Lung function, respiratory symptoms, and the menopausal transition

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Background: There is limited information on potential changes in respiratory health when women enter the menopausal transition.
Objective: We sought to investigate whether the menopausal transition is related to lung function and asthma and whether body mass index (BMI) modifies associations.
Methods: Four thousand two hundred fifty-nine women from 21 centers (ECRHS II, 2002) responded to a questionnaire concerning women's health. Women aged 45 to 56 years not using exogenous sex hormones (n = 1274) were included in the present analysis. Lung function measurements (n = 1120) and serum markers of hormonal status (follicle-stimulating hormone, luteinizing hormone, and estradiol; n = 710) were available. Logistic and linear regression analyses were adjusted for BMI, age, years of education, smoking status, center, and height.
Results: Women not menstruating for the last 6 months (n = 432, 34%) had significantly lower FEV_1 values (−120 mL [95% CI, −177 to −63]), lower forced vital capacity values (−115 mL [95% CI, −181 to −50]), and more respiratory symptoms (odds ratio [OR], 1.82 [95% CI, 1.27-2.61]) than those menstruating regularly. Results were similar when restricting analyses to those who never smoked. Associations were significantly stronger in women with BMIs of less than 23 kg/m^2 (respiratory symptoms: OR, 4.07 [95% CI, 1.88-8.80]; FEV_1 adjusted difference: −166 [95% CI, −263 to −70]) than in women with BMIs of 23 to 28 kg/m^2 (respiratory symptoms: OR, 1.10 [95% CI, 0.61-1.97], $P_{interaction}$: .04; FEV_1 adjusted difference, −54 [95% CI, −151 to 43], $P_{interaction}$ = .06).
Conclusions: Menopause is associated with lower lung function and more respiratory symptoms, especially among lean women. (J Allergy Clin Immunol 2008;121:72-80.)

Key words: *Menopause, lung function, asthma, allergy, body mass index, sex hormones, estrogens, follicle-stimulating hormone, hormone replacement therapy, European Community Respiratory Health Survey*

There is very limited information on potential changes in respiratory health when women enter the menopausal transition. Sex hormones play an important role in women's lung health,[1-6] but the literature is contradictory and confusing. Reasons for this are many. Endogenous hormone levels vary according to menarche, menstrual phase, menstrual irregularity, pregnancy, lactation, or proximity to menopause. Furthermore, many women use exogenous sex hormones: oral contraceptives, hormone replacement therapy, or infertility therapy. Sex hormone levels might also vary according to factors not necessarily related to reproduction but to metabolic situation and varying insulin sensitivity, such as polycystic ovarian syndrome,[7,8] obesity,[9-11] or physical activity,[12] which further complicate the picture. In addition, the effects of sex hormones on inflammation,[13] immunity,[14] or metabolism,[15] which can all influence the airways, appear to be complex, in some cases even multidirectional.[16]

The menopausal transition implies a series of hormonal and metabolic changes. As ovarian function decreases and fertility disappears, circulating estrogen levels are first increased and then decrease,[11] and there is a shift in estrogen production from the ovaries to extragonadal sites.[11,17,18] With menopause, women also become more insulin resistant,[16] followed by increased risk for

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Abbreviations used
BMI: Body mass index
COPD: Chronic obstructive pulmonary disease
ECRHS: European Community Respiratory Health Survey
FSH: Follicle-stimulating hormone
FVC: Forced vital capacity
GAM: Generalized additive model
HRT: Hormone replacement therapy
LH: Luteinizing hormone
OR: Odds ratio
RHINE: Respiratory Health in Northern Europe

cardiovascular diseases.[19,20] Furthermore, with the appearance of climacteric symptoms, exogenous hormones are widely used; these hormones interact with a changing preexisting hormonal and metabolic status.[16]

The literature on menopause and lung health is scarce. From casuistic reports, we know that asthma in some women starts or worsens around the age of menopause[21]; no epidemiologic study has clearly confirmed that assertion. On the contrary, an analysis of the Nurses' Health Study found lower risk of asthma in postmenopausal women not using hormone replacement therapy (HRT).[6] A population-based study from 5 northern European countries (Respiratory Health in Northern Europe [RHINE]) found no convincing association of menopause with asthma symptoms.[4] Both studies were questionnaire based and did not include objective data. To our knowledge, there is no study addressing potential changes in lung function related to menopause.

The aim of the present study was to elucidate the possible associations of lung function and respiratory symptoms with menstrual status in perimenopausal women while taking into consideration potential differences according to body mass index (BMI). Women 45 to 56 years old, not using exogenous hormones, and participating in the European Community Respiratory Health Survey (ECRHS) were included in the present analysis. In addition to questionnaires about respiratory health and women's specific issues, objective data were included: blood samples with measurements of sex hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH], and estradiol) and specific IgE and measurements of lung function (FEV_1 and forced vital capacity [FVC]).

METHODS

Study design

The present study includes a cross-sectional analysis of ECRHS II.[22] ECRHS I[23] was an international survey carried out in 1992-1994 including randomly selected individuals from general populations within administrative boundaries of 36 centers in 16 countries. A random sample and a smaller symptomatic sample were invited to a follow-up study, ECRHS II, which took place in 1998-2002. The examinations carried out at both surveys included an interviewer-led questionnaire, lung function measurements, and blood samples for measurement of sex hormones and serum specific IgE. The study is described in detail at www.ecrhs.org. Ethical approval was obtained for each study center from the appropriate institutional or regional ethics committee, and each participant provided informed written consent.

Women's questionnaire and study population

Four thousand two hundred fifty-nine women from 21 centers answered a standardized questionnaire concerning women's specific issues in face-to-face interviews performed by trained field workers. Women 45 to 56 years were included in the present analyses. Younger women were excluded *a priori* because 45 years is the average age for onset of the perimenopausal transition,[11] and menstrual irregularity or amenorrhea before this age might be due to hormonal conditions other than menopause. Women currently using oral contraceptives (OC) (n = 88) or HRT (n = 388) and pregnant women (n = 2) were excluded to obtain a hormonally well-defined study population. Thus 1274 women were left for analyses.

Classification of the study population according to menstrual status

Women were asked the following: "If the last period was within the last 6 months, are your periods regular?" (alternative answers were "yes," "no, they have never been regular" and "no, they have been irregular for a few months") and "If the last period was more than 6 months ago, did your periods stop: naturally, because of surgery, or other?"

Based on these questions, the following groups were defined[24]: women with regular menstruations (n = 570), women with irregular menstruations for a few months (n = 272), and women with amenorrhea for 6 months or longer (n = 432). Women answering "No, they have never been regular" to the question "If the last period was within the last 6 months, are your periods regular?" (n = 72) were excluded because long-lasting menstrual irregularity might be due to hormonal conditions not necessarily associated with the menopausal transition.

Hormone samples

Serum measurements of FSH, LH, and estradiol were available for women from 13 of the 21 study centers, including 710 (56%) women in the present analyses. Serum samples were processed by means of chemiluminescence in an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany) at the Hôpital Xavier Bichat, Paris.

Outcome variables

Current asthma was defined as answering yes to the questions "Have you had an asthma attack in the last 12 months?," "Are you currently taking any asthma medicines?," or both. *Respiratory symptoms* were defined as having 3 or more of the following symptoms during the last 12 months: wheeze, wheeze with shortness of breath, wheeze when not having a cold, waking with tightness in the chest, shortness of breath at rest in the daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.[25] *Chronic cough and phlegm* was defined as answering yes to the questions "Do you cough like this on most days for as much as 3 months each year?" and "Do you bring up phlegm like this on most days for as much as 3 months each year?"; this corresponds to Global Initiative for Chronic Obstructive Lung Disease chronic obstructive pulmonary disease (COPD) classification stage 0.[26] *COPD* was defined as having an FEV_1/FVC ratio of less than 70%, which corresponds to Global Initiative for Chronic Obstructive Lung Disease stage 1 or higher.[26]

Specific IgE levels were measured by using the Pharmacia CAP system, and measurements were available for 1069 women. Specific IgE levels were judged to be positive if in excess of 0.35 kU/L of the specific allergen, the detection limit of the assay. Atopy was defined as specific IgE against any of the following allergens: house dust mites *(Dermatophagoides pteronyssinus)*, cat dander, timothy grass, and/or *Cladosporium herbarum*. *Three or more respiratory symptoms and allergy* was defined as having both 3 or more respiratory symptoms and allergy as compared with having none of these; "3 or more respiratory symptoms and no allergy" was defined as having 3 or more respiratory symptoms but not allergy compared with having none of these.

FEV_1 and FVC were recorded by using a standard spirometric method.[27] Height and weight were measured before measurement of lung function.

Covariates

BMI was based on measured weight and height. Pack-years of smoking were calculated based on questions about ever smoking and, among smokers, additional questions about age at starting smoking, current smoking, cutting down

TABLE I. Characteristics of the study population (1298 women* aged 45-56 years) by center

Center (n = 21)	Study population (n)	Median age (y)	Median BMI (kg/m^2)	Current smokers (%)	Amenorrhea (6 mo or longer [%])	Irregular menstruations (for a few months [%])†	Regular menstruations (%)	Asthma (%)‡	Respiratory symptoms (%)§	Chronic cough and phlegm (GOLD stage 0 [%])	Median FEV_1 (mL)	FEV_1/FVC <70% (GOLD stage 1 or higher [%])
S. Antwerp	47	50	24.5	14	34	30	36	2	13	4.4	3230	0
Antwerp	47	49	23.3	25	28	23	49	8.5	15	11	3000	11
Barcelona	59	50	25.7	27	53	3.4	44	6.8	29	3.4	2560	12
Galdakao	65	49	27.9	17	42	20	38	6	18	3.1	2660	5
Albacete	74	49	26.7	32	38	23	39	11	35	8	2595	8
Oviedo	74	49	26.7	32	41	16	43	9.5	30	1.4	2530	4
Huelva	41	48	28.3	27	34	12	54	12	37	15	2455	12
Bordeaux	25	48	24.5	34	33	21	46	4	16	0	2625	0
Grenoble	58	50	22.2	20	34	31	34	10	17	0	2660	7
Montpellier	28	53	22.9	11	46	21	32	14	21	3.6	2645	0
Paris	57	51	22.6	17	39	22	40	12	23	3.6	2650	4
Ipswich	64	50	25.7	12	34	27	39	11	27	0	2690	5
Norwich	58	49	27.6	16	17	26	57	21	22	3.5	2785	7
Reykjavik	51	49	25.3	25	30	8.5	62	7.8	18	6	2660	14
Bergen	91	49	25	31	28	26	46	7.9	21	2.3	2655	12
Gothenburg	85	50	27.2	25	28	24	48	20	33	3.6	2890	4
Umeå	94	49	23.4	22	26	25	49	17	25	5.3	2970	10
Uppsala	90	49	23.8	18	28	24	48	12	27	3.4	2960	6
Basel	87	50	24.0	31	54	10	36	14	24	3.4	2905	15
Portland	53	48	27.1	17	20	37	43	12	19	7.6	2745	0
Tartu	50	49	25.9	41	30	14	56	2	26	0	3000	4
Total	1298	49	25.1	23	34	21	45	11	24	4	2775	7

*Women currently using OC or HRT and pregnant women were excluded.
†Women answering "No, they have never been regular" to the question "Are your periods regular?" were excluded.
‡Asthma was defined as current asthma medication use, asthma attacks, or both during the last 12 months.
§Respiratory symptoms were defined as having 3 or more of the following 8 asthma symptoms in the last 12 months: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in the chest, shortness of breath in the daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.

or having stopped smoking, and amount smoked now and previously. Age at completed full-time education was used as a marker for educational level.

Statistical analysis

Logistic regression models were used to assess associations between menstrual status and dichotomous outcome variables. Linear regression models were used to assess associations with continuous variables: FEV_1, FVC, and lung function decrease. Adjustments were made for height (lung function), age, center, BMI (continuous variable), pack-years of smoking, and years of education. Differences between subgroups were analyzed by means of stratified logistic and linear regression models and by including interaction terms of menstrual status with BMI in analyses of respiratory symptoms and lung function. The interaction between menstrual status and BMI was assessed, reporting the lowest BMI category as reference. Stratification by BMI was made according to BMI in tertiles. Potential heterogeneity between countries was studied by means of random-effects meta-analyses.[28]

Graphic descriptions with generalized additive models (GAMs)[29] were made to visualize the prevalence of respiratory symptoms and level of FVC and FEV_1 with increasing age and according to menstrual status. For respiratory symptoms, GAMs with binomial distribution and a logistic link were used; for lung function, GAMs specifying Gaussian distribution and with an identity link for lung function were used. Adjustments were made for height (lung function), BMI, and smoking status.

RESULTS

In this population of 1298 women 45 to 56 years of age, amenorrhea in the last 6 months was reported by 34%, varying from 17% in Norwich to 54% in Basel. Irregular menstruations for a few months were reported by 21%, whereas 45% menstruated regularly (Table I).

Women with amenorrhea were heavier, older, less well educated, and more often current smokers than those menstruating regularly (Table II).

Hormone levels varied significantly according to menstrual status: women menstruating regularly had low levels of FSH and LH, those menstruating irregularly for a few months had higher levels, and those with amenorrhea had the highest levels. Estradiol was highest in women menstruating regularly and lowest in women with amenorrhea (Table III).

Women with amenorrhea had significantly lower FEV_1 and FVC values and more respiratory symptoms, both with and without allergy, than those menstruating regularly, whereas there was no significant association with chronic cough and phlegm or COPD. There were no significant differences in associations with respiratory symptoms or lung function between women menstruating irregularly for a few months and those menstruating regularly (Table IV).

There was no significant heterogeneity among countries in the association between amenorrhea and asthma symptoms ($P_{\text{heterogeneity}} = .23$; Fig 1, *A*) and amenorrhea and FEV_1 ($P_{\text{heterogeneity}} = .38$; Fig 1, *B*).

Amenorrheic women had more respiratory symptoms compared with women menstruating regularly at all ages; this was possibly more pronounced among women 45 to 50 years of age

TABLE II. Characteristics of the study population (1274* women† aged 45-56 years) according to menstrual status

	Regular menstruations (n = 570 [45%])	Irregular menstruations (for a few months; n = 272 [21%])‡	Amenorrhea (≥6 mo; n = 432 [34%])	Whole population (n = 1274 [100%])
Median age (y)	48	49.5	51	49
Median BMI (kg/m^2)	24.8	25.3	25.3	25.1
Never smoked (%)	48	49	46	48
Exsmokers (%)	29	31	27	29
Current smokers (%)	22	18	26	23
Mean pack-years	6.9	7	8.6	7.5
Median age at completed education (y)	20	20	18	19

*Difference from n = 1298 in Table I is due to missing data on menstrual status.
†Women currently using OC or HRT and pregnant women were excluded.
‡Women answering "No, they have never been regular" to the question "Are your periods regular?" were excluded.

TABLE III. Hormonal levels according to menstrual status in 710* women† aged 45 to 56 years

	Regular menstruations (n = 322)	Irregular menstruations (for a few months; n = 137)‡	Amenorrhea (≥6 mo; n = 251)	*P* value§
Median FSH (IU/L [25-75 percentile])	8 (4.9-13.8)	33 (13-68)	63 (39-83)	.0001
Median LH (IU/L [25-75 percentile])	6.6 (3.7-12)	21 (8.4-36)	29 (20-37)	.0001
Median estradiol (nmol/L [25-75 percentile])	0.31 (0.17-0.55)	0.16 (0.07-0.31)	0.08 (0.05-0.18)	.0001

*Subgroup with data on hormone measurements.
†Women currently using OC or HRT and pregnant women were excluded.
‡Women answering "No, they have never been regular" to the question "Are your periods regular?" were excluded.
§*P* value for difference according to the Kruskal-Wallis test.

TABLE IV. Associations of menstrual status with lung function and respiratory symptoms in 1274* women† aged 45-56 years

	Regular menstruations (n = 570)	Irregular menstruations (for a few months; n = 272)‡		Amenorrhea (≥6 mo; n = 432)	
Lung function	**Mean**	**Mean**	**Adjusted difference (95% CI)§**	**Mean**	**Adjusted difference (95% CI)§**
FEV_1 (mL)	2881	2780	−30 (−91 to 31)	2609	−120 (−177 to −63)
FVC (mL)	3628	3512	−23 (−93 to 47)	3322	−115 (−181 to −50)
Symptoms	**Percentage**	**Percentage**	**OR (95% CI)§**	**Percentage**	**OR (95% CI)§**
Current asthma‖	11	11	1.25 (0.74-2.10)	12	1.43 (0.89-2.31)
≥3 Respiratory symptoms¶	21	19	1.05 (0.70-1.58)	32	1.82 (1.27-2.61)
≥3 Respiratory symptoms¶ and allergy#	5.5	7.3	1.39 (0.73-2.66)	7.4	1.91 (1.03-3.53)
≥3 Respiratory symptoms¶ and no allergy#	13	8.5	0.75 (0.43-1.31)	20	1.76 (1.14-2.73)
Chronic cough and phlegm	4.1	4.5	1.41 (0.60-3.31)	5.2	1.60 (0.73-3.50)
COPD**	6.3	4.8	0.85 (0.43-1.69)	9.5	1.51 (0.88-2.59)

*Numbers included in each analysis varied slightly according to missing data for each variable.
†Women currently using OC or HRT and pregnant women were excluded.
‡Women answering "No, they have never been regular" to the question "Are your periods regular?" were excluded.
§Linear regressions adjusted for BMI, height, age, years of education, center, and pack-years of smoking are shown. Logistic regressions adjusted for BMI, age, years of education, center, and pack-years of smoking are shown. "Regular menstruation" was used as the reference group.
‖Current asthma was defined as current asthma medication use, asthma attacks, or both in the last 12 months.
¶Respiratory symptoms were defined as having 3 or more of the following 8 asthma symptoms in the last 12 months: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in chest, shortness of breath in the daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.
#Allergy was defined as 1 or more specific IgEs against any of the following allergens: house dust mite *(Dermatophagoides pteronyssinus)*, cat dander, timothy grass, and/or *Cladosporium herbarum*.
**COPD was defined as an FEV_1/FVC ratio of less than 70 according to the GOLD classification.

(Fig 2, *A*). Both FEV_1 and FVC values were lower in amenorrheic women than in women menstruating regularly at all ages; there was an indicated increase in difference with increasing age (Fig 2, *B* and *C*).

Increasing BMI was significantly associated with lower FEV_1 (adjusted difference, −13 mL; 95% CI, −17 to −9) and FVC (adjusted difference, −19 mL; 95% CI, −24 to −14) values and with increasing respiratory symptoms (odds ratio [OR], 1.09; 95% CI, 1.06-1.11) per unit increase in kilograms per square meter.

When stratifying by BMI in tertiles, the association of amenorrhea with lower lung function and respiratory symptoms was particularly strong and significant for women in the lower tertile and significantly associated with lower lung function in the highest tertile, whereas there was no association among women

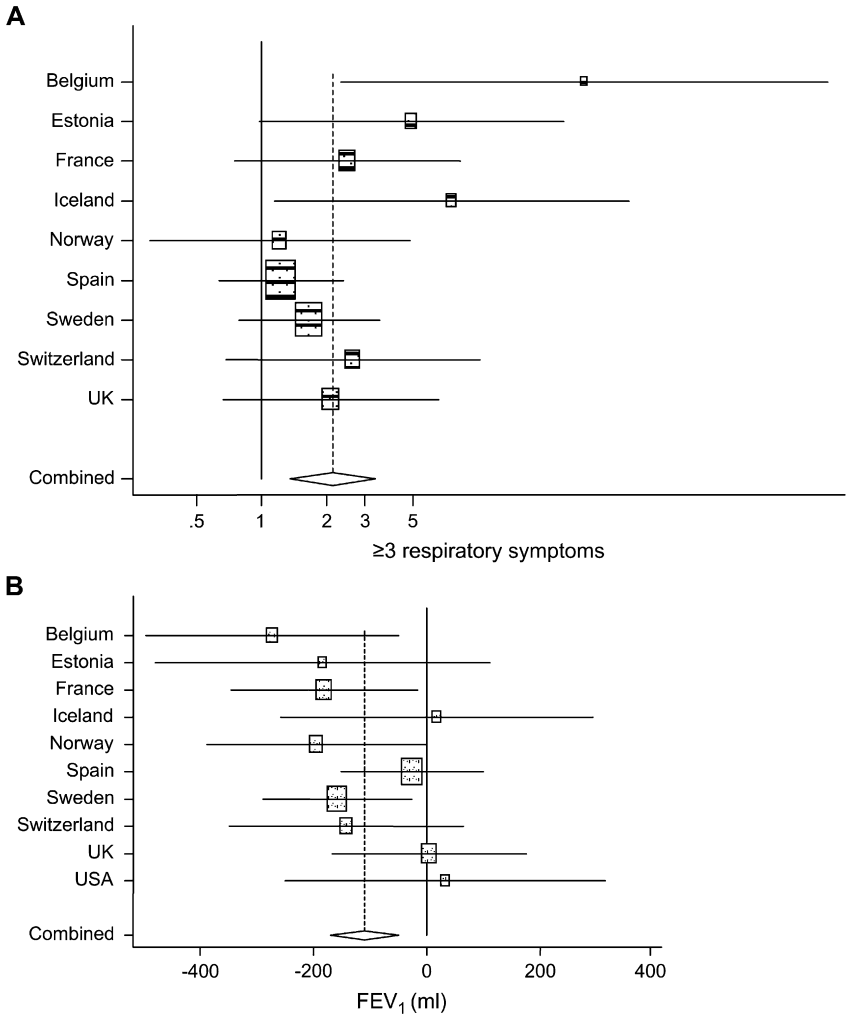

FIG 1. A, OR for the associations between amenorrhea (≥6 months) and 3 or more respiratory symptoms among 1274 women aged 45 to 56 years by country ($P_{heterogeneity}$ = .232). **B**, Adjusted differences for the associations between amenorrhea (≥6 months) and FEV_1 among 1120 women aged 45 to 56 years by country ($P_{heterogeneity}$ = .384). For each center, *horizontal lines* indicate 95% CIs. For the combined estimates, the *diamonds* indicate 95% CIs from model, with country as random effect. The size of each *square* is proportional to the sample size. *UK*, United Kingdom; *USA*, United States of America.

in the medium tertile (Table V). The interactions between BMI and menstrual status were significant in association with FEV_1 ($P_{interaction}$ = .04) and borderline significant in association with respiratory symptoms ($P_{interaction}$ = .06).

When limiting analyses to those who had never smoked (n = 606), those reporting amenorrhea had significantly lower FEV_1 values, indicated lower FVC values, and indicated more respiratory symptoms (see Table E1 in the Online Repository at www.jacionline.org). Furthermore, when stratifying those who never smoked by BMI in tertiles, the associations of amenorrhea with lung function and respiratory symptoms were strongest and significant for women in the lower and upper tertiles (data not shown).

DISCUSSION

In this analysis of a multinational population of women 45 to 56 years old, those not menstruating had significantly worse lung function and more respiratory symptoms than women of the same age menstruating regularly. Allergy-related respiratory symptoms were as strongly increased as respiratory symptoms without allergy. The findings were especially pronounced among lean women, whereas no increase in risk was observed in medium-weight women. The results were similar when limited to those who never smoked, and the findings were consistent between geographically and culturally different centers. Measured levels of FSH, LH, and estradiol showed that the classification of menstrual status based on questionnaire data[24] was very good.[10,30]

Lower lung function among menopausal women is a novel finding. To the authors' knowledge, lung function in relation to menopause has not been studied previously. Similarly, potential interactions between BMI and menopausal status have not been investigated earlier. An interaction between BMI and HRT in associations with respiratory symptoms has been published: increased asthma risk related to HRT was found only among lean women.[4] Increased respiratory symptoms in association with menopause, as observed in the present study, was not supported by previous literature; the RHINE study[4] showed no association

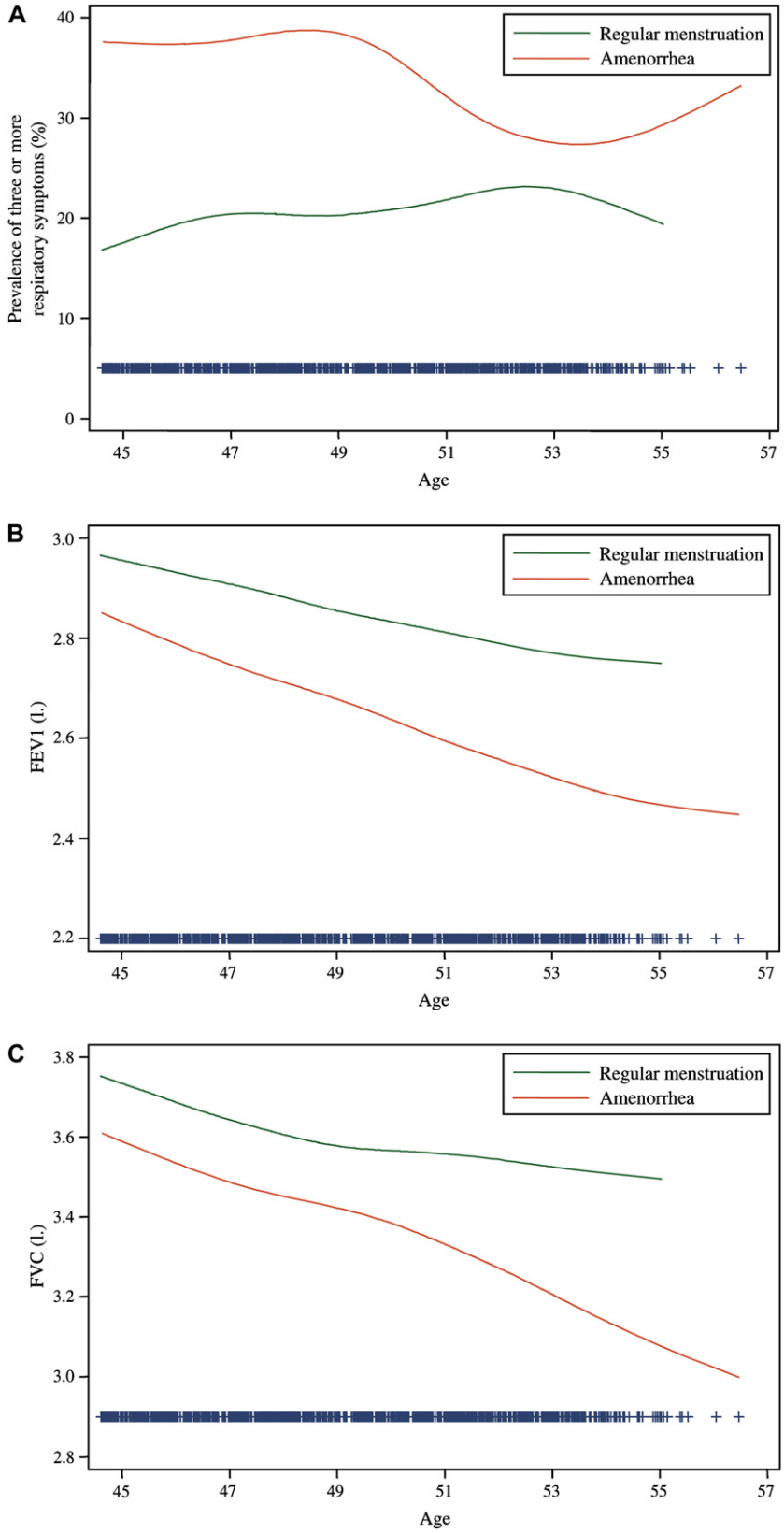

FIG 2. GAM curves showing the prevalence of 3 or more respiratory symptoms **(A)**, the level of FEV_1 **(B)**, and the level of FVC **(C)**, all 3 according to age in women with regular menstruation or amenorrhea for 1082 (Fig 2, *A*) and 1079 (Fig 2, *B* and *C*) women aged 45 to 56 years with complete data adjusted for height, BMI, and smoking. The *thicker blue line* at the bottom of each graph consists of individual crosses—one cross for each observation.

TABLE V. Associations of menstrual status with lung function and respiratory symptoms in 1261* women† aged 45 to 56 years stratified by BMI

	Lower tertile, BMI <23 (n = 344)			Medium tertile, BMI 23-28 (n = 439)			Upper tertile, BMI >28 (n = 478)		
	Regular menstruations (n = 173)	Amenorrhea (≥6 mo; n = 102)		Regular menstruations (n = 186)	Amenorrhea (≥6 mo; n = 146)		Regular menstruations (n = 203)	Amenorrhea (≥6 mo; n = 180)	
Lung function	Mean	Mean	Adjustable difference‡ (95% CI)	Mean	Mean	Adjusted difference‡ (95% CI)	Mean	Mean	Adjusted difference‡ (95% CI)
FEV_1 (mL)	3006	2690	−166 (−263 to −70)	2860	2672	−54 (−151 to 43)	2748	2462	−149 (−258 to −41)
FVC (mL)	3766	3456	−128 (−241 to −14)	3634	3416	−81 (−191 to 29)	3438	3092	−170 (−296 to −43)

Symptoms	Percentage	Percentage	OR‡ (95% CI)	Percentage	Percentage	OR‡ (95% CI)	Percentage	Percentage	OR‡ (95% CI)
Current asthma§	9.7	14	3.07 (1.23-7.7)	11	10	0.66 (0.29-1.50)	12	13	1.79 (0.75-4.30)
≥3 Respiratory symptoms‖	12	27	4.07 (1.88-8.8)	23	28	1.10 (0.61-1.97)	28	37	1.74 (0.91-3.31)
≥3 Respiratory symptoms‖ and allergy¶	8.9	16	3.70 (1.14-12.0)	9.5	13	1.25 (0.42-3.73)	11	13	2.47 (0.61-10.02)
≥3 Respiratory symptoms‖ and no allergy¶	7.4	26	5.71 (1.94-16.70)	25	25	0.82 (0.39-1.73)	28	41	1.91 (0.91-3.99)
Chronic cough and phlegm	3.7	5.3	1.51 (0.35-6.60)	5.4	4.6	0.95 (0.30-3.01)	3.3	5.7	2.21 (0.55-8.90)
COPD#	6.8	17.3	2.78 (1.16-6.70)	7.5	9.5	1.08 (0.46-2.55)	4.8	5.0	1.19 (0.41-3.44)

*Numbers included in each analysis varied slightly according to missing data for each variable.

†Women currently using OC or HRT and pregnant women were excluded.

‡Linear regressions adjusted for BMI, height, age, years of education, center, and pack-years of smoking are shown. Logistic regressions adjusted for BMI, age, years of education, center, and pack-years of smoking are shown. "Regular menstruation" was used as the reference group.

§Current asthma was defined as current asthma medication use, asthma attacks, or both last 12 months.

‖Respiratory symptoms were defined as having 3 or more of the following 8 asthma symptoms in the last 12 months: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in the chest, shortness of breath in the daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.

¶Allergy was defined as 1 or more specific IgEs against any of the following allergens: house dust mite *(Dermatophagoides pteronyssinus)*, cat dander, timothy grass, and/or *Cladosporium herbarum*.

#COPD was defined as an FEV_1/FVC ratio of less than 70 according to the GOLD classification.

between asthma and menopause, whereas the Nurses' Health Study[6] showed lower asthma risk in menopausal women. However, these studies did not stratify by BMI. Repeated analysis of RHINE data revealed that menopause was associated with more respiratory symptoms among lean women, which is in accordance with the present analysis (unpublished data). The estimate for the association of asthma with menopause as reported by Troisi et al[6] (relative risk, 0.66) is similar to the corresponding estimate in our analysis for women with a BMI of 23 to 28 kg/m^2 (Table V). Discordance between the studies might further be related to different selection mechanisms when excluding women using HRT, different BMI distributions, and different age spans.

Strengths of the present study are the availability of objective data: (1) measurements of lung function (FEV_1 and FVC); (2) blood samples with measurements of sex hormones (FSH, LH, and estradiol), validating questionnaire data about menstrual status; and (3) measurements of IgE for assessment of allergic asthma symptoms. In addition, women participating were randomly selected from the general population, thus avoiding selection bias. Furthermore, because of the multinational nature of the study and because findings were consistent across countries, the results are more likely due to a biologic mechanism than to potential sociocultural confounders that would have been heterogeneous between centers. Moreover, the questionnaire data about respiratory health and women's specific issues was collected by trained interviewers. Another advantage of this study is that the women were relatively young, providing a possibility to register onset of respiratory symptoms and changes in lung function at the age of the menopausal transition.[31]

The cross-sectional design of the analysis is a limitation in interpretation of the results. Longitudinal analysis of the data had low statistical power but indicated a larger function decrease and increased new onset of respiratory symptoms in amenorrheic women, which is consistent with cross-sectional results (see Table E2 in the Online Repository at www.jacionline.org). A possible source of error is that women could systematically report climacteric complaints as respiratory symptoms. This, however, does not explain the association of menopause with respiratory symptoms associated with allergy or the observed decrease in lung function. Smoking is another possible source of error because smoking is related to both earlier menopause,[11,32] probably because of its antiestrogenic effect,[33,34] and worsening respiratory health; amenorrheic women in our study were more often current smokers and smoked more. However, all analyses were adjusted for pack-years of smoking, there was a significant association with respiratory symptoms associated with allergy, and results remained when limiting analyses to those who had never smoked.

The availability of HRT is an important source of selection bias inherent to any study concerning perimenopause: women using HRT are highly selected, as well as women not using hormone treatment. The main indication for HRT in our age group is climacteric complaints; thus women using HRT are likely to be those with the most complaints, and exclusion of these women could imply a dilution of the observed results. The opposite seems unlikely: that those with the most climacteric complaints and therefore excluded from analyses because of HRT use should have particularly high lung function and low risk of asthma. Studies with many years of follow-up might exclude an increasing number of selected HRT users and thus not be able to show the true effects of menopause. Differences in selection caused by HRT might thus contribute to explain apparent discordance in results between studies.

Women undergo important hormonal and metabolic changes during the menopausal transition: endogenous estrogens are first increased and then decrease[11]; in addition, women become more insulin resistant.[11,16,19] A role of insulin resistance in the association of oligomenorrhea with lower lung function and increased respiratory symptoms has been suggested in previous analyses.[2,5] Other studies have observed a decrease in lung function in association with insulin resistance.[35-39] Thus lower lung function in menopausal women could be explained by increased insulin resistance in menopause. Furthermore, because insulin resistance is a proinflammatory condition,[40-42] this could explain the increase in respiratory symptoms associated with menopause. The effect modification of BMI on the effects of menopause might depend on the individual's level of available estrogen and metabolic status,[43] both of them partly determined by the adipose tissue[15,17] and reflected by BMI.[10,44] Thus estrogen production in adipose tissue might exert a protective role in normal-weight women, but in obese women this protective effect might be overshadowed by insulin resistance associated with increasing BMI.

In conclusion, menopause was associated with lower lung function and more respiratory symptoms, especially among lean women. The main clinical implication of the presented findings is that women undergoing the menopausal transition might be at risk of deteriorating lung health. However, this applies to lean women and, to some extent, to obese women. A BMI of between 23 and 28 kg/m^2 appears to be optimal in perimenopausal women with regard to respiratory health.

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Clinical implications: Clinicians should be aware of increased asthma risk and lower lung function in women reaching menopause. These problems appeared to be less pronounced among women with a BMI of approximately 25 kg/m^2.

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TABLE E1. Associations of menstrual status with lung function and respiratory symptoms in 606* women who never smoked† aged 45 to 56 years

	Regular menstruations (n = 274)	Irregular menstruations (for a few months; n = 134)‡		Amenorrhea (≥6 mo; n = 198)	
Lung function	**Mean**	**Mean**	**Adjusted difference§ (95% CI)**	**Mean**	**Adjusted difference§ (95% CI)**
FEV_1 (mL)	2870	2741	−27 (−115 to 60)	2587	−101 (−186 to −17)
FVC (mL)	3589	3440	−5 (−110 to 100)	3249	−96 (−197 to 4)
Symptoms	**Percentage**	**Percentage**	**OR§ (95% CI)**	**Percentage**	**OR§ (95% CI)**
≥3 Respiratory symptoms‖	24	19	0.94 (0.53-1.68)	30	1.44 (0.85-2.45)
≥3 Respiratory symptoms‖ and allergy¶	11	11	1.22 (0.45-3.34)	15	1.83 (0.72-4.67)
≥3 Respiratory symptoms‖ and no allergy¶	22	16	0.67 (0.30-1.46)	30	1.40 (0.74-2.67)

*Difference with n = 1298 in Table I is due to available data on women who never smoked.
†Women currently using OC or HRT and pregnant women were excluded.
‡Women answering "No, they have never been regular" to the question "Are your periods regular?" were excluded.
§Linear regressions adjusted for BMI, height, age, years of education, center, and pack-years of smoking are shown. Logistic regressions adjusted for BMI, age, years of education, center, and pack-years of smoking are shown. "Regular menstruation" was used as the reference group.
‖Respiratory symptoms were defined as having 3 or more of the following 8 asthma symptoms in the last 12 months: wheeze, wheeze with breathlessness, wheeze when not having a cold, waking with tightness in the chest, shortness of breath in the daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.
¶Allergy was defined as 1 or more specific IgEs against any of the following allergens: house dust mite *(Dermatophagoides pteronyssinus)*, cat dander, timothy grass, and/or *Cladosporium herbarum.*

TABLE E2. Associations of menstrual status with lung function decrease* and new onset of respiratory symptoms† in women‡ aged 45 to 56 years

	Amenorrhea (≥6 mo)§
Lung function (n = 985)	**Adjusted difference‖ (95% CI)**
Decline ΔFEV_1 (mL)	−2.58 (−7.09 to 1.93)
Symptoms¶ (n = 748)	**RR‖ (95% CI)**
Wheeze with breathlessness	1.26 (0.63-2.51)
Waking with tightness in chest	1.75 (0.83-3.66)
Shortness of breath in daytime	1.90 (0.48-7.44)
Shortness of breath after strenuous activity	1.11 (0.67-1.83)
Waking with shortness of breath	3.53 (1.04-12.03)

Women with menopause before ECRHS I (baseline) were excluded.
RR, Relative risk.
*FEV_1 in ECRHS II minus FEV_1 in ECRHS I.
†New onset of respiratory symptoms in ECRHS II when all women with asthma ever or current respiratory symptoms in ECRHS I were excluded.
‡Women currently using OC or HRT and pregnant women were excluded.
§"Regular menstruation" was used as the reference group.
‖Linear regressions adjusted for mid-BMI, change in BMI, height, midage, country, and change in smoking habits are shown. Binary regressions adjusted for BMI, age, country, and smoking are shown.
¶Symptoms included in the variable "≥3 symptoms of asthma."