Early Age at Menarche, Lung Function, and Adult Asthma

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***Rationale*: Hormonal and metabolic status appears to influence lung health in women, and there are findings suggesting that early menarche may be related to asthma, cardiovascular disease, diabetes, and breast cancer.**

***Objectives*: This study investigates whether age at menarche is related to adult lung function and asthma.**

***Methods*: Among participants in the European Community Respiratory Health Survey II, 3,354 women aged 27–57 years from random population samples in 21 centers responded to a questionnaire concerning women's health (1998–2002). Of these women, 2,873 had lung function measurements, 2,136 had measurements of bronchial hyperreactivity, and 2,743 had IgE measurements. Logistic, linear, and negative binomial regression analyses included adjustment for age, height, body mass index, education, smoking, family size, and center.**

***Measurements and Main Results*: FEV_1 and FVC were lower and asthma was more common in women with early menarche. Women reporting menarche at age 10 years or less, as compared with women with menarche at age 13 years (reference category), had lower FEV_1 (adjusted difference, −113 ml; 95% confidence interval [CI], −196 to −33 ml) and FVC (−126 ml; 95% CI, −223 to –28 ml); also lower FEV_1 expressed as a percentage of the predicted value (−3.28%; 95% CI, −6.25 to −0.30%) and FVC expressed as a percentage of the predicted value (−3.63%; 95% CI, −6.64 to −0.62%). Women with early menarche more often had asthma symptoms (odds ratio, 1.80; 95% CI, 1.09–2.97), asthma with bronchial hyperreactivity (odds ratio, 2.79; 95% CI, 1.06–7.34), and higher asthma symptom score (mean ratio, 1.58; 95% CI, 1.12–2.21).**

***Conclusions*: Women with early menarche had lower lung function and more asthma in adulthood. This supports a role for metabolic and hormonal factors in women's respiratory health.**

Keywords: menarche; lung function; asthma; body mass index; European Community Respiratory Health Survey

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Asthma and asthma symptoms are related to early age at menarche. Lung function in adult age has not been investigated.

What This Study Adds to the Field

Women with early menarche had lower lung function and more asthma symptoms. Mechanism related to onset of menarche appears to play a role in lung health.

Age at menarche signals the start of women's reproductive life and is determined by environmental and genetic factors (1, 2). Early menarche is associated with several aspects of adult health. Women with early menarche have an increased risk of cardiovascular disease, breast cancer, and metabolic syndrome, including obesity and diabetes type 2 (3, 4). During the last 100 years the median age at menarche has decreased from 16–17 years to less than 13 years (1, 5). There is evidence that age at menarche is decreasing in the Western world, and as childhood obesity is associated with earlier menarche, this change may be partly explained by the global obesity epidemics (1, 5–8).

Level of lung function is a strong predictor of respiratory health as well as general health (9). The literature shows that lung function is related to hormonal and metabolic factors. Real and colleagues showed that lung function was lower in menopausal women (10), and that women with irregular menstruation had lower lung function (11); furthermore, lung function is associated with body mass index (BMI) (11, 12). Developmental factors are important for adult lung function (13), also suggested by studies showing associations between low birth weight and adult lung function (14, 15).

The literature gives several indications that hormonal and metabolic factors play a role in asthma. Asthma is more prevalent among boys than girls; this relationship is reversed on reaching puberty, so that the incidence of asthma among adolescent girls is higher than among adolescent boys (16). In a study of subjects with asthma, airway responsiveness was more severe among postpubertal girls than among boys (17). After puberty women appear to have more asthma than men (18–20). Increasing BMI is associated with higher asthma risk (11, 21) and severity (22), especially among women (23). Girls who become overweight have a sevenfold risk, in comparison with

(*Received in original form December 18, 2009; accepted in final form August 24, 2010*)

Supported by a grant from the Norwegian Foundation for Health and Rehabilitation (F.M.).

A list of investigators and funding is provided in the online supplement.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 183. pp 8–14, 2011
Originally Published in Press as DOI: 10.1164/rccm.200912-1886OC on August 23, 2010
Internet address: www.atsjournals.org

boys, of developing asthma symptoms (24). Developmental aspects play an important role in asthma; there is literature indicating that impaired fetal growth influences adult asthma risk (21, 25). Studies by Varraso and colleagues (23), Guerra and colleagues (26), and Salam and colleagues (27) indicate higher asthma risk among women with early menarche. Whether age at menarche is associated with lung function or bronchial reactivity has not been investigated to our knowledge.

We wanted to investigate whether age at menarche is related to subsequent respiratory health. In the present analysis, using data from the multinational European Community Respiratory Health Survey II (ECRHS II), we investigated the associations of age at menarche with adult lung function, and the associations of age at menarche with asthma, asthma symptoms, and bronchial reactivity.

Some of the results of these studies have previously been reported in the form of an abstract (28).

METHODS

Participants in ECRHS I, a multicenter study including random population samples born in 1945–1970 (29), were invited to a follow-up study, ECRHS II (30), including an interviewer-led questionnaire, measurements of lung function, BHR, and serum-specific IgE.

This analysis includes 3,354 women aged 27–57 years from 21 ECRHS II centers who answered a questionnaire concerning age at menarche, pregnancy, menstrual cycle, menopause, contraception, use of exogenous sex hormones, and menopause. The question "How old where you when you had your first period?" defined age at menarche. Women reporting asthma before menarche were excluded (n = 220).

FEV_1 and FVC were determined by a standard spirometry procedure and recorded. The maximal FEV_1 and FVC, of up to five technically acceptable maneuvers, were registered (12). The ratio between FEV_1 and FVC was calculated.

Methacholine challenge was performed with a dosimeter (Mefar, Brescia, Italy). FEV_1 was recorded 2 minutes after each inhalation of methacholine, and the test was stopped when either a 20% fall in FEV_1 was achieved or after a final maximal dose of 2 mg of methacholine. "Asthma with BHR" was defined as having current asthma and a 20% fall in FEV_1 when challenged with methacholine. Current asthma was defined by the question "Have you had an asthma attack in the last 12 months?", ever asthma by "Have you ever had asthma?" Wheeze was defined as wheezing or whistling in the chest during the last 12 months. The following symptoms reported during the last 12 months were included in the variable "three or more asthma symptoms": wheeze, waking with tightness in chest, shortness of breath in daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.

The asthma score represents the sum of positive answers to the following five symptoms in the last 12 months: breathless while wheezing, waking with tightness in chest, shortness of breath in daytime, shortness of breath after strenuous activity, and waking with shortness of breath (31).

"Allergic sensitization" was defined as specific IgE against house dust mite (*Dermatophagoides pteronyssinus*), cat dander, timothy grass, and/or *Cladosporium herbarum*.

BMI was based on measured weight and height, and calculated as weight in kilograms divided by the square of the height in meters.

TABLE 1. CHARACTERISTICS OF STUDY POPULATION* ACCORDING TO AGE AT MENARCHE

		Age at Menarche (*yr*)							
	Total	⩽10	11	12	13	14	15	⩾16	
	3,354	114	431	776	953	656	275	149	
	100%	3.4%	13%	23%	28%	20%	8.2%	4.4%	*P* Value
Adult characteristics									
Height, m (mean)	1.64	1.62	1.63	1.63	1.65	1.65	1.65	1.66	<0.001†
Age, yr (mean)	42.7	43.2	42.8	42.4	42.3	43.0	43.9	43.4	0.042†
BMI, kg/m^2 (mean)	25.0	27.6	26.6	25.5	24.6	24.1	24.2	23.4	<0.001†
BMI <20, %	9.1	4.0	5.9	7.0	10	8.5	15	16	<0.001‡
BMI 20–25, %	51	37	40	50	52	57	51	57	
BMI 25–30, %	21	33	31	28	27	28	22	21	
BMI >30, %	13	27	23	15	11	6.4	11.4	5.8	
Smoking status, %									0.017‡
Never-smokers	45	38	47	45	45	44	47	39	
Ex-smokers	26	26	22	28	25	27	25	29	
0–10 pack-years	7.6	6.1	8.8	4.8	9.2	8.5	6.2	9.4	
10–20 pack-years	8.3	8.8	7.7	10	8.2	6.4	7.6	9.4	
>20 pack-years	8.8	18	10	8.1	8.3	8.5	9.5	6.0	
Educational level,§ %									0.8‡
High	31	29	27	31	30	31	31	27	
Medium	29	25	30	29	32	29	31	28	
Low	40	46	43	40	38	40	38	45	
Region‖									<0.001‡
North	34	1.5	11	25	30	22	8.5	3.6	
Middle	42	3.1	13	20	28	20	9.4	5.9	
South	21	6.6	16	25	27	17	5.9	3.0	
Non-Europe	3.3	6.4	14	33	26	14	4.6	2.7	
Early life factors									
Year of birth, median	1958	1957	1957	1958	1958	1958	1956	1956	0.025†
Single child, %	9.4	7.0	12.6	9.3	9.9	5.4	9.1	9.4	0.001‡
>3 siblings, %	20	23	17	20	16	18	17	15	
Parental asthma %	13	12	13	14	12	13	13	9.6	0.7‡
Maternal smoking, %	24	18	27	24	24	23	22	22	0.5‡

Definition of abbreviation: BMI = body mass index.

* Study population included 3,354 women aged 27–57 years.

† *P* for trend.

‡ *P* from chi-square test.

§ Educational level in tertiles specified for each country.

‖ North: Iceland, Norway, Sweden; middle: France, Belgium, United Kingdom, Switzerland, Estonia; south: Spain; non-Europe: Portland, Oregon.

Categorization as "current-smokers," "ex-smokers," and "never-smokers" was defined by the answer to the question "Have you ever smoked for as long as a year?" If the answer was yes, "Do you smoke now, as of one month ago?" Current smokers were grouped into three categories by number of pack-years. Education was defined by age at completed full-time education and was divided in three tertiles specific for each country.

Age at menarche was categorized in whole years with the median value, 13 years, as the reference group. Linear regression models were used to assess the effects of age at menarche on the continuous variables, FEV_1 and FVC. Symptom score was analyzed by negative binomial regressions. Logistic regression models were used to assess the effects of age at menarche on the dichotomous outcome variables, asthma and asthma symptoms. Adjustments were made for age, height, BMI in categories, smoking, education, birth order, and center. Lung function analyses also included adjustment for age squared. All analysis was performed with Stata SE10 (Stata Corporation, College Station, TX).

This study was approved by local ethics committees in all the study centers.

RESULTS

Characteristics of the 3,354 women aged 27–57 years are presented in Table 1 according to age at menarche. Women with early menarche were shorter and had a higher BMI (Table 1). Women with early and late menarche were more often ex- and current smokers (Table 1), and heavy smoking was more prevalent in women with early menarche. The same group also had less education, indicating lower social class. There were regional differences so that early menarche was more frequent in southern Europe and in Portland, Oregon. Women with early menarche more often came from a large family and were less often a single child.

Adult FEV_1 and FVC were consecutively higher with increasing age at menarche (Table 2). Analyses adjusting for height, BMI, center, and a range of potential confounding factors revealed that adult lung function was significantly lower for women with menarche at 10 years of age or less (Table 3 and Figure 1A). FEV_1 percent predicted and FVC percent predicted were also significantly lower in women with early menarche (Table 3 and Figure 1B). These associations were similar in normal-weight women and women with BMI greater than 25 kg/m^2. For women with menarche at 10 years of age or less and BMI less than 25, FEV_1 was 117 ml lower (not significant) and for BMI greater than 25, 124 ml lower (−235 to −13). In the group with menarche at 10 years of age or less and BMI less than 25, FVC was 134 ml lower (not significant) and for BMI greater than 25 FVC was 135 ml lower (−264 to −5). For the same age group and BMI less than 25, FEV_1 percent predicted was 3.6% lower (not significant) and for BMI greater than 25 FEV_1 percent predicted was 4.3% lower (−8.3 to −0.3). In the same age group and BMI less than 25, FVC percent predicted was 3.4% lower (not significant) and for BMI greater than 25, FVC percent predicted was 4.1% lower (−8.1 to −0.1). Impairment in FEV_1 and FVC appeared to be proportionally similar, and no association with lower FEV_1/FVC ratio was indicated. Adult lung function was not significantly associated with age at menarche within the range of 11–15 years, and higher lung function was indicated but not significant in women with late menarche (Figures 1A and 1B). Analyses of age at menarche as a continuous variable did not show a significant linear association with lung function (data not given).

Adult asthma assessed as wheeze, three or more symptoms, and asthma score was more prevalent among women with early menarche (Table 2). With adjustment for potential confounding factors, women with menarche at 10 years of age or less showed significantly higher risk for wheeze, three or more asthma symptoms, and asthma symptoms with bronchial hyperreactivity, as well as a higher asthma score (Table 3 and Figure 2). The strongest association was found for the most specific asthma outcome, asthma symptoms with positive BHR. An association with nonatopic asthma appeared stronger than for atopic asthma, but did not reach statistical significance (Table 3). Analyses stratified by BMI gave similar findings. There were no consistent indications that late menarche was associated with impaired adult lung health (Table 2), and multivariate analyses of women with late menarche compared with the reference group (menarche at age 13 yr) showed no significant differences (data not given).

TABLE 2. LUNG FUNCTION, ASTHMA SYMPTOMS, AND BRONCHIAL HYPERREACTIVITY ACCORDING TO AGE AT MENARCHE

		Age at Menarche (*yr*)							
	Total	⩽10	11	12	13	14	15	⩾16	
	3,354	114	431	776	953	656	275	149	*P* Value
Lung function									
FEV_1, ml/s	3,012	2,806	2,949	2,997	3,067	3,020	2,985	3,102	<0.001
FVC, ml	3,722	3,471	3,641	3,708	3,774	3,749	3,691	3,847	<0.001
FEV_1/FVC ratio	81	81	81	81	81	81	81	80	0.46
FEV_1, % predicted	107	104	108	108	108	107	106	109	0.35
FVC, % predicted	114	110	114	114	114	114	113	116	0.12
Asthma symptoms and BHR									
Asthma, ever, %	10	11	6.8	4.3	5.9	5.8	7.0	3.4	0.09
Woken by shortness of breath, %	5.7	10	6.8	4.3	5.9	5.8	6.6	3.4	0.09
Wheeze, %	20	33	24	19	18	19	18	21	0.002
⩾3 symptoms,* %	13	23	16	10	12	12	13	12	0.003
⩾3 symptoms* + allergic sensitization,† %	6.3	9.5	7.8	5.1	6.3	7.1	4.5	6.2	0.62
⩾3 symptoms* – allergic sensitization, %	11	21	13	8.5	9.6	11	13	11	0.03
⩾3 symptoms* and BHR,%	5.2	12	5.8	4.5	4.0	4.7	7.3	6.6	0.15
BHR PD_{20}, %	16	25	15	16	15	14	19	13	0.25
Symptom score‡	0.55	1.00	0.65	0.51	0.51	0.55	0.49	0.46	0.002

Definition of abbreviations: BHR = bronchial hyperreactivity; PD_{20} = provocative dose causing 20% decrease in FEV_1.

* Three or more of the following eight asthma symptoms: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in chest, shortness of breath in daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.

† Allergic sensitization defined as one or more specific IgEs against any of the following allergens: house dust mite (*Dermatophagoides pteronyssinus*), cat dander, timothy grass, and/or *Cladosporium herbarum.*

‡ Score ranges from 0 to 5. The items were as follows: (*1*) breathless while wheezing, (*2*) waking with tightness in chest, (*3*) shortness of breath in daytime, (*4*) shortness of breath after strenuous activity, and (*5*) waking with shortness of breath.

TABLE 3. ASSOCIATION OF RESPIRATORY SYMPTOMS AND LUNG FUNCTION WITH AGE AT MENARCHE, COMPARING MENARCHE AT AGE 10 YEARS OR LESS WITH MENARCHE AT AGE 13 YEARS (MEDIAN), EXCLUDING THOSE REPORTING ASTHMA BEFORE AGE AT MENARCHE

	Menarche ⩽ 10 yr (*n* = *114*)		Menarche at 13 yr (*n* = *953*)
Lung Function	Adjusted Difference (95% CI)*	*P* Value	Reference Value
FEV_1, ml/s	−113 (−195 to −32)	0.006	3,286
FVC, ml	−123 (−220 to −27)	0.01	4,069
FEV_1/FVC ratio	0.20 (−1.13 to 1.54)	0.77	82.00
FEV_1, % predicted	−3.28 (−6.25 to −0.30)	0.03	109
FVC, % predicted	−3.63 (−6.64 to −0.62)	0.02	115
Asthma Symptoms and BHR†	OR (95% CI)‡	*P* Value	Reference Value
Asthma, ever	1.18 (0.65–2.16)	0.58	1
Woken by shortness of breath	1.63 (0.82–3.24)	0.16	1
Wheeze	1.64 (1.02–2.64)	0.04	1
⩾3 symptoms§	1.80 (1.09–2.97)	0.02	1
⩾3 symptoms + allergic sensitization‖	1.47 (0.56–3.85)	0.45	1
⩾3 symptoms + no allergic sensitization	1.81 (0.92–3.58)	0.08	1
⩾3 symptoms and BHR	2.79 (1.06–7.34)	0.04	1
BHR	1.56 (0.85–2.86)	0.15	1
	Mean Ratio (95% CI)¶	*P* Value	Reference Value
Symptom score**	1.58 (1.12–2.21)	0.01	1

Definition of abbreviations: BHR = bronchial hyperreactivity; BMI = body mass index; CI = confidence interval; OR = odds ratio; PD_{20} = provocative dose causing 20% decrease in FEV_1.

* Analyzed by linear regression, adjusted for BMI in categories, age, age squared, smoking intensity, education specific for countries, order of sibling, height, and center as random effect.

† BHR defined as $\log(PD_{20}) \leqslant 0$.

‡ Analyzed by linear regression, adjusted for BMI in categories, age, smoking intensity, education specific for countries, order of sibling, height, and center as random effect.

§ Three or more of the following eight asthma symptoms: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in chest, shortness of breath in daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.

‖ Allergic sensitization defined as one or more specific IgEs against any of the following allergens: house dust mite (*Dermatophagoides pteronyssinus*), cat dander, timothy grass, and/or *Cladosporium herbarum.*

¶ Analyzed by negative binomial regressions for symptom score. Adjustments were made for height, age, center, BMI in categories, smoking intensity, and education in tertiles for each country with linear regression, adjusted for BMI in categories, age, smoking intensity, and education specific for countries, order of sibling, height, and center as random effect.

** Score ranges from 0 to 5. The items were as follows: (*1*) breathless while wheezing in the last 12 months, (*2*) woken up with a feeling of chest tightness in the last 12 months, (*3*) attack of shortness of breath at rest in the last 12 months, (*4*) attack of shortness of breath after exercise in the last 12 months, (*5*) woken by attack of shortness of breath in the last 12 months.

Analyses of lung function were stratified for asthma and three or more asthma symptoms, and similar results were found for FEV_1, FVC, FEV_1 percent predicted, and FVC percent predicted (data not given).

We could not detect any time trend in the period covered by our study, a cohort born between 1945 and 1972. Neither did stratification by birth cohorts in tertiles indicate any differences in the association of age at menarche with adult lung function between these cohorts.

Meta-analysis by center was performed for associations between menarche at 10 years of age or less and FEV_1, percent predicted FEV_1, and three or more respiratory symptoms. No significant heterogeneity between study centers was found (*see* the online supplement).

DISCUSSION

In this multicultural population study, reported age at menarche was significantly and consistently associated with adult lung function and adult asthma. FEV_1 and FVC were lower in women with early menarche and women with early menarche had lower FEV_1 and FVC than predicted. These findings were consistent when adjusting for a range of potential confounding factors, in overweight and normal weight women, in subjects with asthma as well as those without asthma, and across centers. An association with FEV_1/FVC ratio was not identified. Women with early menarche also had more asthma symptoms and more asthma with bronchial hyperreactivity in adulthood, consistent with stratification by BMI or by center. The findings were robust to adjustment for irregular menstruation or when excluding menopausal or currently smoking women. However, we did not observe a dose–response relationship of age at menarche with lung function or asthma; impaired lung health mainly appears to be related to menarche before the age of 11 years.

To our knowledge an association of lower lung function with early menarche is a novel finding. Higher asthma risk in women with early menarche as demonstrated in the present analysis is in accordance with previous findings: Varraso and colleagues (23) found an association between increasing BMI and asthma severity, being stronger in women with early menarche. The strong association of early menarche with asthma and bronchial reactivity in the present analysis supports a role particularly in severe asthma, but we could see no evidence of an interaction of BMI with age at menarche. Guerra and colleagues (26) found a relationship between early menarche, obesity, and later asthma, and Salam and colleagues (27) showed an association between low age at menarche and increased risk of asthma. Our findings are consistent with these observations. The strengths of this study include the large number of study subjects, the multicenter study design, the standardized lung function measurements, objective measurements of specific IgEs and bronchial hyperresponsiveness, as well as an extensive interview concerning women's health. Age at menarche is an important

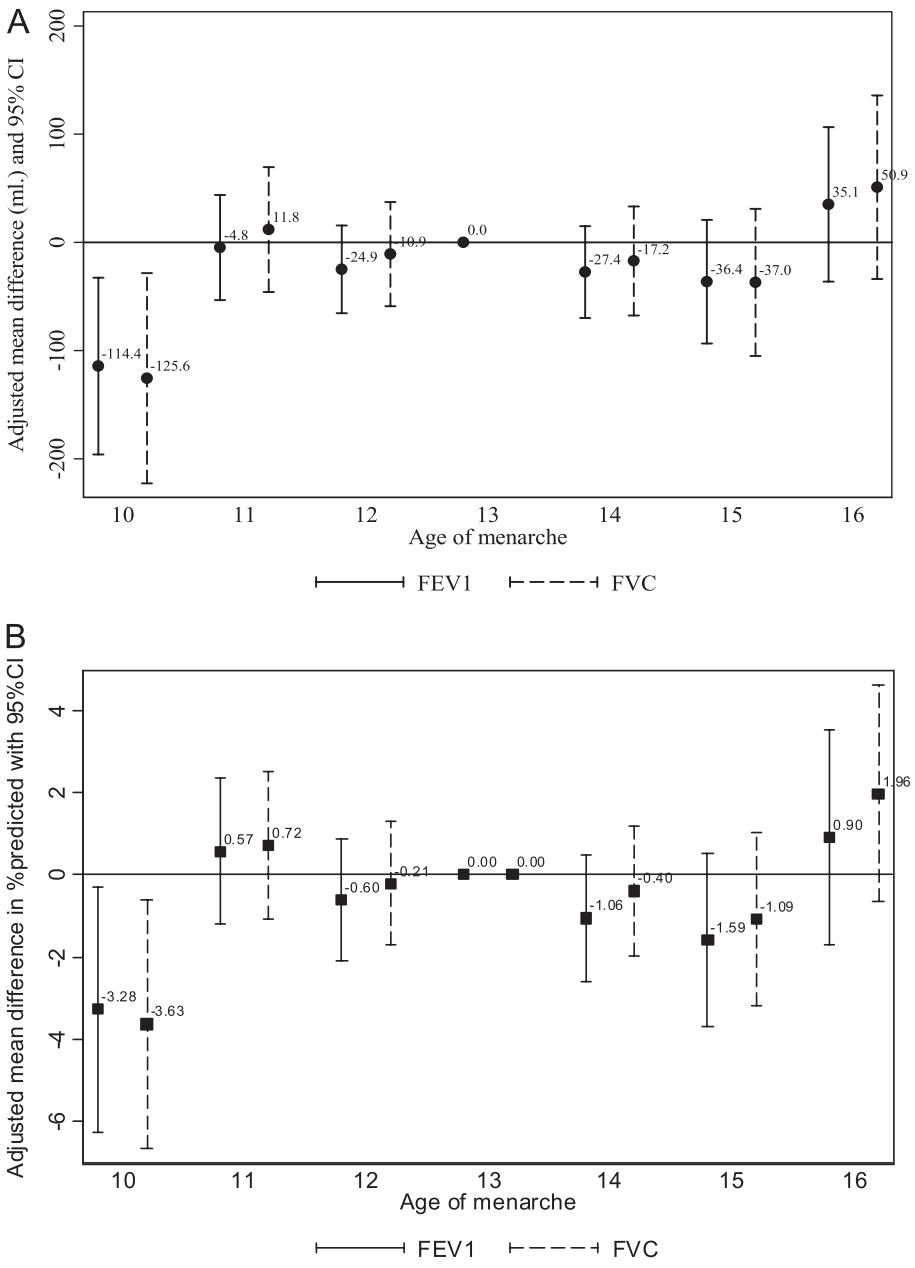

Figure 1. (*A*) Adjusted difference (ml) and 95% confidence interval (CI) for the association between age at menarche and FEV_1 and FVC among 3,354 women aged 27 to 57 years. Menarche at 13 years of age is used as reference. Data were analyzed by linear regression, adjusted for age, age squared, height, body mass index (BMI) in categories, smoking intensity, education in tertiles for each country, order of birth, and center as random effect. (*B*) FEV_1 and FVC, expressed as a percentage of the predicted value, and 95% CI for the association between age at menarche and predicted lung function values. Menarche at 13 years is used as reference Data were analyzed by linear regression, adjusted for age, age squared, height, BMI in categories, smoking intensity, education in tertiles for each country, order of birth, and center as random effect.

event in a woman's life and recall bias appears to be small (32). It is unlikely that reporting of menarche should be systematically biased regarding asthma or lung function. We do not have information about childhood BMI, which is an important determinant for the timing of menarche. We do, however, have information about adult BMI, which is closely correlated with childhood BMI (33). Adjustment for adult BMI did not alter our findings, but it is possible that our findings are related to childhood obesity. We do not have information about birth weight, which has been shown to influence lung function and asthma in adult life (14, 25). Maternal smoking was slightly less frequent in women reporting early menarche, even though these women smoked more heavily and had lower education in adulthood. This could be explained by geographical differences in maternal smoking; women in southern Europe barely smoked in the postwar period as opposed to mothers in northern Europe, and southern European women have earlier menarche. Meta-analyses on center level were performed for menarche at 10 years age or less for FEV_1, predicted FEV_1, and three or more symptoms and showed no significant heterogeneity. Although we cannot rule out some residual confounding we believe we have taken into account all the main possible confounders.

Height is a strong predictor of lung function, both for FVC and FEV_1. Height is also closely related to age at menarche (1). Menarche occurs in adolescence relatively constantly after the peak growth velocity has passed (1). Menarche signals the closure of the diaphyses and thus contributes to determine the subject's final height. Early menarche was related to short stature in our data. During the last century age at menarche has decreased as height has steadily increased. Given the complex role of height, we adjusted for height in our analyses. However, this may imply that the developmental component linking age at menarche with adult lung function has in part been adjusted for and is thus underestimated.

The Barker hypothesis suggests that the origin of many diseases is developed already in fetal life (34). Lower birth weight with higher BMI during childhood predicts early age at menarche. Blell and colleagues (35) showed that the timing of

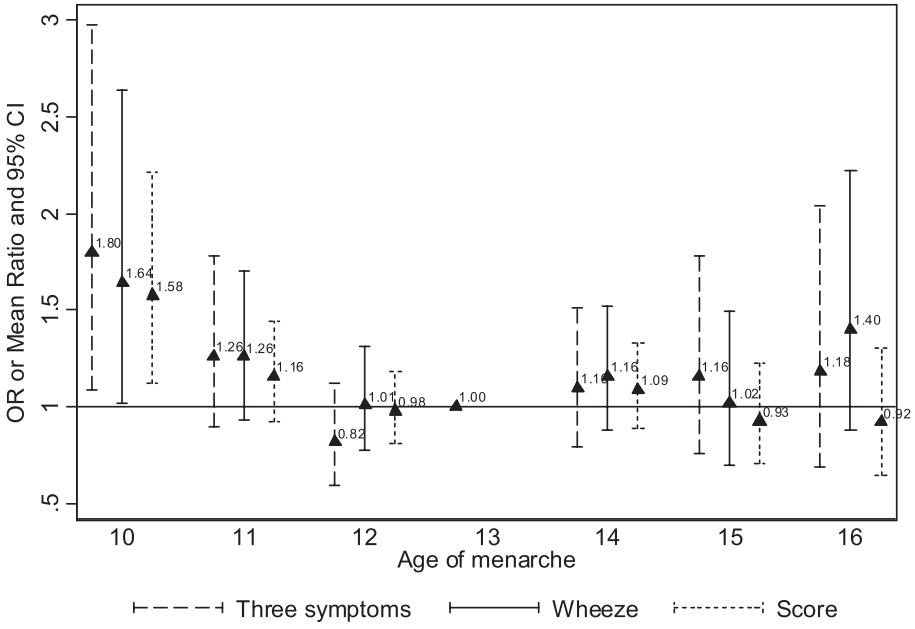

Figure 2. Odds ratios (ORs) and 95% confidence interval (CI) for the association between age at menarche and three or more asthma symptoms, wheeze, and asthma score among 3,354 women aged 27 to 57 years. Menarche at 13 years of age is used as reference. Data were analyzed by linear regression, adjusted for age, height, body mass index (BMI) in categories, smoking intensity, education in tertiles for each country, order of birth, and center as random effect.

menarche was associated with conditions in fetal and early life such as gestational age, maternal age, and BMI at age 9 years. Adult lung health is also related to birth weight, gestational age, and maternal age, suggesting that susceptibility may be determined early in life (14, 15, 21, 25, 36). The association between early menarche and adult lung function and asthma observed in the present study might in part reflect similar developmental factors, such as intrauterine growth or catch-up growth during childhood.

A critical percentage of fat has been shown to be of importance to the initiation of menarche, and leptin is suggested to be the most important messenger that initiates puberty (1). Our study confirms a strong association of age at menarche with BMI (adult BMI is closely linked with adolescent BMI). Higher leptin levels and higher insulin resistance (4) in women with early menarche, influencing inflammation and the innate immunity (37), could contribute to the associations with adult lung health. The associations of early menarche with lung function and asthma were also present when adjusting for BMI; this is plausible as BMI is only one of many indicators of insulin resistance. In our study nonatopic asthma symptoms appeared to be more strongly associated with early menarche than atopic asthma, which supports alteration in insulin resistance as a possible explanatory mechanism. Irregular menstruation, another indicator of insulin resistance, was slightly more common in women with early or late menarche, and has been shown to be associated with lower lung function (11). Adjustment for irregular menstruation did not alter our findings. A role of insulin resistance and systemic inflammation could contribute to explain not only the association of age at menarche with adult respiratory health, but is suggested to explain previously shown associations with cardiovascular disease and diabetes (38).

Environmental factors are important for onset of puberty. Improved living standards, improved antenatal nutrition of the mother, as well as postnatal nutrition of the child contribute to taller and heavier children, leading to earlier maturation and earlier menarche in girls. When the environment is optimal, age at menarche is mainly controlled by genetic factors (11). The decline in age at menarche in the Western world during the last 150 years mirrors greatly improved nutritional status and better living conditions. The smaller reduction in age at menarche during the last five decades possibly reflects optimization of living conditions in this respect.

In conclusion, the present analysis of a large multinational study shows that lung function was lower and asthma more common among adult women with menarche before the age of 11 years; consistent by different ways of analyses and in different subgroups. Relating adult respiratory health to an adolescent factor, this observation supports previous literature suggesting that adult respiratory health is partly determined early in life. Further, these findings support previous literature suggesting that hormonal and metabolic factors play an important role in women's respiratory health. Concerning secondary prevention, one might want to be alert regarding the potential increased asthma risk in girls with early menarche; programs focusing on, for example, smoking prevention in adolescents might include early menarche as an indicator of increased risk for impaired respiratory health.

Author Disclosure: F.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.G.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.P. is employed by Novartis (she was not working at Novartis at the time of writing this article) and by the Center for Research in Environment (she was working there at the time of producing this article). J.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.J. received lecture fees from GlaxoSmithKline (up to $1,000). E.R.O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.Z. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.L. received lecture fees from GlaxoSmithKline (up to $1,000). C.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank the ECRHS researchers and the ECRHS study participants.

References

1. Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
2. Perry JR, Stolk L, Franceschini N, Lunetta KL, Zhai G, McArdle PF, Smith AV, Aspelund T, Bandinelli S, Boerwinkle E, *et al.* Meta-

analysis of genome-wide association data identifies two loci influencing age at menarche. *Nat Genet* 2009;41:637–638.
3. Golub MS, Collman GW, Foster PM, Kimmel CA, Rajpert-De Meyts E, Reiter EO, Sharpe RM, Skakkebaek NE, Toppari J, *et al.* Public health implications of altered puberty timing. *Pediatrics* 2008;121: S218–S230.
4. Heys M, Schooling CM, Jiang C, Cowling BJ, Lao X, Zhang W, Cheng KK, Adab P, Thomas GN, Lam TH, *et al.* Age of menarche and the metabolic syndrome in China. *Epidemiology* 2007;18:740–746.
5. de Muinich Keizer SM, Mul D. Trends in pubertal development in Europe. *Hum Reprod Update* 2001;7:287–291.
6. Kaplowitz PB. Link between body fat and the timing of puberty. *Pediatrics* 2008;121:S208–S217.
7. Aksglaede L, Sorensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. *Pediatrics* 2009;123:e932–e939.
8. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. *Pediatrics* 2002;110:e43.
9. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;313:711–715, discussion 15–16.
10. Real FG, Svanes C, Omenaas ER, Anto JM, Plana E, Jarvis D, Janson C, Neukirch F, Zemp E, Dratva J, *et al.* Lung function, respiratory symptoms, and the menopausal transition. *J Allergy Clin Immunol* 2008;121:72–80.e3.
11. Real FG, Svanes C, Omenaas ER, Anto JM, Plana E, Janson C, Jarvis D, Zemp E, Wjst M, Leynaert B, *et al.* Menstrual irregularity and asthma and lung function. *J Allergy Clin Immunol* 2007;120: 557–564.
12. Chinn S, Jarvis D, Melotti R, Luczynska C, Ackermann-Liebrich U, Anto JM, *et al.* Smoking cessation, lung function, and weight gain: a follow-up study. *Lancet* 2005;365:1629–1635; discussion 1600–1601.
13. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, de Marco R, Norback D, Raherison C, Villani S, *et al.* Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;65:14–20.
14. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;303:671–675.
15. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. *Thorax* 2005;60:851–858.
16. Nicolai T, Illi S, Tenborg J, Kiess W, v Mutius E. Puberty and prognosis of asthma and bronchial hyper-reactivity. *Pediatr Allergy Immunol* 2001;12:142–148.
17. Tantisira KG, Colvin R, Tonascia J, Strunk RC, Weiss ST, Fuhlbrigge AL. Airway responsiveness in mild to moderate childhood asthma: sex influences on the natural history. *Am J Respir Crit Care Med* 2008; 178:325–331.
18. Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992;268:3437–3440.
19. Harju T, Keistinen T, Tuuponen T, Kivela SL. Hospital admissions of asthmatics by age and sex. *Allergy* 1996;51:693–696.
20. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999;54:1119–1138.
21. Shaheen SO, Sterne JA, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. *Thorax* 1999;54:396–402.
22. ENFUMOSA Study Group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J* 2003;22:470–477.
23. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005;171:334–339.
24. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001;163:1344–1349.
25. Svanes C, Omenaas E, Heuch JM, Irgens LM, Gulsvik A. Birth characteristics and asthma symptoms in young adults: results from a population-based cohort study in Norway. *Eur Respir J* 1998;12: 1366–1370.
26. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004;170:78–85.
27. Salam MT, Wenten M, Gilliland FD. Endogenous and exogenous sex steroid hormones and asthma and wheeze in young women. *J Allergy Clin Immunol* 2006;117:1001–1007.
28. Macsali F, Real FG, Plana E, Sunyer J, Anto J, Dratva J, Janson C, Jarvis D, Omenaas ER, Zemp E, *et al.* Age of menarche, lung function and adult asthma [abstract]. Presented at the Annual Congress of the European Respiratory Society, September 12–16, 2009, Vienna, Austria.
29. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954–960.
30. European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. *Eur Respir J* 2002;20:1071–1079.
31. Sunyer J, Pekkanen J, Garcia-Esteban R, Svanes C, Kunzli N, Janson C, de Marco R, Anto JM, Burney P. Asthma score: predictive ability and risk factors. *Allergy* 2007;62:142–148.
32. Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, Rand WM. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol* 2002;155:672–679.
33. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Prev Med* 1993;22:167–177.
34. Barker DJ. Maternal nutrition, fetal nutrition, and disease in later life. *Nutrition* 1997;13:807–813.
35. Blell M, Pollard TM, Pearce MS. Predictors of age at menarche in the Newcastle Thousand Families Study. *J Biosoc Sci* 2008;40: 563–575.
36. Laerum BN, Svanes C, Wentzel-Larsen T, Gulsvik A, Toren K, Norrman E, Gislason T, Janson C, Omenaas ER. Young maternal age at delivery is associated with asthma in adult offspring. *Respir Med* 2007;101:1431–1438.
37. Fernandez-Real JM, Pickup JC. Innate immunity, insulin resistance and type 2 diabetes. *Trends Endocrinol Metab* 2008;19:10–16.
38. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 2004;25:4–7.