Clinical Communications

Menopause is not associated with asthma or severe asthma

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Clinical Implications

The effect of menopause on asthma outcomes is confounded by age, obesity, and female sex hormone use. A better understanding of this complex relationship between aging, inflammation, and hormone use is needed to guide future personalized approaches in asthma care.

Asthma is a chronic inflammatory airway disease that varies significantly in prevalence and severity across the lifespan. Asthma's prevalence and severity are higher among prepubescent boys than girls. A hormonal switch occurs with puberty, when asthma becomes more severe and prevalent among pubescent girls and adult women. Asthma incidence and severity then improve with menopause when sex hormones wane.[1,2] However, the effect of menopause on lung function, asthma severity, exacerbations, and health care utilization has not been well studied. This study uses a population-based dataset to investigate the impact of menopause and sex hormone use on asthma prevalence, severity, and outcomes.

We analyzed publicly available data from 9 consecutive 2-year cycles (1999-2000 to 2015-2016) of the National Health and Nutrition Examination Survey (NHANES). NHANES provides a nationally representative dataset that is approved by the institutional review board of the National Center for Health Statistics. Lifetime asthma was defined as a positive response to the NHANES survey question, "Has a doctor or other health professional ever told you that you have asthma?", active asthma as a positive response to "Do you still have asthma?", and an asthma exacerbation as a positive response to "Had an asthma attack in the past year?". Severe asthma was identified based on Global Initiative for Asthma treatment steps 4 and 5.[3] All adult women aged 18 years and older were included in the final analysis. Participants were classified as postmenopausal if they had undergone bilateral oophorectomy or had apositive response to the question, "Did not have a menstrual period in the past 12 months?" in alignment with the "Stages of Reproductive Aging Workshop" (STRAW)+10 definition.[4] A sensitivity analysis was conducted among women who had never used female hormones or oral contraceptives (OCP). NHANES pregnant participants and those with missing outcome data (ie, unknown asthma status) were excluded. Weighted regression models accounted for confounders, including age, race, body mass index (BMI), smoking status, blood eosinophil count, and a history of female sex hormone use such as OCP or hormone replacement therapy (HRT). The interaction between menopause and age was assessed across different outcome models. When the interaction was significant, the odds of asthma outcomes by menopause status were reported at selected age levels. Correlations between independent variables in the regression models were assessed using the variance inflation factor (vif). All analyses adhered to NHANES analytic guidelines and were conducted using the SURVEY package in R (R Foundation for Statistical Computing, Vienna, Austria).

Compared with premenopausal women (weighted n = 48,990,738), postmenopausal women (weighted n = 52,915,559) had higher rates of severe asthma (4.8% vs 2.0%). However, there were no significant difference in the prevalence of lifetime asthma (15.6% vs 16.6%, $P = .159$) or active asthma (9.0% vs 9.4%, $P = .308$) between post- and premenopausal women. Notably, postmenopausal women had a higher BMI (weighted median [interquartile range (IQR)]: 28.0 [24.1; 33.1] vs 26.3 [22.5; 32.2] kg/m^2, $P < .001$), older age at asthma onset (weighted median [IQR]: 28 [4; 48] vs 12 [2; 23] years, $P < .001$), longer asthma duration (weighted median [IQR]: 19.0 [7.0-40.0] vs 15.0 [8.0-24.0] years, $P < .001$), and lower percent predicted forced expiratory volume in 1 second (FEV_1%) and FEV_1/forced vital capacity (FVC) ratio ($P < .001$), which is suggestive of an obstructive pattern. A lower percent predicted forced vital capacity (FVC%) among postmenopausal women was noted, which suggests a restrictive defect versus air trapping. In the absence of lung volume measurements in NHANES, such differentiation is difficult (Table I). Among the 4,785,445 postmenopausal women with active asthma, 36.1% had their asthma onset after menopause. Of the 13,501,463 women (weighted n) who reported menopause before age 52 years, 58.5% had natural menopause.

There was no collinearity between age and menopausal status for asthma (vif = 3.4) or active asthma (vif = 3.4) among all individuals aged 18 years and older. Similarly, no collinearity was observed between menopausal status and age for severe asthma (vif = 3.0), asthma exacerbations (vif = 3.2), or asthma-related emergency care visits (vif = 3.2) among individuals with active asthma. In addition, an interaction was identified between menopause and age for lifetime asthma ($P_{interaction} = .025$), and active asthma ($P_{interaction} = .006$), but not severe asthma ($P_{interaction} = .322$). The adjusted odds ratios (ORs) at specific ages are presented in Figure 1. Of note, this interaction was not observed in women who had never used OCP or female hormone therapy; in this group, menopause was not associated with lifetime asthma (adjusted OR, 1.006; 95% confidence interval [CI], 0.826-1.226), active asthma (adjusted OR, 0.875; 95% CI, 0.493-1.552), or severe asthma (adjusted OR, 1.128; 95% CI, 0.691-1.842). In contrast, a higher risk of lifetime asthma was associated with a history of postmenopausal HRT (adjusted OR, 1.184; 95% CI, 1.032-1.359) and a prior history of OCP use at a younger age (adjusted OR, 1.317; 95% CI, 1.189-1.484).

The clinical characteristics of participants with active asthma stratified by menopausal status are listed in Table I. Among women with active asthma, menopause was not associated with a higher risk for severe asthma (adjusted OR, 1.362; 95% CI, 0.832-2.331), asthma exacerbations (adjusted OR, 1.167; 95% CI, 0.803-1.696), or emergency care visits for asthma (adjusted OR, 1.389; 95% CI, 0.886-2.178) in the year before survey

TABLE I. Clinical characteristics stratified by menopausal status across this overall cohort and among participants with active asthma

	Entire cohort			Active asthma		
Characteristic	**Premenopausal**	**Postmenopausal**	***P***	**Premenopausal**	**Postmenopausal**	***P***
n	48,990,738	52,915,559		4,626,937	4,785,445	
Demographics						
Age (y)	34 [26; 43]	60 [51; 70]	<.001	34 [25; 42]	60 [52; 68]	<.001
BMI (kg/m^2)	26.3 [22.5; 32.2]	28.0 [24.1; 33.1]	<.001	28.6 [23.9; 35.0]	30.7 [26.0; 36.0]	<.001
Age at asthma onset (y)	12 [2; 23]*	28 [4; 48]*	<.001	15 [5; 25]	38 [16; 53]	<.001
Asthma duration (y)	15 [8; 24]	19 [7; 40]	<.001	14 [7; 23]	17 [6; 35]	<.001
Race			<.001			.006
Non-Hispanic White	31,247,151 (63.8)	39,843,799 (75.3)		3,205,540 (69.3)	3,566,417 (74.5)	
Non-Hispanic Black	6,285,314 (12.8)	5,638,056 (10.7)		645,451 (13.9)	601,164 (12.6)	
Hispanic	7,988,311 (16.3)	4,988,057 (9.4)		523,828 (11.3)	355,287 (7.4)	
Others	3,469,963 (7.1)	2,445,647 (4.6)		252,118 (5.5)	262,577 (5.5)	
Laboratory measurements						
Absolute eosinophil count ($\times 10^3$ cells/μL)	0.1 [0.1; 0.2]	0.2 [0.1; 0.2]	<.001	0.2 [0.1; 0.3]	0.2 [0.1; 0.3]	.576
Testosterone (ng/dL)	29.5 [24.0; 38.4]	27.9 [23.5; 35.3]	.002	29.4 [23.6; 37.9]	22.4 [26.6; 33.6]	.056
SHBG (nmol/L)	63.7 [41.8; 101.6]	62.7 [42.2; 91.0]	.033	68.0 [44.6; 105.8]	54.8 [38.5; 86.6]	.008
Estradiol (pg/mL)	68.6 [32.0; 131.0]	6.51 [3.5; 13.2]	<.001	69.4 [36.4; 129.0]	6.0 [3.5; 10.9]	<.001
Free testosterone (ng/dL)	0.41 [0.27; 0.63]	0.39 [0.27; 0.60]	.848	0.42 [0.26; 0.60]	0.35 [0.24; 0.49]	.100
Medications use						
Short-acting β-agonists only	1,620,489 (3.3)	2,533,371 (4.8)	<.001	1,299,235 (28.1)	1,594,020 (33.3)	.045
Inhaled corticosteroids	1,808,849 (3.7)	3,486,652 (6.6)	<.001	820,049 (17.7)	1,534,771 (32.1)	<.001
Inhaled corticosteroids—Long-acting β-agonists	443,920 (0.9)	1,198,922 (2.3)	<.001	399,109 (8.6)	887,133 (18.5)	<.001
Oral corticosteroids	482,201 (1.0)	1,298,797 (2.5)	<.001	104,843 (2.3)	336,060 (7.0)	<.001
History of female hormone therapy	2,071,641 (4.2)	22,038,736 (41.6)	<.001	253,529 (5.5)	2,096,424 (43.8)	<.001
History of oral contraceptive use	37,173,379 (75.8)	34,552,590 (65.3)	<.001	3,688,083 (79.7)	3,483,022 (72.8)	.002
Lung function						
FEV_1 (%)	102.4 [93.4; 111.5]	98.4 [85.9; 108.7]	<.001	98.2 [86.6; 106.1]	86.5 [72.6; 100.7]	<.001
FVC (%)	99.6 [90.9; 107.7]	97.0 [86.5; 107.2]	<.001	98.9 [88.9; 106.8]	89.5 [79.4; 100.5]	<.001
FEV_1/FVC ratio	0.82 [0.78; 0.86]	0.77 [0.72; 0.81]	<.001	0.79 [0.74; 0.84]	0.75 [0.68; 0.80]	<.001
Asthma outcomes						
Lifetime asthma	8,136,590 (16.6)	8,275,157 (15.6)	.159			
Active asthma	4,626,937 (9.4)	4,785,445 (9.0)	.308			
Severe asthma	962,322 (2.0)	2,562,710 (4.8)	<.001	522,124 (11.8)	1,232,606 (25.8)	<.001
Asthma exacerbations				2,512,689 (54.3)	2,471,086 (51.6)	.335
Asthma-related emergency department visits				667,394 (14.4)	723,222 (15.1)	.680

Data are expressed as weighted median [interquartile range] or weighted counts (weighted %)
BMI, body mass index; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *SHBG*, sex hormone-binding globulin.
*For lifetime asthma.

completion. In postmenopausal women with asthma, HRT use was not associated with higher risk of asthma exacerbations (adjusted OR, 1.179; 95% CI, 0.878-1.583) or emergency care visits (adjusted OR, 0.965; 95% CI, 0.599-1.553). In premenopausal women, OCP use was not associated with higher risk of asthma exacerbations (adjusted OR, 0.811; 95% CI, 0.548-1.200) or emergency care visits (adjusted OR, 1.091; 95% CI, 0.679-1.753).

Lung function measurements were available for 471 postmenopausal and 755 premenopausal women with asthma. Among postmenopausal women with asthma, HRT was not associated with changes in FEV_1% (adjusted estimate β: 3.315, $P = .190$) or FVC% (adjusted estimate β: −0.096, $P = .961$). In contrast, OCP use was associated with higher FEV_1% (adjusted estimate β: 6.967, $P < .001$) and FVC% (adjusted estimate β: 6.088, $P < .001$) among premenopausal women with asthma.

In this population-based analysis using NHANES data, we found that, in the absence of exogenous female sex hormone use, menopause was not associated with higher risk for asthma. Instead, the higher prevalence of asthma among postmenopausal women is confounded by aging, age-related comorbidities, and female sex hormone use. This aligns with results from the RHINE study, a cross-sectional analysis of 2206 women between the age of 46 and 54 years from Denmark, Estonia, Iceland, Norway, and Sweden.[5] In addition, our analysis revealed that menopause alone does not worsen clinical asthma control reflected by exacerbations and emergency care utilization. The absence of an observed direct effect of menopause on asthma might suggest that menopausal hormonal changes alone are insufficient to substantially modify asthma risk. Rather, these hormonal shifts may interact with other aging-related factors, obesity-driven inflammation, and chronic comorbidities, ultimately shaping asthma phenotypes in postmenopausal women.

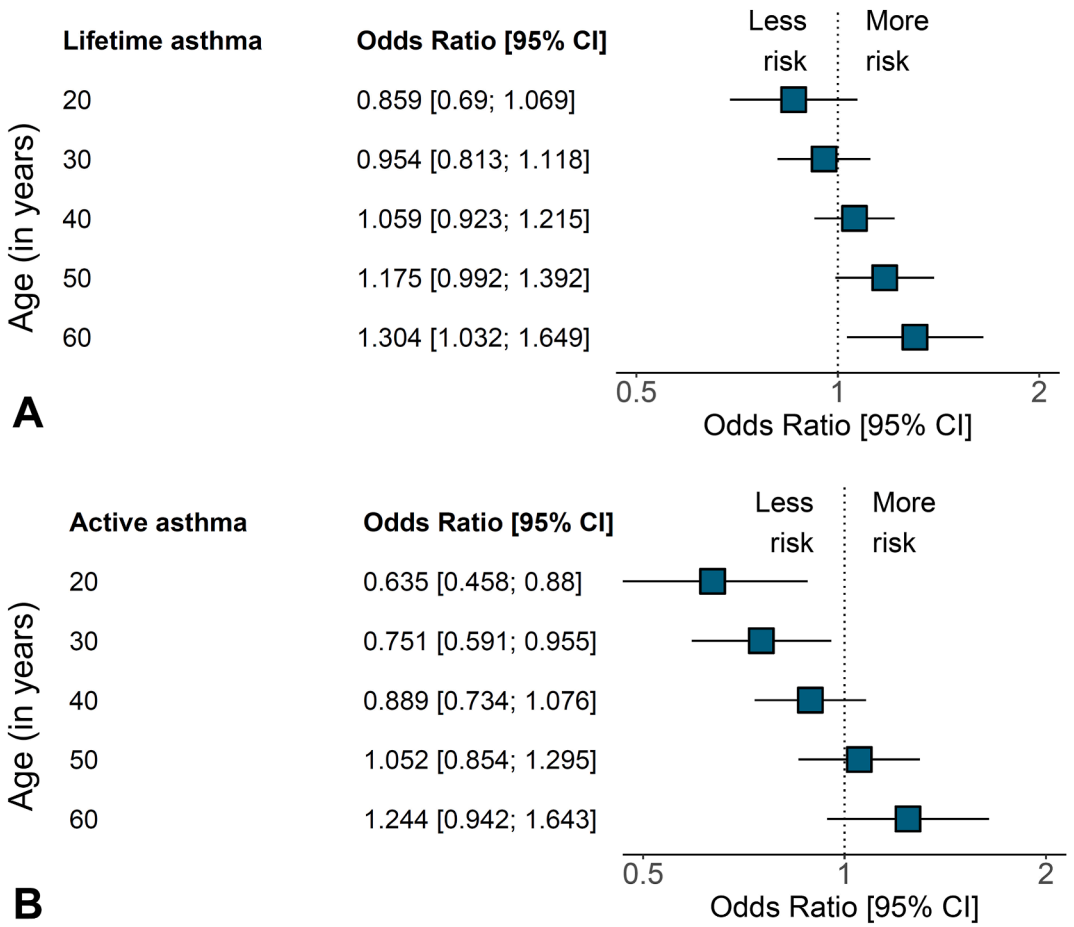

FIGURE 1. Adjusted odds ratios and 95% confidence intervals (CIs) for (**A**) lifetime asthma and (**B**) active asthma by menopausal status, assessed at specific age levels. We set the upper age limit at 60 because 99.8% of women in this cohort experienced menopause before that age. The association between lifetime asthma, active asthma, and menopause is modified by age.

The decline in female sex hormones during menopause coincides with age-related biological changes, such as immunosenescence, systemic inflammation, impaired immune responses, and reduced lung function. Biological aging can increase the risk of asthma, exacerbate asthma severity, and contribute to a distinct phenotype in older adults. This phenotype is characterized by airway remodeling, air trapping, and increased small airway resistance.[6] In this study, postmenopausal women had older age at asthma onset and longer asthma duration as compared with premenopausal women. Longer asthma duration has been associated with accelerated cellular aging (ie, senescence) evidenced by shortened leukocyte telomere length, a phenomenon associated with chronic eosinophilic inflammation.[7] These findings underscore the need to address age-related comorbidities when managing asthma in postmenopausal women.

Obesity is a critical driver of asthma risk and severity, particularly in postmenopausal women. During menopause, declining estrogen and progesterone levels as well as exogenous sex hormone use alter adipose tissue function and systemic inflammation, amplifying the impact of obesity's impact.[8] Adipokines such as IL-6 rise in obesity and activate airway epithelial cells and smooth muscle, promoting bronchoconstriction and hyperresponsiveness.[8] Elevated IL-6 levels further promote non-T2 inflammation through Th17-cell differentiation and IL-17 production, which contributes to steroid resistance. This IL-6-driven pathway appears to be modulated by female sex hormones, highlighting the interplay between obesity, hormonal changes, and asthma severity during menopause.[9] For these reasons, it is important for women to enter menopause with a healthy weight to minimize adiposity-driven inflammation and its detrimental effects on respiratory health.

We also found that a prior history of OCP use at a younger age was associated with increased risk for asthma but had no effect on lung function among postmenopausal women. This increased risk of asthma could simply reflect the increased cumulative lifetime exposure to female sex hormones. This association has been frequently used to explain the higher prevalence of asthma related to early menarche and multiparity. In contrast, the improvement of lung function found among premenopausal women receiving OCP could be attributed to estrogen-mediated bronchodilation and anti-inflammatory effects on lung function. Alternatively, this observation might reflect a confounding by indication bias, where women with better lung function are more likely to tolerate OCP and use them. Thereby, it is important to consider women's hormonal trajectory over the lifespan when assessing asthma risk and tailoring management strategies.

Our study provides novel insights into the intersection of menopause, aging, obesity, female sex hormone use, and asthma outcomes. Although menopause was not directly associated with significant changes in asthma prevalence or severity, the associations observed with hormone therapy warrant further investigation. Understanding the complex relationship between biological aging, inflammation, and hormone use can guide more personalized asthma management strategies, ultimately improving outcomes for postmenopausal women. Future research should explore the mechanisms underlying these relationships to inform clinical practice and public health initiatives.

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