

Original article

Menstrual irregularity and asthma and lung function

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Background: Oligomenorrhea was associated with more asthma (Respiratory Health in Northern Europe study), but a possible association with lung function has not been investigated previously.

Objective: To investigate whether oligomenorrhea was related to lung function and asthma, and whether body mass index and physical activity modified associations.

Methods: Women age 28 to 44 years (n = 1631) participating in the European Community Respiratory Health Survey were included. Women who were taking exogenous sex hormones, were pregnant, or had recently given birth were excluded.

Results: Long or irregular menstrual cycles were reported by 313 women (19%). Oligomenorrhea was significantly associated with more asthma symptoms (odds ratio [OR], 1.76; 95% CI, 1.29-2.40), allergic asthma (OR, 2.46; 95% CI, 1.43-4.23), and lower forced vital capacity (FVC; adjusted difference, 63 mL; 95% CI, -124 to -1). When excluding women using asthma medication, very lean women, or women exercising daily, these associations remained significant. Effects of oligomenorrhea were additive to those of body mass index (BMI) on asthma and

FVC. Asthma symptoms increased significantly with BMI. FVC and FEV₁ increased with BMI until 25 kg/m² and thereafter decreased with increasing BMI. Excluding women exercising daily, asthma symptoms increased significantly with decreasing physical activity (OR, 1.09; 95% CI, 1.001-1.19) per category of physical activity) independently of oligomenorrhea. Among women exercising daily, oligomenorrhea predicted very high risk for asthma symptoms (OR, 12.6; 95% CI, 3.7-43).

Conclusion: Women with oligomenorrhea have reduced lung function and more asthma, particularly allergic asthma, independent of BMI and physical activity. Airways pathology may have not only a hormonal but also a metabolic component. Clinical implications: Women with oligomenorrhea should be investigated with regard to asthma and lung function. Underlying metabolic disturbance should be considered in asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Irregular menstruation, oligomenorrhea, asthma, lung function, allergy, body mass index, physical activity, insulin resistance, ECRHS

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There is a growing awareness that sex hormones play an important role in the development of airways pathology in women, but the pathophysiologic mechanisms remain unclear. The literature provides some intriguing pieces of information: women with asthma may have abnormal sex hormone levels,^{1,2} and use of asthma medication is more common in women with infertility.³ Obesity is related to higher risk for asthma⁴⁻⁷ and lower lung function.⁸ Subjects with low physical activity showed higher bronchial responsiveness.⁹ Moreover, some evidence has been provided that reduced lung function may be associated with increased insulin resistance.¹⁰⁻¹⁴ There could be a common denominator behind these apparently unrelated conditions: insulin resistance is related to abnormal sex hormones levels, infertility, low physical activity, and increased body mass index (BMI).¹⁵

Long and/or irregular menstrual cycles are a common phenomenon among women in fertile age, with a prevalence of about 20%.¹⁶ Oligomenorrhea is usually a symptom of polycystic ovarian syndrome (PCOS),¹⁷⁻¹⁹ accompanied by hormonal changes and subfertility. Today we know that PCOS is a proinflammatory condition²⁰ and a manifestation of insulin resistance that is sometimes treated with

Abbreviations used

BHR:	Bronchial hyperresponsiveness
BMI:	Body mass index
ECRHS:	European Community Respiratory Health Survey
FVC:	Forced vital capacity
GAM:	Generalized Additive Model
HRT:	Hormone replacement therapy
IM:	Irregular menstruation
OR:	Odds ratio
PCOS:	Polycystic ovarian syndrome

insulin-sensitizing drugs.^{15,21-23} Oligomenorrhea is associated with increased risk for diabetes mellitus,²³ cardiovascular diseases,^{24,25} and diabetes in pregnancy.²⁶

An association of irregular menstruation (IM) with increased risk for asthma and hay fever was observed in the Respiratory Health in Northern Europe study,²⁷ a daughter study of the European Community Respiratory Health Survey (ECRHS) conducted by postal questionnaire in a Nordic-Baltic population. A study from The Netherlands indicated that IM was associated with non-specific lung disease and allergic disease.²⁸ To the authors' knowledge, there is no previous study investigating a possible association between IM and lung function.

The aim of the current study was to investigate whether menstrual irregularity is associated with lung function and asthma, and further to investigate whether potential associations are modified by BMI and physical activity.

METHODS

Study design

This study is a cross-sectional analysis of the ECRHS II. ECRHS I²⁹ was an international survey performed from 1991 to 1992 in randomly selected individuals from the 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,³⁰ which took place from 1998 to 2002. The examinations performed at both surveys included an interviewer-led questionnaire and measurements of lung function, bronchial hyperresponsiveness (BHR), and serum IgE. Ethical approval was obtained for each study center from the appropriate institutional or regional ethics committee, and informed written consent was provided by each participant.

Women's questionnaire and study population

There were 4259 women from 21 centers in ECRHS II who answered a questionnaire concerning women specific issues. Women age 28 to 44 years were included in the current analyses. Older women were excluded *a priori* because 45 years is the average age for onset of the perimenopausal transition¹⁵ and menstrual irregularity after this age may be a result of the perimenopause (see Fig E1 in this article's Online Repository at www.jacionline.org). Nonmenopausal women younger than 45 years with amenorrhea >6 months (n = 192) were excluded because of the structure of the questionnaire. Among these, menstruation stopped because of surgery in 59 women and for other reasons in 133 women. To obtain a hormonally well defined study population, women using hormone replacement

therapy (HRT) since the last survey (n = 166) or currently using oral contraceptives (n = 500), pregnant women (n = 62), and women who had given birth within the last 6 months (n = 52) were excluded because these factors influence the pattern of menstrual bleedings. Thus, 1631 women were left for analyses. Of these, 1623 had complete data concerning IM, and the number included in each analysis within this group varies because of a varying number of missing data for each variable.

Definition of IM

Irregular menstruation, used synonymously with "oligomenorrhea" and "irregular menstrual cycles and/or cycles longer than 32 days," was defined as (1) answering "No, they have never been regular" or "No, they have been irregular for a few months" (n = 295) when asked, "Are your periods regular?" and/or (2) answering "more than 32 days" (n = 106) to the question, "What is the usual interval between your periods? (from the first day of one period to the first day of the next)" (alternatives: "less than 24 days," "24-26 days," "27-29 days," "30-32 days," and "more than 32 days."

Of the 313 women thus defined as having IM, only 18 women with long cycles did not report menstrual irregularity as well. These questions were asked by trained field-workers during face-to-face interviews by using standardized questionnaires. This definition corresponds to the classic definition of oligomenorrhea,¹⁵ and is relatively similar to definitions used in other epidemiologic studies.^{23-25,27}

Outcome variables

Current asthma was defined as answering yes to the questions, "Have you had an asthma attack in the last 12 months?" and/or "Are you currently taking any asthma medicines?" "Asthma symptoms" was defined as having had 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 chest, shortness of breath at rest in daytime, shortness of breath after strenuous activity, waking with shortness of breath, and waking by attack of cough.³¹

Methacholine challenge was performed with a dosimeter (Mefar, Brescia, Italy).³² FEV₁ was recorded 2 minutes after each inhalation with methacholine, and the test was stopped when either a 20% fall in FEV₁ was achieved or a final maximum dose of 2 mg methacholine had been given. "Asthma with BHR" was defined as having current asthma and a 20% fall in FEV₁ when challenged with methacholine.

Specific IgEs were measured using the Pharmacia CAP system. Specific IgE was 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*. "Allergic asthma" was defined as having both asthma and atopy, compared with having neither asthma nor atopy; "nonallergic asthma" was defined as having asthma but not atopy, compared with having neither asthma nor atopy. Similarly, subjects having asthma symptoms with or without atopy were compared with those not having asthma symptoms or atopy.

FEV₁ and forced vital capacity (FVC) were recorded by a standard spirometric method. The ratio between FEV₁ and FVC was calculated and referred to as FEV₁/FVC ratio; this was used as a continuous variable.⁸ Height and weight were measured before lung function.

Covariates

Physical exercise was defined by the question, "How often do you usually exercise so much that you get out of breath or sweat?" with 7 alternative answers according to decreasing frequency; those answering "every day" defined "daily exercise" (121 subjects). BMI was based on measured weight and height and calculated as weight in

TABLE I. Characteristics of 1631 women age 28 to 44 years*

Center (n = 21)	No.	Median age (y)	IM† (%)	BMI, median (kg/m ²)	Daily exercise‡ (%)	Current smokers (%)	Current asthma§ (%)	Asthma symptoms (%)	FVC, median (L)	FEV ₁ , median (L)
S Antwerp	35	37	14	23	17	34	5.7	23	4.11	3.47
Antwerp	46	38	15	21.9	17	30	8.7	22	3.95	3.30
Barcelona	96	38	18	23.1	6.3	40	12.5	23	3.74	3.01
Galdakao	118	37	27	24.1	10	47	8.5	19	3.67	3.09
Albacete	116	36	23	23.8	5.3	51	5.2	31	3.69	3.04
Oviedo	71	39	17	23.7	4.3	52	12.7	35	3.76	3.14
Huelva	88	37	22	24	3.4	47	10.2	31	3.55	2.94
Bordeaux	23	37	26	22.3	8.7	39	22	26	3.61	2.92
Grenoble	43	38	21	21.6	2.3	35	14	28	3.74	3.03
Montpellier	26	39	12	21.2	0	23	4	7.7	3.57	3.21
Paris	72	39	21	21.9	4.2	44	8.3	15	3.54	3.11
Ipswich	82	37	26	25.7	6.7	27	27	44	3.96	3.14
Norwich	73	40	19	25	6.9	16	18	22	3.89	3.15
Reykjavik	99	39	10	23.7	2.0	26	9.1	16	3.74	3.09
Bergen	101	39	7.1	24.4	4.0	35	9.2	19	3.82	3.04
Gothenburg	90	37	12	23.7	7.8	29	13.3	26	3.80	3.19
Umeå	109	37	22	23.9	4.6	18	21	36	4.05	3.28
Uppsala	125	36	16	22.5	10	18	20	19	4.01	3.23
Basel	81	38	28	22.1	5.0	28	11	28	3.97	3.20
Portland	43	39	23	26	4.7	19	7.5	24	3.80	3.11
Tartu	94	36	24	23	26	39	1.1	18	4.08	3.40
Totals	1631	37	19	23.5	7.5	34	12.1	25	3.82	3.14

*Oral contraceptive and HRT users, pregnant women, and women who had given birth within the last 6 months were excluded.

†Defined as reporting irregular menstrual cycles and/or cycles longer than 32 days.

‡Daily strenuous exercise.

§Asthma defined as current asthma medication and/or asthma attacks last 12 months.

||Three or more of the following 8 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.

kilograms divided by the square of height in meters. Categorization into “current smokers,” “exsmokers,” and “never-smokers” was based on the question, “Have you ever smoked for as long as a year?” If answering yes, the subjects were asked, “Do you smoke now, as of 1 month ago?” Age at completed full time education was used as a marker for educational level.

Statistical analysis

Logistic regression models were used to assess the effects of IM on the dichotomous outcome variables asthma and asthma symptoms, with adjustments for center, age, BMI (as a continuous variable), smoking, and years of education. Linear regression models were used to assess the effects of IM on the continuous variables FEV₁, FVC, and FEV₁/FVC ratio. Adjustments were made for height, age, center, BMI (as a continuous variable), smoking, and years of education. Differences between subgroups were analyzed by including interaction terms of IM with BMI or with physical exercise in analyses of asthma and lung function.

Potential heterogeneity between countries was studied by meta-analyses according to DerSimonian and Laird,³³ using logistic regressions of binary outcomes and linear regression of continuous outcomes, with adjustment for age, BMI, smoking, and years of education; lung function was also adjusted for height.

Graphic descriptions using Generalized Additive Models (GAMs)³⁴ were made to visualize the prevalence of IM by BMI and the prevalence of 3 or more symptoms of asthma or level of FVC and FEV₁, with increasing BMI in women with regular and IM. For 3 or more symptoms of asthma, a GAM with binomial distribution and logistic link was used. For lung function, a GAM specifying Gaussian distribution and with identity link for lung function was used.

TABLE II. Characteristics of the study population according to the presence of regular or irregular menstruation*

	Regular menstruation (n = 1310)	IM† (n = 313)	P value
Mean age (y)	37.5	36.7	.003
Median BMI (kg/m ²)	23.5	23.5	.8
Strenuous exercise			.3
Daily (%; n = 120)	7.3	8.3	
Never (%; n = 468)	29	31.4	
Current smokers (%)	33	37	.13
Years of education	21	20	.04

*Oral contraceptive and HRT users, pregnant women, and women who had given birth within the last 6 months were excluded.

†Defined as reporting irregular menstrual cycles and/or cycles longer than 32 days.

RESULTS

Of 1631 women age 28 to 44 years participating in the study, 313 (19 %) reported having irregular menstrual cycles and/or cycles longer than 32 days. The prevalence of IM varied between 28% in Basel and 7.1% in Bergen (Table I). The median BMI varied from 21.2 kg/m² in Montpellier to 26 kg/m² in Portland.

Women with IM were slightly younger and less educated than the controls, and had about the same median

TABLE III. Associations of IM with asthma, asthma symptoms, and lung function in 1623 women aged 28 to 44 years*

	Regular menstruation (n = 1310) Percent	IM† (n = 313) Percent	Adjusted association‡ OR (95% CI)
Asthma and symptoms			
Asthma, ever	18	23	1.37 (0.98-1.92)
Asthma, current§	19	26	1.56 (1.03-2.36)
Asthma, current§ + BHR	19	30	1.87 (1.00-3.51)
Wheeze when not having a cold	18	25	1.52 (1.07-2.18)
Waking with tightness in chest	18	24	1.54 (1.10-2.16)
Shortness of breath in daytime	18	30	1.79 (1.20-2.68)
Shortness of breath after strenuous activity	17	26	1.50 (1.09-2.06)
≥3 Asthma symptoms¶	17	27	1.76 (1.29-2.40)
Nonallergic asthma			
Nonallergic asthma#	18	15	0.89 (0.42-1.91)
≥3 Asthma symptoms¶ and no atopy#	16	25	1.70 (1.10-2.62)
Allergic asthma			
Allergic asthma#	18	35	2.46 (1.43-4.23)
≥3 Asthma symptoms¶ and atopy#	16	34	2.58 (1.63-4.08)
	Mean	Mean	Adjusted difference** (95% CI)
Lung function			
FEV ₁ (L/mL)	3.141	3.131	-15 mL (-69 to 39)
FVC (L/mL)	3.851	3.791	-63 mL (-124 to -1)
FEV ₁ /FVC ratio (%)	81.8%	828%	0.9% (0.03 to 1.8)

*Oral contraceptive and HRT users, pregnant women, and women who had given birth within the last 6 months were excluded.

†Defined as reporting irregular menstrual cycles and/or cycles longer than 32 days.

‡Logistic regressions of binary outcomes, linear regression of continuous outcomes, with adjustment for age, BMI, smoking, years of education, and center.

Lung function also adjusted for height.

§Asthma defined as current asthma medication and/or asthma attacks in the last 12 months.

||BHR defined as 20% fall in FEV₁ when challenged with methacholine.

¶Three or more of the following 8 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.

#Compared with subjects with no asthma/symptoms and no atopy. Atopy defined as 1 or more specific IgE against any of the following allergens: house dust mite (*Dermatophagoides pteronyssinus*), cat dander, timothy grass, and/or *Cladosporium herbarum*.

**Adjusted difference = β coefficient.

BMI (Table II). Women with IMs did not differ significantly from the controls regarding strenuous exercise or current smoking. An indicated U-shaped association between BMI and IM (see Fig E2 in this article's Online Repository at www.jacionline.org) was not statistically significant when analyzed by using logistic regression, adjusting for age, smoking status, years of education, and physical activity.

Asthma and asthma symptoms, particularly allergic asthma, were significantly more common in women with IMs (Table III). FVC was significantly lower in women with IMs, whereas a weakly indicated association between IM and FEV₁ was not statistically significant (Table III). The results were consistent between centers for asthma symptoms (P for heterogeneity = .328; see Fig E3, A, in this article's Online Repository at www.jacionline.org) and for FVC (P for heterogeneity = .265; see Fig E3, B, in this article's Online Repository at www.jacionline.org). When excluding 151 women currently using asthma medication, the estimates of the associations of IMs with asthma and lung function remained unchanged (asthma symptoms: odds ratio [OR], 1.80; 95% CI, 1.27-2.56; FVC: adjusted difference, -59 mL; 95% CI, -123 to 0). Similarly, the results remained unchanged when excluding 70 women with BMI <19 kg/m² (data not shown). When 120 women reporting daily strenuous physical exercise were excluded,

the results were still significant and the estimates basically unchanged: the association of IMs with asthma symptoms was slightly attenuated (OR, 1.76 [95% CI, 1.29-2.40] vs OR, 1.48 [95% CI, 1.06-2.07]), whereas the association with FVC was slightly stronger (adjusted difference, -63 mL [95% CI, -124 to -1] vs adjusted difference, -76 mL [95% CI, -140 to -11]; Tables III and IV).

Asthma symptoms increased significantly with BMI (OR, 1.04; 95% CI, 1.02-1.07, per kg/m²) independent of menstrual irregularity. Women with IMs had higher prevalence of asthma symptoms for all values of BMI (Fig 1, A). The effects of IM on asthma symptoms were additive to those of BMI, and there was no interaction of IM with BMI. The same was true for other asthma definitions, such as wheezing when not having a cold (see Fig E4 in this article's Online Repository at www.jacionline.org). FVC and FEV₁ increased with increasing BMI to a maximum at approximately 25 kg/m² and thereafter decreased with increasing BMI (Fig 1, B and C). FVC was consistently lower in women with IMs (Fig 1, B). An interaction of IM with BMI on FEV₁ was borderline significant (P = .065; Fig 1, C).

Asthma symptoms were extremely prevalent among women with IM exercising daily (see Fig E5 in this article's Online Repository at www.jacionline.org). When excluding women exercising daily and analyzing all women

TABLE IV. Associations of irregular menstruation* with asthma symptoms and lung function among women with daily strenuous exercise (25 with IM*), and among women not exercising daily (283 with IM*), among 1606 women with complete information†

	Daily exercise (n = 120)	Not daily exercise (n = 1486)	
	Adjusted associations‡	Adjusted associations‡	P _{interaction} §
Asthma symptoms	OR (95% CI)	OR (95% CI)	
≥3 Symptoms	12.56 (3.65-43.24)	1.48 (1.06-2.07)	.001
≥3 Asthma symptoms and no atopy¶	27.60 (3.74-203.49)	1.31 (0.83-2.07)	.001
≥3 Asthma symptoms and atopy¶	21.49 (3.07-150.07)	2.19 (1.39-3.45)	.015
Lung function	Adjusted difference# (95% CI)	Adjusted difference# (95% CI)	
FEV ₁	100 mL (−103 to 303)	−27 mL (−85 to 30)	.36
FVC	72 mL (−158 to 302)	−76 mL (−140 to −11)	.36

*Defined as reporting irregular menstrual cycles and/or cycles longer than 32 days.

†Oral contraceptive and HRT users, pregnant women, and women who had given birth within the last 6 months were excluded.

‡Logistic regressions of binary outcomes, linear regression of continuous outcomes, with adjustment for age, BMI, smoking, years of education, and center. Lung function also adjusted for height.

§P value for interaction term of IM with daily strenuous exercise.

||Three or more of the following 8 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.

¶Compared with subjects with no asthma/symptoms and no atopy. Atopy defined as 1 or more specific IgE against any of the following allergens: house dust mite (*Dermatophagoides pteronyssinus*), cat dander, timothy grass, and/or *Cladosporium herbarum*.

#Adjusted difference = β coefficient.

together by multivariate logistic regression analysis (adjusted for BMI, smoking, age, education, and center), the increase in asthma symptoms with decreasing physical activity as suggested by Fig E5 (see this article's Online Repository at www.jacionline.org) was significant with an OR of 1.09 (95% CI, 1.001-1.19) per category of physical activity ($P_{\text{trend}} = .046$; categories of physical activity as presented in Fig E5 in this article's Online Repository at www.jacionline.org), and the effect of physical activity on asthma symptoms did not interact significantly with IM ($P = .611$ for interaction term of physical activity and IM in model as described). In the small subgroup of women exercising daily, IM was associated with greatly increased risk for asthma symptoms, and these interactions were significant ($P_{\text{interactions}} \leq .015$; Table IV).

DISCUSSION

In this cross-sectional analysis of a multinational population, women reporting long or irregular menstrual cycles had significantly lower FVC and more asthma, particularly allergic asthma. These associations were not modified by BMI or physical activity. On the other hand, FVC was lower in women with oligomenorrhea at any level of BMI, and asthma was more common in women with oligomenorrhea at any level of BMI or physical activity. The associations were consistent across centers, and remained significant when excluding women using asthma medication, very lean women, or women exercising daily. The well documented association of asthma with BMI was confirmed. A novel finding, however, was that in these women in fertile age, FVC and FEV₁ increased with BMI until a maximum of approximately 24 to 25 kg/m² and thereafter decreased with further increasing BMI. Lower physical activity was associated with higher asthma

risk when excluding women exercising daily. Thus, oligomenorrhea and BMI were independently associated with lung function, and oligomenorrhea, BMI, and physical activity were all independently associated with asthma.

This is the first study to show an association between menstrual irregularity and lung function. Concerning asthma symptoms, the findings are in accordance with our analysis of Respiratory Health in Northern Europe, where an association between menstrual irregularity and increased risk for asthma and allergy was found.²⁷ The observed association of lung function with BMI, with an optimum at about 25 kg/m² and lower lung function among the very lean and the overweight, to our knowledge has not been described previously. This pattern seems biologically plausible, and an attempt should be made to reproduce it in another population of young women. The association of asthma with lower physical activity agrees with a previous analysis of exercise and bronchial responsiveness in the ECRHS.⁹

Self-reporting of menstrual patterns in the menopausal transition has been validated in other studies and is considered to be reliable.³⁵ In an attempt to validate self-reporting of menstrual irregularity in our cohort, we analyzed 564 women in our study population who had answered to a question concerning menstrual irregularity ("Are your periods regular?" with response alternatives yes/no/don't know) in a postal questionnaire 1 to 3 years before the current study.²⁷ The agreement was 86% and the κ for agreement 0.41 (moderate agreement), even if there was a time lag of 1 to 3 years between the 2 studies, the study method was different (postal questionnaire vs face-to-face interview), and the response alternatives were different. Self-reporting of menstrual irregularity among younger women was also validated in the Nurses Health Study, where the prevalence of menstrual irregularity was compared in 2 cohorts of women and was found to

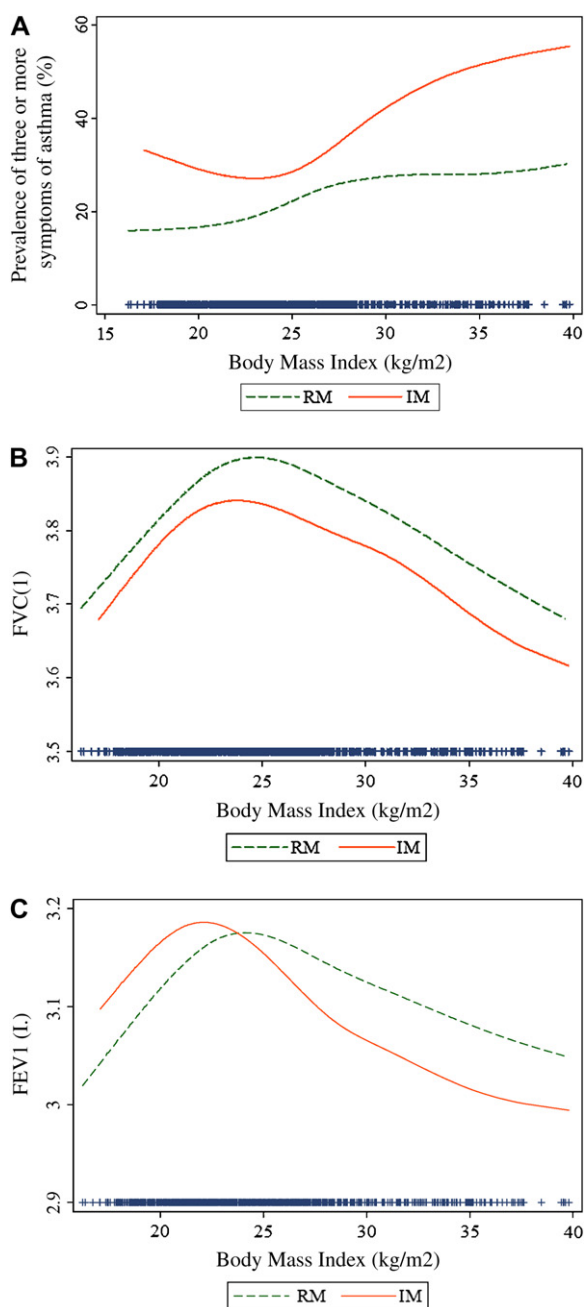


FIG 1. GAM curves showing (A) prevalence of ≥ 3 asthma symptoms, (B) level of FVC, and (C) level of FEV₁; all 3 according to BMI in women with regular menstruation (RM) and IM for 1334 (A) and 1350 (B and C) women age 28 to 44 years with complete data.

be similar.^{23,24} Oligomenorrhea is classically defined as length of menstrual cycles 35 days or longer and irregular cycles. Women included in the current analyses were asked whether their cycles were longer than 32 days. The variable IM thus mostly corresponds with the classic definition of oligomenorrhea, and the prevalence of oligomenorrhea in the current study is similar to that reported in the literature.^{15,24,25,27} Analyses were performed separately for each of the questions concerning IM (“Do you

have cycles longer than 32 days?” $n = 106$; or “Do you have irregular menstruations?” $n = 295$), showing similar results. The exclusion of women with amenorrhea for 6 months or longer could imply a dilution of the observed results, because the women with the most serious oligomenorrhea were not investigated.

Women with oligomenorrhea might have their asthma diagnosed more often than women with regular menstruation. However, among current patients with asthma, those with oligomenorrhea had less doctor-diagnosed asthma than those with regular menstrual cycles (52% vs 46%). Moreover, among women with ≥ 3 asthma symptoms, those with oligomenorrhea reported a lower use of asthma medication compared with those with regular cycles (data not shown). This suggests that our findings are unlikely to be explained by increased physician contact in women with IM.

All analyses were performed adjusting for smoking status. With adjustment for smoking intensity (pack-years), the results were similar; thus, the associations were not a result of residual confounding by smoking. Because of the cross-sectional design of this study, it is not possible to determine the time relationship between oligomenorrhea and asthma/lung function.

Analyses were performed excluding women using current asthma medication, and the associations of oligomenorrhea with asthma symptoms and FVC were still significantly present. Thus, it seems unlikely that oligomenorrhea was caused by current asthma medication. It is possible that the stress of severe asthma might cause oligomenorrhea, but the fact that the associations were present when those using asthma medication were excluded suggests that this was uncommon and did not explain the findings. Menstrual irregularity is usually a symptom of PCOS but may also develop as a consequence of emotional or physical stress¹⁵ related to anorexia nervosa, poor nutrition, chronic illness, or strenuous physical activity.³⁶ The associations of oligomenorrhea with FVC and asthma symptoms remained when excluding women with BMI < 19 kg/m² and when excluding the subgroup of women reporting daily exercise. Thus, menstrual irregularity caused by anorexia nervosa or strenuous physical exercise was not driving the main associations.

Menstrual disturbances among lean women might be related to eating disorders or intense exercising. As expected, the subgroup of women with BMI < 19 ($n = 72$) had a higher prevalence of oligomenorrhea (30%) compared with the whole study group (20 %). However, only 7 women with BMI < 19 exercised daily, and only 1 of these reported IM. Therefore, the high prevalence of IM among lean women could not be explained by intense physical activity.

It has been argued that oligomenorrhea reflects insulin resistance in women more precisely than other diagnostic criteria,³⁷ and there is an increasing awareness of the role of PCOS as a risk factor for cardiovascular diseases and diabetes mellitus.^{15,38-40} Analyses of the Nurses’ Health Study II showed that women with oligomenorrhea were at higher risk of developing both diabetes mellitus²³ and cardiovascular diseases.²⁴ This was explained by the

metabolic abnormalities underlying oligomenorrhea and could not be explained by obesity alone.²³ Insulin resistance is a proinflammatory condition^{41,42} expressed by increased inflammation markers such as C-reactive protein, TNF- α ,⁴³ and IL-6,⁴⁴⁻⁴⁶ among others.

Our study showed that oligomenorrhea, BMI, and physical activity were all independently related to asthma. It seems plausible that insulin resistance may be a common denominator for these findings: lower lung function, particularly FVC, appears to be associated with insulin resistance and diabetes,^{10-14,47} in agreement with the lower FVC observed in women with oligomenorrhea. The association of asthma and lung function with BMI may be explained by insulin resistance and inflammation related to obesity.^{15,44,48} The observed association of physical activity with lower prevalence of asthma symptoms may be explained by increased physical activity leading to improved insulin sensitivity, and thus to less inflammation. A role of insulin resistance in respiratory health is further supported by the literature showing that the balance of oxidants and antioxidants in the diet is of importance for obstructive lung disease,⁴⁹⁻⁵¹ with oxidative stress an important aspect of insulin resistance.⁵²⁻⁵⁴

A small subgroup of women with very high asthma risk was identified: women with oligomenorrhea who reported daily exercise. It seems unlikely that this could be accounted for by misclassification of asthma, because reported symptoms among the subjects with asthma did not differ substantially between women exercising more or less frequently (see Table E1 in this article's Online Repository at www.jacionline.org). The importance of this finding is unclear; the finding may possibly reflect particular physiologic mechanisms.

In conclusion, oligomenorrhea was associated with lower FVC and increased prevalence of asthma. These associations were independent and additive to the associations of asthma and lung function with obesity and low physical activity. Oligomenorrhea, obesity, and low physical activity are each related to insulin resistance. Our findings suggest that airways pathology in women may have not only a hormonal but also a metabolic component. The clinical implications of these findings are, first, that women with oligomenorrhea and other symptoms of metabolic disturbance should be investigated with regard to respiratory health, and second, that the possibility for underlying metabolic disturbance should be considered in subjects with asthma or impaired lung function. The presented findings may imply that not only dietary and lifestyle intervention but also insulin sensitizing agents may in the future contribute to improve respiratory health in people with insulin resistance.

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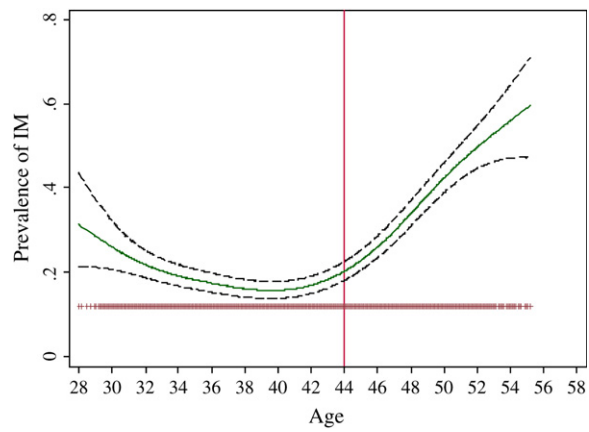


FIG E1. Prevalence and 95% CI of IM by age for 2588 women age 28 to 56 years in 21 centers. Oral contraceptive and HRT users, pregnant women, and women who had given birth within the last 6 months were excluded.

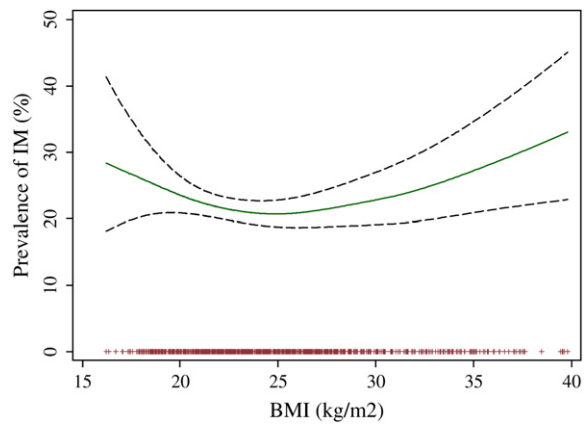


FIG E2. Prevalence and 95% CI of IM according to BMI among 1356 women age 28 to 44 years. Oral contraceptive and HRT users, pregnant women, and women who had given birth within the last 6 months were excluded.

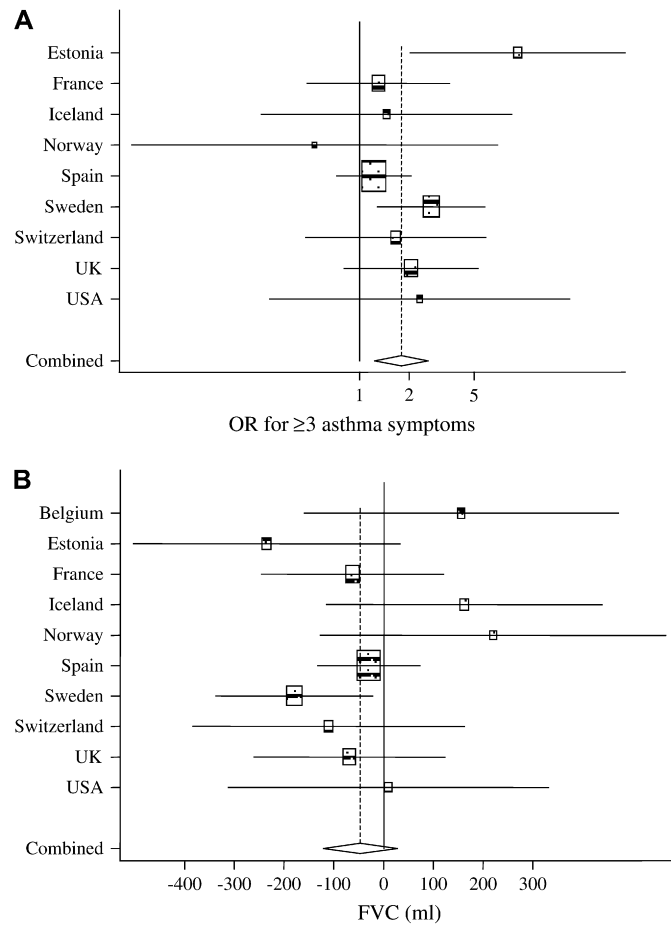


FIG E3. A, OR for the associations between IM and ≥ 3 asthma symptoms among 1623 women age 28 to 44 years by country ($P_{\text{heterogeneity}} = .328$). For each center, *horizontal lines* indicate 95% CI. For the combined estimates, the *diamonds* indicate 95% CI from model with country as random effect. The size of each *square* is proportional to the sample size. **B**, Adjusted differences (β coefficient) for the associations between IM and FVC among 1359 women age 26 to 44 years by country ($P_{\text{heterogeneity}} = .265$). For each center, *horizontal lines* indicate 95% CI. For the combined estimates, the *diamonds* indicate 95% CI from model with country as random effect. The size of each *square* is proportional to the sample size.

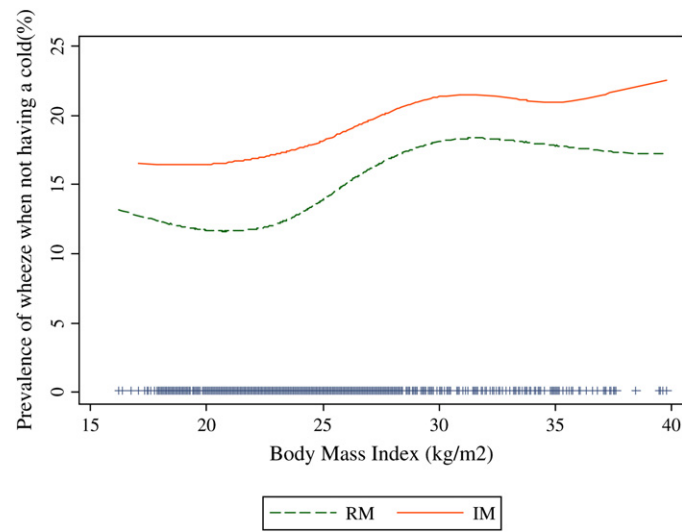


FIG E4. GAM curves showing prevalence of wheeze when not having a cold by BMI in women with regular menstruation (*RM*) and *IM*. A total of 1343 women age 28 to 44 years were included. Oral contraceptive and HRT users, pregnant women, and women who had given birth within the last 6 months were excluded.

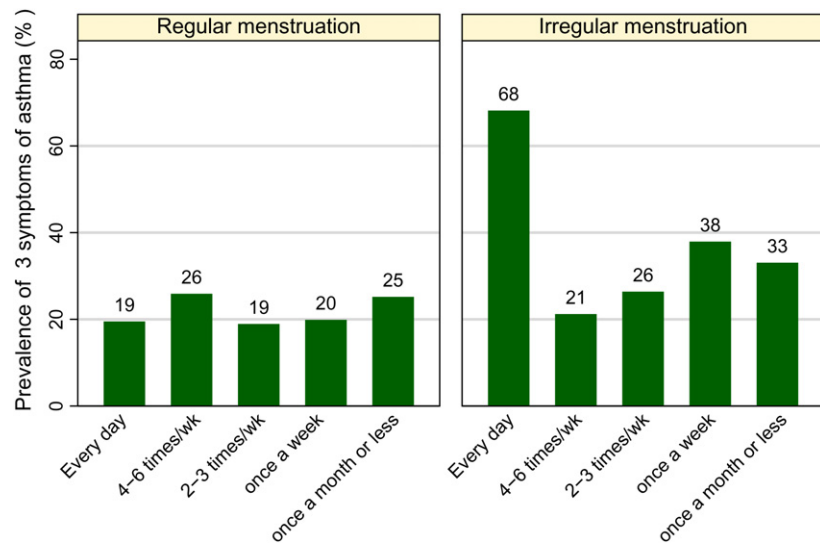


FIG E5. Prevalence of ≥ 3 asthma symptoms according to frequency of physical activity, in women with regular menstruation (*RM*) and *IM*. A total of 1582 women age 28 to 44 years with complete data were included.

TABLE E1. Prevalence of symptoms among 393 women with asthma (defined as having ≥ 3 symptoms of asthma) according to level of physical exercise*

Symptoms of asthma	Women exercising no more than once a week	Women exercising at least twice a week	All
Wheeze	82	87	84
Wheeze with shortness of breath	63	75	67
Wheeze when not having a cold	59	56	58
Waking with tightness in chest	66	55	62
Shortness of breath at rest in daytime	42	30	38
Shortness of breath after strenuous activity	60	57	59
Waking with shortness of breath	35	34	34
Waking by attack of cough	68	61	66

*Subjects with asthma exercising rarely more often reported waking with tightness in chest and shortness of breath at rest, whereas subjects with asthma exercising often reported more wheeze with shortness of breath.