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 Malinovschi, 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 [a]Clinical Science and [d]Occupational Medicine and [e]the Core Facility for Metabolomics, University of Bergen; [b]the Department of Electronic Engineering National University of Ireland, Maynooth; [c]the Faculty of Medicine, University of Iceland, Reykjavik; [f]the Allergy and Lung Health Unit, Melbourne School of Population Health, University of Melbourne; [g]the Department of Public Health and Epidemiology, Swiss Tropical and Public Health Institute, Basel; [h]the University of Basel; [i]the Department of Surgical and Perioperative Sciences, Umeå University; [j]the Department of Respiratory Medicine and Sleep, Landspitali–the National University Hospital of Iceland, Reykjavik; [k]the Department of Occupational and Environmental Medicine, University of Gothenburg; [l]the Department of Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College, London; [m]Inserm UMR1152 Team of Epidemiology, Paris; [n]the Department of Medical Sciences, Lung Medicine and Allergology, Uppsala University; [o]the Department of Medical Sciences, Clinical Physiology, Uppsala University; [p]the Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen; [q]the Department of Medical Sciences, Occupational and Environmental Medicine, University of Uppsala; [r]the Department of Applied Mathematics, Málaga University; and [s]the Department of Public Health, Aarhus University.

K.T. has received a PhD scholarship from the Norwegian Research Council (project no. 228174). This project also funded the estrogen measurements. Respiratory Health in Northern Europe (RHINE) was supported financially by the Norwegian Research Council (grant no. 214123), the Bergen Medical Research Foundation, the Western Norwegian Regional Health Authorities (grant nos. 911 892 and 911 631), the Norwegian Labour Inspection, the Norwegian Asthma and Allergy Association, the Faculty of Health of Aarhus University (project no. 240008), the Wood Dust Foundation (project no. 444508795), the Danish Lung Association, the Swedish Heart-Lung Foundation, the Vårdal Foundation for Health Care Science and Allergy Research, the Swedish council for working life and social research, the Bror Hjerpstedt Foundation, the Swedish Asthma and Allergy Association, the Icelandic Research Council, and the Estonian Science Foundation (grant no. 4350).

Disclosure of potential conflict of interest: K. Triebner has received grants from the Norwegian Research Council (project no. 228174, grant no. 214123), the Bergen Medical Research Foundation, the Western Norwegian Regional Health Authorities (grant nos. 911 892 and 911 631), the Norwegian Labour Inspection, the Norwegian Asthma and Allergy Association, the Faculty of Health of Aarhus University (project no. 240008), the Wood Dust Foundation, the Danish Lung Association, the Swedish Heart and Lung Foundation, the Vårdal Foundation for Health Care Science and Allergy Research, the Swedish Council for Working Life and Social Research, Bror Hjerpstedt Foundation, the Swedish Asthma and Allergy Association, the Icelandic Research Council, and the Estonian Science Foundation (grant no. 4350) and has received travel support from EPINOR. L. Puggini has received grants from the Norwegian Research Council (project no. 228174, grant no. 214123) and NUI Maynooth and has been employed by Google. B. Benediktsdóttir and E. Saure have received grants from the Norwegian Research Council (project no. 228174, grant mo. 214123), the Bergen Medical Research Foundation, the Western Norwegian Regional Health Authorities (grant nos. 911 892 and 911 631), the Norwegian Labour Inspection, the Norwegian Asthma and Allergy Association, the Faculty of Health of Aarhus University (project no. 240008), the Wood Dust Foundation, the Danish Lung Association, the Swedish Heart and Lung Foundation, the Vårdal Foundation for Health Care Science and Allergy Research, the Swedish Council for Working Life and Social Research, Bror Hjerpstedt Foundation, the Swedish Asthma and Allergy Association, the Icelandic Research Council, and the Estonian Science Foundation (grant no. 4350). T. Gislason has received grants from the University of Iceland and Landspitali University Hospital. D. Jarvis has received a grant from the Medical Research Council. F. J. Rodriguez is employed by the Department of Applied Mathematics at Malaga University. V. Schlünssen has received a grant from the Faculty of Health of Aarhus University (project no. 240008), has received a consulting fee or honorarium from the Wood Dust Foundation and has consultant arrangements with the Danish National Board of Industrial Injuries and the Danish Labour Union HK Denmark. F. Gómez Real has received a grant, travel support, and provision of writing assistance, medicines, equipment, or administrative support for this work from the Norwegian Research Council. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 11, 2015; revised July 24, 2015; accepted for publication August 5, 2015.

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.

0091-6749

http://dx.doi.org/10.1016/j.jaci.2015.08.019

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 2015;■■■:■■■-■■■.)

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

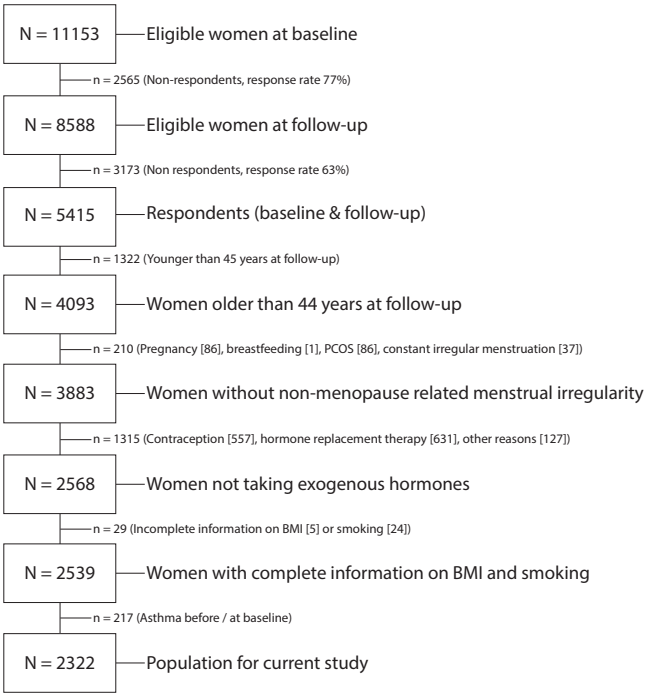

FIG 1. Study population with inclusion and exclusion criteria.

The Respiratory Health in Northern Europe[17] 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).