

Asthma and lower airway disease

Menopause as a predictor of new-onset asthma: A longitudinal Northern European population study



Kai Triebner, MSc,^a Ane Johannessen, PhD,^a Luca Puggini, MSc,^b Bryndís Benediktsdóttir, MD, PhD,^c Randi J. Bertelsen, PhD,^d Ersilia Bifulco, PhD,^{a,e} Shyamali C. Dharmage, MD, PhD,^f Julia Dratva, MD, MPH,^{g,h} Karl A. Franklin, MD, PhD,ⁱ Thórarinn Gíslason, MD, PhD,^{c,j} Mathias Holm, MD, PhD,^k Deborah Jarvis, MD, PhD,^l Bénédicte Leynaert, PhD,^m Eva Lindberg, MD, PhD,ⁿ Andrei Malinovsky, MD, PhD,^o Ferenc Macsali, MD, PhD,^p Dan Norbäck, MD, PhD,^q Ernst R. Omenaas, MD, PhD,^a Francisco J. Rodríguez, PhD,^r Eirunn Saure, MD,^d Vivi Schlünssen, MD, PhD,^s Torben Sigsgaard, MD, PhD,^s Trude D. Skorge, MD, PhD,^d Gunilla Wieslander, MD, PhD,^q Elisabeth Zemp, MD, PhD,^{g,h} Cecilie Svanes, MD, PhD,^d Steinar Hustad, MD, PhD,^{a,e} and Francisco Gómez Real, MD, PhD^{a,p}
Bergen, Norway, Maynooth, Ireland, Reykjavik, Iceland, Melbourne, Australia, Basel, Switzerland, Umeå, Gothenburg, and Uppsala, Sweden, London, United Kingdom, Paris, France, Málaga, Spain, and Aarhus, Denmark

Background: There is limited and conflicting evidence on the effect of menopause on asthma.

Objectives: We sought to study whether the incidence of asthma and respiratory symptoms differ by menopausal status in a longitudinal population-based study with an average follow-up of 12 years.

Methods: The Respiratory Health in Northern Europe study provided questionnaire data pertaining to respiratory and reproductive health at baseline (1999-2001) and follow-up (2010-2012). The study cohort included women aged 45 to 65 years at follow-up, without asthma at baseline, and not using

exogenous hormones (n = 2322). Menopausal status was defined as nonmenopausal, transitional, early postmenopausal, and late postmenopausal. Associations with asthma (defined by the use of asthma medication, having asthma attacks, or both) and respiratory symptoms scores were analyzed by using logistic (asthma) and negative binomial (respiratory symptoms) regressions, adjusting for age, body mass index, physical activity, smoking, education, and study center.

Results: The odds of new-onset asthma were increased in women who were transitional (odds ratio, 2.40; 95% CI, 1.09-5.30), early postmenopausal (odds ratio, 2.11; 95% CI,

From the Departments of ^aClinical Science and ^dOccupational Medicine and ^ethe Core Facility for Metabolomics, University of Bergen; ^bthe Department of Electronic Engineering National University of Ireland, Maynooth; ^cthe Faculty of Medicine, University of Iceland, Reykjavik; ^fthe Allergy and Lung Health Unit, Melbourne School of Population Health, University of Melbourne; ^gthe Department of Public Health and Epidemiology, Swiss Tropical and Public Health Institute, Basel; ^hthe University of Basel; ⁱthe Department of Surgical and Perioperative Sciences, Umeå University; ^jthe Department of Respiratory Medicine and Sleep, Landspítali—the National University Hospital of Iceland, Reykjavik; ^kthe Department of Occupational and Environmental Medicine, University of Gothenburg; ^lthe Department of Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College, London; ^mInserm UMR1152 Team of Epidemiology, Paris; ⁿthe Department of Medical Sciences, Lung Medicine and Allergology, Uppsala University; ^othe Department of Medical Sciences, Clinical Physiology, Uppsala University; ^pthe Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen; ^qthe Department of Medical Sciences, Occupational and Environmental Medicine, University of Uppsala; ^rthe Department of Applied Mathematics, Málaga University; and ^sthe Department of Public Health, Aarhus University.

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Corresponding author: Kai Triebner, MSc, Department of Clinical Science, University of Bergen, Jonas Lies veg 87, 5021 Bergen, Norway. E-mail: kai.triebner@uib.no.

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1.06-4.20), and late postmenopausal (odds ratio, 3.44; 95% CI, 1.31-9.05) at follow-up compared with nonmenopausal women. The risk of respiratory symptoms increased in early postmenopausal (coefficient, 0.40; 95% CI, 0.06-0.75) and late postmenopausal (coefficient, 0.69; 95% CI, 0.15-1.23) women. These findings were consistent irrespective of smoking status and across study centers.

Conclusions: New-onset asthma and respiratory symptoms increased in women becoming postmenopausal in a longitudinal population-based study. Clinicians should be aware that respiratory health might deteriorate in women during reproductive aging. (*J Allergy Clin Immunol* 2016;137:50-7.)

Key words: Amenorrhea, asthma, estrogens, longitudinal, menopausal asthma, menopause, respiratory symptoms, reproductive aging, Respiratory Health in Northern Europe, sex hormones

Since Aristotle's time, menopause has been known to occur around 50 years of age.^{1,2} However, most women did not live to experience menopause in earlier days. In the last decades, female life expectancy has increased beyond 50 years worldwide,³ and today, the implications of menopause for health and disease are highly relevant. Menopause is associated with profound hormonal and metabolic changes: estrogen levels are low after menopause, and features of the metabolic syndrome become more prevalent paired with increasing risk of chronic conditions, such as diabetes and cardiovascular diseases.⁴ However, our understanding of potential changes of asthma and respiratory health in relation to menopause is still very limited, despite an increasing awareness of the importance of reproductive and hormonal factors in asthmatic patients.⁵⁻⁸ It has been suggested that late-onset asthma can be triggered by a change in systemic inflammation^{9,10} as it happens (ie, with menopause). Airways inflammation in postmenopausal asthmatic patients seems to be different from that of patients with earlier-onset asthma, as characterized by poorer response to anti-inflammatory treatment, as well as more frequent and severe exacerbations.¹⁰

Large epidemiologic studies investigating menopause and asthma are scarce and show contradictory results.¹¹ A lower risk of asthma among postmenopausal compared with nonmenopausal nurses was found in women who had never used hormone replacement therapy (HRT).¹² In contrast, a cross-sectional population-based study of women aged 45 to 55 years and not currently using HRT found more asthma and respiratory symptoms and lower lung function in women who had stopped menstruating compared with those who still had regular menstruations.¹³ Furthermore, an association between impaired respiratory health and menopause has been suggested by studies in which women who underwent surgical menopause had a higher risk of wheeze, independent of previous use of HRT,¹⁴ and that postmenopausal status was associated with increased risk of respiratory symptoms.¹⁵

Research in this field has generally focused on HRT, whereas the underlying condition, namely menopause, has usually not been adequately studied because of the lack of sufficiently detailed information on menstrual patterns and statistical power to conduct the necessary subgroup analyses.⁵ An effect of menopause itself is plausible given that sex differences appear to play a major role in the development of respiratory health as a result of male and female sex hormones acting differently on resident lung cells and immune function.¹⁶

Abbreviations used

BMI: Body mass index
HRT: Hormone replacement therapy
STRAW: Stages of Reproductive Aging Workshop

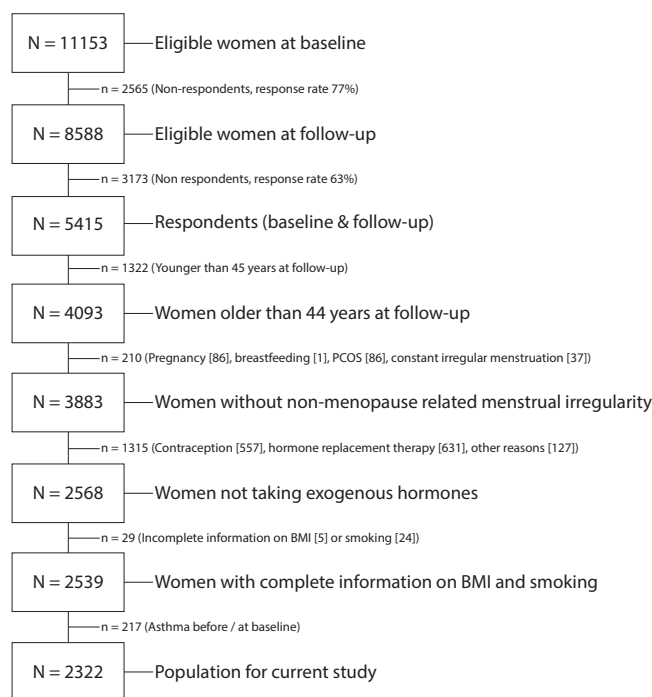


FIG 1. Study population with inclusion and exclusion criteria.

The Respiratory Health in Northern Europe¹⁷ women's study included longitudinal data on reproductive and respiratory health from large general population samples (n = 5415) with a median age of 40 years at baseline and 51 years at follow-up. This provides an extraordinary opportunity to longitudinally study the natural history of asthma and respiratory symptoms during reproductive aging. In the present study we aimed to investigate new-onset asthma and change in respiratory symptoms in relation to change in menopausal status over a 12-year period.

METHODS

Study population

Respiratory Health in Northern Europe is an international, multicenter, longitudinal study (www.rhine.nu) that included 7 Northern European centers (Bergen in Norway, Reykjavik in Iceland, Umea, Uppsala and Gothenburg in Sweden, Aarhus in Denmark, and Tartu in Estonia). At baseline (1999-2001), a respiratory health-focused postal questionnaire was sent to eligible participants (n_{women} = 11,153), 77% (n_{women} = 8,588) of whom responded. The questionnaire included questions concerning menstruation, menopause, and hormone use. At follow-up (2010-2012) 12 years later, 2 separate postal questionnaires, one focused on lung health, background characteristics, and risk factors and another focused on women's health, were sent to all female participants. The response rate for returning both questionnaires was 63% (n_{women} = 5,415).

TABLE I. Characteristics of the study population by change in menopausal status

	All	Nonmenopausal*	Menopausal transition†	Early postmenopause‡	Late postmenopause§
Age (y), median (SD)	54.0 (5.5)	48.0 (3.0)	52.0 (4.4)	55.0 (4.8)	62.0 (3.0)
BMI (kg/m ²), median (SD)	24.7 (4.5)	24.2 (4.3)	24.4 (4.5)	24.8 (4.4)	25.4 (5.0)
Smoking					
Never smoker	1090 (46.9)	235 (54)	150 (51.5)	594 (44)	111 (45.1)
Former smoker	829 (35.7)	138 (31.7)	100 (34.4)	512 (37.9)	79 (32.1)
Current smoker	403 (17.4)	62 (14.3)	41 (14.1)	244 (18.1)	56 (22.8)
Physical activity 					
>1 h/wk (vigorous)	895 (38.5)	201 (46.2)	128 (44)	498 (36.9)	68 (27.6)
>1 h/wk (light)	458 (19.7)	58 (13.3)	50 (17.2)	281 (20.8)	69 (28)
<1 h/wk (vigorous)	268 (11.5)	67 (15.4)	39 (13.4)	145 (10.7)	17 (6.9)
<1 h/wk (light)	325 (14)	52 (12)	41 (14.1)	192 (14.2)	40 (16.3)
None	376 (16.2)	57 (13.1)	33 (11.3)	234 (17.3)	52 (21.1)
Education					
University	1112 (47.9)	255 (58.6)	162 (55.7)	617 (45.7)	78 (31.7)
Secondary	960 (41.3)	163 (37.5)	112 (38.5)	580 (43)	105 (42.7)
Primary	250 (10.8)	17 (3.9)	17 (5.8)	153 (11.3)	63 (25.6)
Symptoms¶					
Breathless while wheezing	182 (7.8)	24 (5.5)	23 (7.9)	111 (8.2)	24 (9.8)
Woken by chest tightness	211 (9.1)	38 (8.7)	23 (7.9)	125 (9.3)	25 (10.2)
Woken by shortness of breath	113 (4.9)	20 (4.6)	8 (2.7)	72 (5.3)	13 (5.3)
Asthma¶					
Asthma attack	56 (2.4)	3 (0.7)	9 (3.1)	35 (2.6)	9 (3.7)
Asthma medication	99 (4.3)	11 (2.5)	14 (4.8)	60 (4.4)	14 (5.7)
New-onset asthma#	109 (4.7)	12 (2.8)	16 (5.5)	64 (4.7)	17 (6.9)
Total	2322	435	291	1,350	246

Values are presented as numbers (percentages), unless otherwise stated.

*Regular menstruation at baseline and follow-up.

†Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

‡Regular menstruation at baseline and postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

§Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

||Exercise frequency per week * duration per session for either light or heavy intensity (frequency per week * duration = numbers of training units per week times their duration [unit: h/wk]).

¶In the last 12 months.

#Current use of asthma medication, asthma attack, or both during the last 12 months in 2010 and no asthma at baseline.

To obtain hormonally well-defined groups, the present analyses excluded women using exogenous hormones, women who were pregnant or breast-feeding at the time of the survey, women reporting persistent irregular menstruation, and women with polycystic ovary syndrome according to the Rotterdam criteria.¹⁸ Women defined as having asthma at baseline (current asthma medication use, asthma attack during the previous 12 months, or both) and/or ever having had asthma (n = 217) were excluded. The study population thus consisted of 2322 women aged more than 44 years at follow-up with complete data (Fig 1). Characteristics of the study population by center can be found in Table E1 in this article's Online Repository at www.jacionline.org. Ethical approval was obtained for each study center from the appropriate institutional or regional ethics committee, and each participant provided informed written consent.

Outcomes

New-onset asthma was defined as current asthma medication use, having had an asthma attack during the last 12 months, or both. A respiratory symptoms score ranging from 0 to 3 was created according to existing literature,^{19,20} adding the numbers of affirmative answers to the following 3 questions: "Have you been breathless while wheezing at any time in the last 12 months?," "Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?," or "Have you been woken by an attack of shortness of breath at any time in the last 12 months?"

Menopausal status

Menopausal status was defined based on criteria of the Stages of Reproductive Aging Workshop (STRAW) clinically oriented classification,²¹

with the exception that a cutoff of 6 months or more of amenorrhea was used instead of 12 months or more because of the definition of menopause in the questionnaire at baseline. The questions used to define menopausal status at baseline and at follow-up are presented in the [Methods](#) section in this article's Online Repository at www.jacionline.org. On the basis of menopausal status at baseline and follow-up, we defined change in menopausal status as follows:

1. *nonmenopausal*: nonmenopausal at both baseline and follow-up (reference category);
2. *transitional*: nonmenopausal at baseline and transitional at follow-up;
3. *early postmenopausal*: nonmenopausal at baseline and menopausal at follow-up; and
4. *late postmenopausal*: menopausal at both baseline and follow-up.

Measurements of estradiol levels in serum

In a subsample of the study population (n = 323), serum estradiol levels at follow-up were measured at the Core Facility for Metabolomics, University of Bergen (www.uib.no/metabolomics) by using liquid chromatography–tandem mass spectrometry. Estradiol concentrations were used to define premenopausal and postmenopausal status according to an established cutoff of 73 pmol/L.²²

Covariates

Self-reported height and weight at follow-up were used to calculate body mass index (BMI [in kilograms per meters squared]). Weight at follow-up was

missing for 58 women, and we calculated BMI at follow-up by adding the average change of the study population's BMI from baseline to follow-up to their baseline BMI. Smoking was categorized according to whether participants were never, current, or former smokers at baseline and follow-up. Age reported at follow-up was used for adjustment. For cases with missing data on age at follow-up ($n = 140$), we added years of follow-up for each participant to reported age at baseline. Physical activity was stratified into 5 groups based on information on frequency, intensity, and duration of exercise reported at follow-up (Russell et al, unpublished data). The following 3 levels of education were reported: university or college, secondary or technical school, and primary school.

Statistical analysis

Logistic regression models were used to analyze the association of change in menopausal status with development of new-onset asthma. Negative binomial regression models suited for high-dispersion data were used to analyze the association of change in menopausal status with change in the respiratory symptoms score. The final regression models were adjusted by age and BMI as continuous variables and smoking, physical activity, education, and study center as categorical variables. Sensitivity analyses were performed in never smokers and women who did not have new-onset asthma. Analyses were stratified by BMI in tertiles, and analysis of interaction by center and BMI were performed by introducing an interaction term. All analyses were performed with STATA software (Version 13; StataCorp, College Station, Tex).

RESULTS

At follow-up, 19% of the women were nonmenopausal, 13% were transitional, 58% were early postmenopausal, and 11% were late postmenopausal. The median age of the study population was 54 years ($\sigma = 5.5$ years), the median age at menopause was 50.2 years ($\sigma = 5.7$ years), and mean BMI was 24.7 kg/m² ($\sigma = 4.5$ kg/m²). The average number of respiratory symptoms was 0.2 (range, 0-3), and there were 109 (5%) cases of new-onset asthma (Table I).

Both women in the menopausal transition and postmenopause were older, heavier, more often current or former smokers, less well educated, and exercised less than nonmenopausal women (Table I).

Among women categorized as nonmenopausal according to questionnaire data, 84% had estradiol levels of 73 pmol/L or greater. Among women categorized as postmenopausal, 78% had estradiol levels of less than 73 pmol/L.

The risk for new-onset asthma was higher for women in the menopausal transition or who were postmenopausal compared with nonmenopausal women who had regular menstruation throughout the study period (Fig 2 and Table II). Age was not an independent predictor for new-onset asthma, and adjustment for age did not alter the association with menopause. Women who became transitional or menopausal during the follow-up period had more than double the risk of new-onset asthma, and women who were postmenopausal at baseline had more than triple the risk of new-onset asthma at follow-up compared with nonmenopausal women.

Women who were in early and late postmenopause at follow-up had a significant increase in the number of respiratory symptoms compared with women who remained nonmenopausal (Fig 3 and Table III). This effect was not driven by women who had new-onset asthma as a sensitivity analysis; excluding these women showed similar results (see Table E2 in this article's Online Repository at www.jacionline.org).

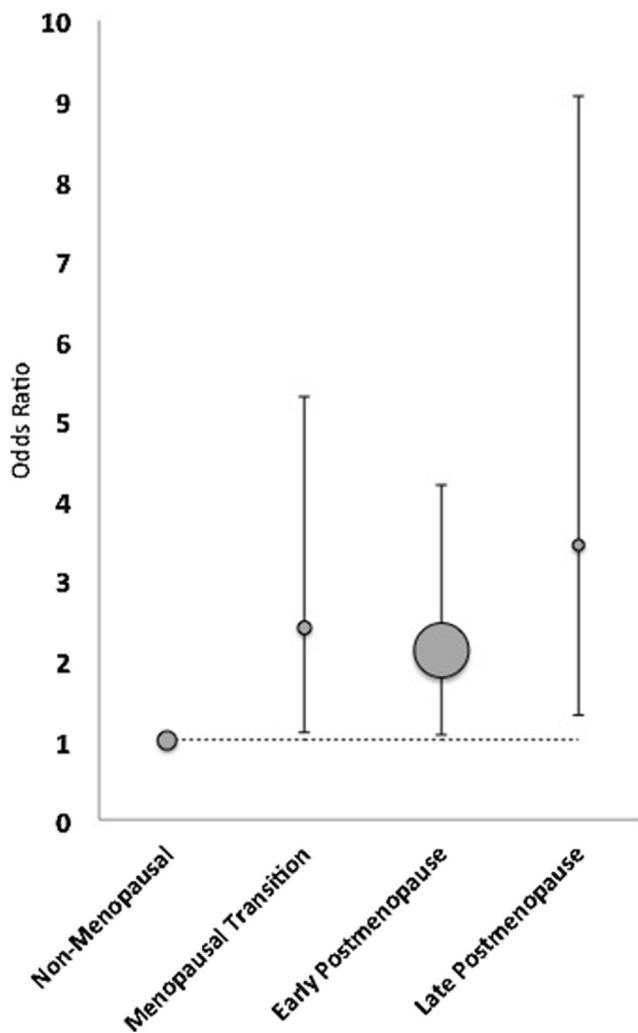


FIG 2. New-onset asthma according to change in menopausal status ($n = 2322$). The size of each circle is proportional to the number of persons in each group.

There was no significant interaction between study center and menopausal status in the associations with new-onset asthma ($P_{\text{heterogeneity}} = .14$) or respiratory symptoms ($P_{\text{heterogeneity}} = .78$). Stratification by smoking showed similar results in never, former, and current smokers for both outcomes (see Tables E3 and E4 in this article's Online Repository at www.jacionline.org). Analysis of effect modification by BMI showed that the effects of menopause on new-onset asthma were stronger for those with higher BMI (continuous variable; $P_{\text{interaction}} = .054$ for interaction with early postmenopause; $P_{\text{interaction}} = .047$ for interaction with late postmenopause; see Table E5 in this article's Online Repository at www.jacionline.org).

DISCUSSION

This study showed that the risk of new-onset asthma was significantly higher in women who were transitional or postmenopausal at follow-up compared with women who were nonmenopausal at baseline and follow-up. Furthermore, the number of respiratory symptoms was higher in women who

TABLE II. New-onset asthma according to change in menopausal status and covariates (n = 2322)

	Percent (no./N)	Unadjusted		Adjusted	
		OR (95% CI)	P value	OR (95% CI)*	P value
Menopausal status					
Nonmenopausal†	2.8 (12/435)	Reference		Reference	
Menopausal transition‡	5.5 (16/291)	2.05 (0.96-4.40)	.07	2.40 (1.09-5.30)	.03
Early postmenopause§	4.7 (64/1350)	1.75 (0.94-3.28)	.08	2.11 (1.06-4.20)	.03
Late postmenopause	6.9 (17/246)	2.62 (1.23-5.57)	.01	3.44 (1.31-9.05)	.01
Age		1.00 (0.96-1.03)	1.0	0.97 (0.92-1.01)	.2
BMI		1.06 (1.02-1.09)	.004	1.06 (1.02-1.10)	.003
Smoking					
Never smoker		Reference		Reference	
Former smoker		1.44 (0.92-2.26)	.11	1.35 (0.85-2.14)	.2
Current smoker		2.23 (1.36-3.65)	.001	1.92 (1.15-3.22)	.01
Physical activity¶					
>1 h/wk (vigorous)		Reference		Reference	
>1 h/wk (light)		0.82 (0.47-1.41)	.5	0.82 (0.47-1.44)	.5
<1 h/wk (vigorous)		0.51 (0.23-1.14)	.10	0.49 (0.22-1.11)	.09
<1 h/wk (light)		0.79 (0.42-1.48)	.5	0.70 (0.36-1.36)	.3
None		1.35 (0.81-2.23)	.2	1.11 (0.65-1.90)	.7
Education					
University		Reference		Reference	
High school		0.97 (0.64-1.48)	.9	0.81 (0.53-1.26)	.4
Primary		1.55 (0.88-2.74)	.13	1.21 (0.65-2.26)	.5

Boldface indicates estimates with a P value less than .05 (statistical significance).

OR, Odds ratio.

*Logistic regressions mutually adjusted for all covariates.

†Regular menstruation at baseline and follow-up.

‡Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

§Regular menstruation at baseline and postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

||Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

¶Exercise frequency per week * duration per session for either light or heavy intensity (frequency per week * duration = numbers of training units per week times their duration [unit: h/wk]).

were postmenopausal at follow-up. This was found in women who were nonasthmatic at baseline and had not had asthma previously. The findings remained consistent after adjustment for age, BMI, and lifestyle factors. Age was not an independent predictor of new-onset asthma in the studied age span, and the findings could not be attributed to general aging. Sensitivity analyses in never smokers showed similar results, and findings were consistent across study centers. There was significant effect modification by BMI because the association of new-onset asthma with menopause was significantly stronger with higher BMI.

To our knowledge, this is the first longitudinal population-based study that addresses respiratory health in relation to menopause. Previous cross-sectional analyses show results that agree with the present longitudinal analysis, with higher prevalence of asthma, respiratory symptoms, or both in postmenopausal compared with nonmenopausal women.¹³⁻¹⁵

A negative association between menopause and asthma risk was reported in an analysis of the Nurses' Health Study.¹² Differences in study populations and in definition of exposure and outcome might explain the discordant results; furthermore, North American nurses might not be representative of the overall female population.^{5,23} The present study included random samples of general populations from different Northern European countries.

The presence of interaction between reproductive factors (menopause) and BMI is consistent with previous analyses.^{7,24,25} Further research should focus on intervention because our results suggest that women have less impairment in respiratory health during menopause if they commence the menopausal transition with a normal BMI.

In our study menopause was based on women reporting their menstrual status²⁶ and use of hormones in a questionnaire. Menopausal status was defined according to the STRAW classification,²¹ with the exception that a cutoff of 6 months or more for amenorrhea was used instead of 12 months or more because of the definition of menopause at baseline. Levels of measured estradiol corresponded well with expected levels of estradiol among postmenopausal and nonmenopausal women²² and confirmed that the definition based on questionnaire data was acceptable. This is in agreement with literature showing that women report reproductive data with high reliability.^{7,13,26-29} Although menopause for clinical purposes is defined retrospectively as the first day of the last menstruation followed by 12 months without menstruations,²¹ menopausal status in biological terms is a continuum and any definition based on categories will have limitations.²⁷ Although results were very consistent for the early and late postmenopausal groups, the group in the menopausal transition showed less consistent findings. This transitional stage is difficult to assess and needs further investigation with more refined methods for defining hormonal status.

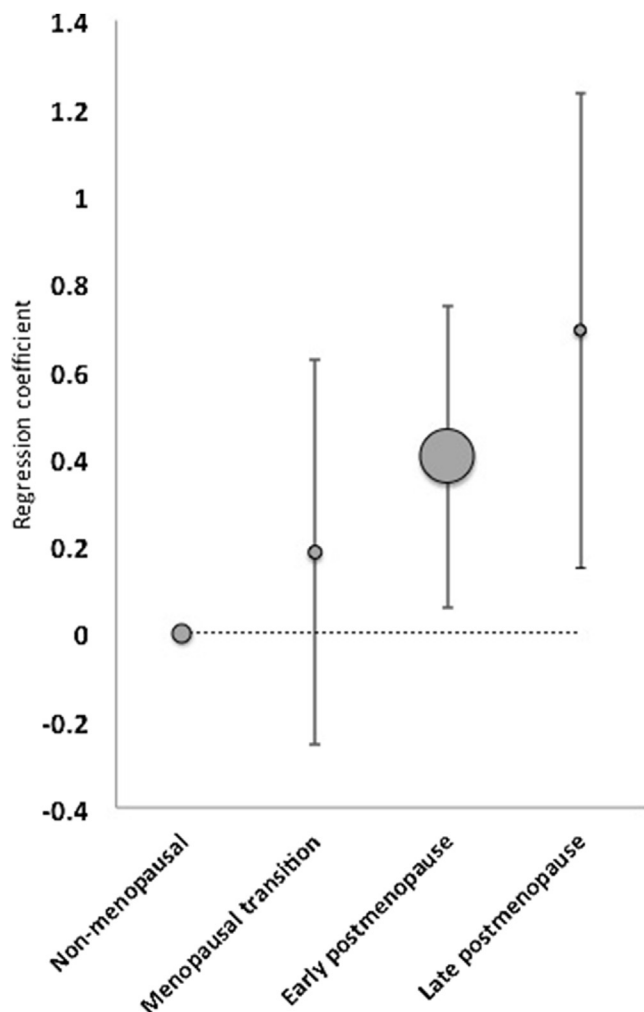


FIG 3. Change in number of respiratory symptoms according to change in menopausal status (n = 2322). The size of each circle is proportional to the number of persons in each group.

Our findings are biologically plausible because asthma is an inflammatory condition of the airways^{30,31} in which systemic inflammation is important in the pathophysiology,³² and sex steroids have an effect on the immune regulation, with estradiol showing both proinflammatory and anti-inflammatory properties.^{30,33-35} The effects of estrogens on eosinophils and mast cells might be particularly relevant for asthma.³⁶⁻³⁸ Decreasing estradiol levels because of menopause potentially reduce protective influences on the lungs and thereby increase susceptibility to asthma and respiratory symptoms. Because asthma is a complex disease, it is plausible that more than 1 pathway is responsible for exacerbation or the development of late-onset asthma.^{9,39} It is suggested that a sex steroid pathway might play a distinct role in reaching a threshold that could trigger a noticeable difference in bronchial reaction.⁹ Furthermore, increased systemic inflammation caused by metabolic dysfunction among postmenopausal women might also contribute to our findings.⁴⁰

Our study has clear advantages over previous studies because it is the first population-based longitudinal study in the field. The external validity is high because it is a multinational multicentric study; furthermore, the study is large enough to allow relevant subgroup analysis. Menopausal status was defined in several categories, and the sample size made it possible to distinguish between women in the menopausal transition and women in early and late stages of postmenopause. Measurements of estradiol levels in a subsample supported the questionnaire-based definitions of these menopausal stages. A limitation was that information collected at baseline did not detail the causes for irregular menstruation. Therefore women with irregular menstruation at baseline were excluded, and the longitudinal changes in respiratory health in women who were in the menopausal transition at baseline could not be addressed.

Another limitation of the study is the definition of the outcome variables according to questionnaire data. However, to elucidate more objective descriptions poses a challenge because asthma is a heterogeneous condition, airway obstruction fluctuates, and a gold standard to define asthma is still to be determined.⁴¹⁻⁴³ In the present analyses we used 2 measures of asthma, one more specific for diagnosed asthma and another based on asthma symptoms. It cannot be ruled out that respiratory symptoms might sometimes reflect respiratory tract infections; however, our approach is based on common operational definitions reflecting asthma on a population basis. Questionnaire data concerning asthma for epidemiologic studies have been validated in other studies reporting strong positive associations with a clinical diagnosis of asthma.^{42,44,45} The sensitivity and specificity of self-reported asthma are generally high⁴³ and highlight why questionnaire data for the definition of asthma are widely used.

In conclusion, the present analysis indicates that there is a strong and consistent association between change in menopausal status and risk of new-onset asthma and respiratory symptoms. The findings should be confirmed in different populations in future studies. Mechanisms relating respiratory health to reproductive aging, as well as the potential effect of modifiable risk factors, such as being overweight, need to be further investigated. Considering the projected increase in the number of older adults globally, reproductive aging and postmenopausal quality of life are increasingly relevant, and policymakers should consider the burden of disease and the costs related to menopausal asthma. Moreover, clinicians should be aware that women might experience deterioration of respiratory health and have asthma during menopause.

Dr Jordi Sunyer and Natalia Vilor Tejedor from CREAL in Barcelona contributed to the respiratory symptoms score. Dr Adrian McCann contributed to improve language and grammar.

Clinical implications: Health care professionals should be aware that women are more susceptible to asthma and respiratory symptoms when they become menopausal.

TABLE III. Change in number of respiratory symptoms* according to change in menopausal status and covariates (n = 2322)

	Unadjusted		Adjusted	
	Coefficient (95% CI)	P value	Coefficient (95% CI)†	P value
Menopausal status				
Nonmenopausal‡	Reference		Reference	
Menopausal transition§	-0.02 (-0.45 to 0.42)	.9	0.18 (-0.26 to 0.62)	.4
Early postmenopause	0.19 (-0.12 to 0.50)	.2	0.40 (0.06 to 0.75)	.02
Late postmenopause¶	0.29 (-0.14 to 0.72)	.2	0.69 (0.15 to 1.23)	.01
Age	-0.02 (-0.04 to 0.00)	.11	-0.04 (-0.07 to -0.01)	.003
BMI	0.05 (0.02 to 0.07)	< .001	0.04 (0.02 to 0.07)	< .001
Smoking				
Never smoker	Reference		Reference	
Former smoker	0.11 (-0.15 to 0.37)	.4	0.21 (-0.05 to 0.47)	.12
Current smoker	0.68 (0.39 to 0.97)	< .001	0.64 (0.33 to 0.94)	< .001
Physical activity#				
>1 h/wk (vigorous)	Reference		Reference	
>1 h/wk (light)	-0.01 (-0.34 to 0.32)	.9	-0.04 (-0.37 to 0.29)	.8
<1 h/wk (vigorous)	0.07 (-0.32 to 0.46)	.7	0.01 (-0.38 to 0.40)	1.0
<1 h/wk (light)	0.56 (0.23 to 0.89)	.001	0.39 (0.06 to 0.73)	.02
None	0.45 (0.13 to 0.78)	.006	0.26 (-0.07 to 0.59)	.13
Education				
University	Reference		Reference	
High school	0.04 (-0.21 to 0.28)	.8	-0.14 (-0.39 to 0.11)	.3
Primary	0.27 (-0.10 to 0.64)	.2	0.10 (-0.29 to 0.49)	.6

Boldface indicates estimates with a P value less than .05 (statistical significance).

*Respiratory symptoms score (0-3) displays the sum of the following 3 questions answered with "yes": "Have you been breathless while wheezing at any time in the last 12 months?," "Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?," and "Have you been woken by an attack of shortness of breath at any time in the last 12 months?"

†Negative binomial regressions mutually adjusted for all covariates.

‡Regular menstruation at baseline and follow-up.

§Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

||Regular menstruation at baseline and postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

¶Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

#Exercise frequency per week * duration per session for either light or heavy intensity (frequency per week * duration = numbers of training units per week times their duration [unit: h/wk]).

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METHODS

Definition of menopausal status

Menopausal status was defined based on criteria of the STRAW clinically oriented classification,^{E1} with the exception that amenorrhea for 6 months or more was used instead of 12 months or more because of the definition of menopause in the questionnaire at baseline.

At baseline, women answering “yes” (alternatives are “yes,” “no,” and “don’t know”) to the question “Do you have regular periods?” were classified as nonmenopausal. Women answering “yes” (alternatives are “yes,” “no,” and “don’t know”) to the question “Do you have the menopause (six months or more since your last period)?” were classified as menopausal.

At follow-up, women were categorized according to answers given to the following questions:

1. “Do you have regular periods?” (alternatives “yes”; “no, they have never been regular”; “no they have been irregular for a few months”; and “no, my periods have stopped”)
2. “When was your last period? (Please fill in the date of the first day of your last period or the year if you cannot remember the exact date, even if you are no longer menstruating)”
3. “How many periods have you had in the last 12 months?”
4. “If you have had no periods in the last 12 months, what statement best describes the reason you have not had a period in the last 12 months?” (alternatives are “menopause,” “womb removed,” “ovaries removed,” “currently pregnant,” “currently breast-feeding,” “because I have been taking treatments (eg, hormonal IUD, contraceptive implants, chemotherapy),” and “other”)
5. “Have you ever had a hysterectomy (your womb removed)?” (alternatives are “no” and “yes”)
6. “Have you ever had one or both ovaries removed?” (alternatives are “never,” “yes, one ovary,” “yes, two ovaries,” and “don’t know”)

Nonmenopausal was defined as reporting 10 to 14 periods per year.

Transitional was defined as having reported “irregular menstruation for a few months,” cessation of menstruation with less than 183 days since the last period, 3 to 9 periods in the last 12 months, having 1 ovary removed, and/or reporting a hysterectomy.^{E2-E5}

Menopausal was defined as cessation of menstruation for at least 6 months,^{E6} more than 182 days since the last period, less than 3 periods in the last 12 months,^{E5} or having both ovaries removed.

We defined change in menopausal status according to the categories describing menopausal status at baseline and follow-up. We classified women according to change in menopausal status as follows:

1. *nonmenopausal*: nonmenopausal at both baseline and follow-up (reference category);
2. *transitional*: nonmenopausal at baseline and transitional at follow-up;
3. *early postmenopausal*: nonmenopausal at baseline and menopausal at follow-up;
4. *late postmenopausal*: menopausal at both baseline and follow-up.

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TABLE E1. Characteristics of the study population by study center

	All	Aarhus	Reykjavik	Bergen	Gothenburg	Umea	Uppsala	Tartu
Age (y), median (SD)	54 (5.5)	53 (5.0)	53 (5.5)	52 (5.2)	54 (5.6)	56 (5.6)	55 (5.7)	53 (5.2)
Age of menopause (y), median (SD)	50.2 (5.7)	50.0 (4.6)	50.0 (5.2)	49.5 (4.8)	50.2 (5.0)	51.0 (6.6)	51.2 (5.9)	51.0 (7.9)
BMI (kg/m ²), median (SD)	24.7 (4.5)	23.7 (4.8)	25.5 (4.5)	24.4 (3.8)	24.7 (4.5)	25.3 (4.6)	24.6 (4.0)	25.2 (5.1)
Smoking								
Never smoker	1090 (47)	179 (42)	111 (40)	145 (38)	137 (46)	186 (48)	172 (55)	160 (65)
Former smoker	829 (36)	167 (39)	125 (45)	147 (38)	109 (37)	134 (35)	110 (35)	37 (15)
Current smoker	403 (17)	77 (18)	43 (15)	92 (24)	50 (17)	64 (17)	28 (9)	49 (20)
Physical activity*								
>1 h/wk (vigorous)	895 (39)	164 (39)	105 (38)	189 (49)	105 (35)	165 (43)	108 (35)	59 (24)
>1 h/wk (light)	458 (20)	84 (20)	35 (13)	76 (20)	55 (19)	86 (22)	72 (23)	50 (20)
<1 h/wk (vigorous)	268 (12)	42 (10)	28 (10)	47 (12)	38 (13)	37 (10)	48 (15)	28 (11)
<1 h/wk (light)	325 (14)	70 (17)	25 (9)	31 (8)	46 (16)	57 (15)	35 (11)	61 (25)
None	376 (16)	63 (15)	86 (31)	41 (11)	52 (18)	39 (10)	47 (15)	48 (20)
Education								
University	1112 (48)	204 (48)	127 (46)	184 (48)	114 (39)	175 (46)	193 (62)	115 (47)
High school	960 (41)	200 (47)	97 (35)	168 (44)	133 (45)	150 (39)	87 (28)	125 (51)
Primary	250 (11)	19 (4)	55 (20)	32 (8)	49 (17)	59 (15)	30 (10)	6 (2)
Menopausal status at follow-up								
Nonmenopausal†	435 (19)	94 (22)	44 (16)	88 (23)	50 (17)	43 (11)	64 (21)	52 (21)
Menopausal transition‡	291 (13)	58 (14)	29 (10)	41 (11)	46 (16)	45 (12)	41 (13)	31 (13)
Early postmenopause§	1,350 (58)	232 (55)	182 (65)	203 (53)	171 (58)	243 (63)	171 (55)	148 (60)
Late postmenopause	246 (11)	39 (9)	24 (9)	52 (14)	29 (10)	53 (14)	34 (11)	15 (6)
Symptoms¶								
Breathless while wheezing	182 (8)	21 (5)	25 (9)	39 (10)	30 (10)	27 (7)	19 (6)	21 (9)
Woken by chest tightness	211 (9)	45 (11)	25 (9)	37 (10)	21 (7)	22 (6)	19 (6)	42 (17)
Woken by shortness of breath	113 (5)	15 (4)	6 (2)	16 (4)	13 (4)	14 (4)	15 (5)	34 (14)
Asthma¶								
Asthma attack	56 (2)	9 (2)	11 (4)	11 (3)	8 (3)	7 (2)	2 (1)	8 (3)
Asthma medication	99 (4)	13 (3)	13 (5)	25 (7)	16 (5)	12 (3)	10 (3)	10 (4)
New-onset asthma#	109 (5)	16 (4)	16 (6)	30 (8)	16 (5)	12 (3)	9 (3)	10 (4)
Total	2322	423	279	384	296	384	310	246

Values are presented as numbers (percentages), unless otherwise stated.

*Exercise frequency per week * duration per session for either light or vigorous intensity (frequency per week * duration = numbers of training units per week times their duration [unit: h/wk]).

†Regular menstruation at baseline and follow-up.

‡Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

§Regular menstruation at baseline, postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

||Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

¶In the last 12 months.

#Current use of asthma medication, asthma attack, or both during the last 12 months and no asthma at baseline.

TABLE E2. Change in number of respiratory symptoms* according to change in menopausal status for women in whom new-onset asthma did not develop (n = 2213)

	Coefficient (95% CI)†	P value
Menopausal status		
Nonmenopausal‡	Reference	
Menopausal transition§	0.07 (−0.42 to 0.56)	.8
Early postmenopause	0.30 (−0.07 to 0.68)	.11
Late postmenopause¶	0.66 (0.05 to 1.28)	.03

*Respiratory symptoms score (0-3) displays the sum of the following 3 questions answered with “yes”: “Have you been breathless while wheezing at any time in the last 12 months?,” “Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?,” and “Have you been woken by an attack of shortness of breath at any time in the last 12 months?”

†Negative binomial regressions adjusted for age, BMI, physical activity, smoking, education, and center.

‡Regular menstruation at baseline and follow-up.

§Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

||Regular menstruation at baseline and postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

¶Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

TABLE E3. New-onset asthma according to change in menopausal status for never smokers (n = 1090)

	OR (95% CI)*	P value
Menopausal status		
Nonmenopausal†	Reference	
Menopausal transition‡	3.00 (1.00-9.04)	.05
Early postmenopause§	1.73 (0.61-4.91)	.3
Late postmenopause	3.78 (0.77-18.63)	.10

OR, Odds ratio.

*Logistic regressions adjusted for age, BMI, physical activity, smoking, education, and center.

†Regular menstruation at baseline and follow-up.

‡Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

§Regular menstruation at baseline and postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

||Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

TABLE E4. Respiratory symptoms score* according to change in menopausal status for never smokers (n = 1090)

	Coefficient (95% CI) †	P value
Menopausal status		
Nonmenopausal ‡	Reference	
Menopausal transition §	-0.02 (-0.74 to 0.69)	.9
Early postmenopause	0.43 (-0.13 to 0.98)	.13
Late postmenopause ¶	0.56 (-0.38 to 1.51)	.2

*Respiratory symptoms score (0-3) displays the sum of the following 3 questions answered with "yes": "Have you been breathless while wheezing at any time in the last 12 months?," "Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?," and "Have you been woken by an attack of shortness of breath at any time in the last 12 months?"

†Negative binomial regressions adjusted for age, BMI, physical activity, smoking, education, and center.

‡Regular menstruation at baseline and follow-up.

§Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

||Regular menstruation at baseline and postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

¶Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

TABLE E5. New-onset asthma according to change in menopausal status stratified by BMI (tertiles [n = 2322])

	Lower BMI tertile (≤ 23.15 kg/m ² [n = 774]), OR (95% CI)*	Medium BMI tertile (23.15-26.39 kg/m ² [n = 775]), OR (95% CI)*	Upper BMI tertile (≥ 26.42 kg/m ² [n = 773]), OR (95% CI)*
Menopausal status			
Nonmenopausal†	Reference	Reference	Reference
Menopausal transition‡	2.00 (0.53-7.49)	1.16 (0.30-4.52)	13.79 (1.59-119.28)
Early postmenopause§¶	1.22 (0.37-3.96)	1.21 (0.42-3.49)	12.79 (1.61-101.94)
Late postmenopause #	1.71 (0.22-13.42)	1.55 (0.31-7.74)	26.15 (2.62-261.13)

OR, Odds ratio.

*Logistic regressions adjusted for age, BMI, physical activity, smoking, education, and center, including relevant interaction term.

†Regular menstruation at baseline and follow-up.

‡Regular menstruation at baseline and irregular or few menstruations at follow-up (irregular for a few months, 3-9 periods in the last 12 months, no menstruation for <6 months, 1 ovary removed or hysterectomy).

§Regular menstruation at baseline and postmenopause at follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

¶Postmenopause at baseline and follow-up (<3 periods in the last 12 months, amenorrhea for >6 months, both ovaries removed).

¶ $P_{\text{interaction}} = .054$ for interaction between early postmenopause and BMI as continuous variables for new-onset asthma.

$P_{\text{interaction}} = .047$ for interaction between early postmenopause and BMI as continuous variables for new-onset asthma.