI was not associated with current wheeze outcomes or asthma occurrence after puberty in multivariate analyses. Our results are consistent with the findings of these previous studies and add to the growing body of evidence that hormonal factors are important in asthma occurrence after puberty in women.

The contributions of estrogens and progestins to asthma symptoms in women with asthma have been investigated in epidemiologic, clinical, and experimental studies. Hormonal fluctuations during the menstrual cycle are associated with worsening of asthma symptoms[17,18] as well as a predominance of T_H2 over T_H1-mediated immunity during the perimenstrual period.[19] Exogenous sex hormone in the form of OC has been shown to blunt the T_H2 immune response.[19] Most case studies and case series, with few exceptions,[20,21] reported reductions in asthma symptoms, improvement of lung function, and/or reduction in asthma medication use in women taking hormonal preparations (estrogen with progesterone, estrogen only, progesterone only, gonadotropin releasing hormone analogue, or luteinizing hormone releasing hormone agonist).[22-32] Although there are no other published studies to our knowledge that have directly examined the differences in the associations between OC use and wheezing outcomes by asthma status, our finding of a reduced risk of wheeze in women with asthma taking OC is consistent with the findings of studies that examined the effects of OC use on asthma symptoms and physiologic endpoints in premenopausal women with asthma.

On the basis of the findings of the current study, the airways of women with a history of asthma appear to respond differently to exogenous sex hormones than airways of women with no history of asthma. About a third of women with asthma have exacerbations of asthmatic symptoms during the luteal phase of menstruation.[33,34] This may be a result of a change in hormonal milieu resulting from increased progesterone levels. Several studies reported a reduction in asthma symptoms and corticosteroid requirement for asthma control in women with asthma who were given combined OC, estrogen, or gonadotropin releasing hormone analogue.[24,27,28,32,35] Because OC prevents luteinizing hormone surge and suppresses luteinizing hormone secretion, progesterone levels remain at a much lower level throughout the menstrual cycle in women taking OC compared with luteal phase levels of progesterone in women not taking OC.[11] Therefore, it is possible that the observed reduction in asthma symptoms with OC use may be a result of an absence of luteal phase increase in progesterone levels. Moreover, Tan et al[11] observed that AHR to adenosine monophosphate increased during the luteal phase in premenopausal women with asthma not taking OC; however, in women with asthma taking OC, there was no increase in luteal phase AHR. In addition, these authors observed that women with asthma taking OC had reduced diurnal variations in PEFR, whereas OC nonusers had significantly lower PEFR in the morning than in the evening. Thus, women with asthma taking OC may have lower risk of wheezing risk because of reduced AHR and reduced fluctuations in airflow.

Early menarche was associated with asthma occurrence after puberty, and the underlying pathobiology is possibly mediated by estrogen and progesterone. However, OC use, which reduces the levels of these hormones by blocking ovulation, increased the risk of current wheeze in women with no asthma history. Early menarche was not associated with OC use (data not shown), and the positive association between OC use and wheeze was not modified by age at menarche. There could have been some lifestyle factors associated with OC use that we were unable to measure in our study that led to a positive association between OC use and current wheeze in women without asthma. Further studies are warranted to explore this association.

Although participants were representative of the overall nonparticipating female cohort of the CHS on baseline demographic and SES factors (see this article's Table E1 in the Online Repository at www.jacionline.org), we conducted sensitivity analysis restricting to 419 subjects

whose parents had less than some college education and an annual family income between $15,000 and $50,000 at cohort entry to assess the magnitude of any bias from loss to follow-up. This restricted sample was chosen because it provided the largest subsample for analysis in which the distributions of SES factors (eg, family income, parental education, and health insurance coverage) were similar between the participants and the nonparticipants, reducing the potential for selection bias. The results in this restricted sample were consistent with the overall analyses, indicating that selection bias was not likely to account for our results (data not shown).

In this population-based study, we defined a subject's asthma status on the basis of physician-diagnosed asthma. The use of physician-diagnosed asthma has some limitations; however, it has been widely used in epidemiologic studies, and the self-report of asthma has been found to reflect physician diagnosis accurately.[36,37] Another concern in using physician-diagnosed asthma to classify asthma status is that limited access to healthcare may result in underdiagnosis of asthma. In our sample, 81% had medical insurance, which suggests that access to medical care was not limited. To assess this potential source of misclassification of asthma status, we considered the effects of health insurance, income, and education on the risk estimates for wheezing, and found little change in the adjusted risk estimates.

We conclude that sex hormones may play an important role in asthma occurrence. Early menarche was associated with increased asthma risk in young women after puberty, and OC use is associated with increased risk of current wheeze and current exercise-induced wheeze in young women without a history of asthma. In contrast, OC use markedly reduced the occurrence of these wheezing symptoms in women with asthma. Because OC use and asthma are common among young women, these findings are likely to have clinical and public health implications. Because the age of menarche has been decreasing during the period of rapid increases in asthma prevalence, further examination of the role of age at menarche in the rise in asthma is warranted.

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