Hormone replacement therapy and asthma onset in menopausal women: National cohort study

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Background: There is uncertainty about the role of hormonal replacement therapy (HRT) in the development of asthma.
Objective: We investigated whether use of HRT and duration of use was associated with risk of development of asthma in perimenopausal and postmenopausal women.
Methods: We constructed a 17-year (from January 1, 2000, to December 31, 2016) open cohort of 353,173 women (aged 46-70 years) from the Optimum Patient Care Database, a longitudinal primary care database from across the United Kingdom. HRT use, subtypes, and duration of use; confounding variables; and asthma onset were defined by using the Read Clinical Classification System. We fitted multilevel Cox regression models to estimate hazard ratios (HRs) with 95% CIs.
Results: During the 17-year follow-up (1,340,423 person years), 7,614 new asthma cases occurred, giving an incidence rate of 5.7 (95% CI = 5.5-5.8) per 1,000 person years. Compared with nonuse of HRT, previous use of any (HR = 0.83; 95% CI = 0.76-0.88), estrogen-only (HR = 0.89; 95% CI = 0.84-0.95), or combined estrogen and progestogen (HR = 0.82; 95% CI = 0.76-0.88) HRT was associated with a reduced risk of asthma onset. This was also the case with current use of any (HR = 0.79; 95% CI = 0.74-0.85), estrogen-only (HR = 0.80; 95% CI = 0.73-0.87), and combined estrogen and progestogen (HR = 0.78; 95% CI = 0.70-0.87) HRT. Longer duration of HRT use (1-2 years [HR = 0.93; 95% CI = 0.87-0.99]; 3-4 years [HR = 0.77; 95% CI = 0.70-0.84]; and ≥5 years [HR = 0.71; 95% CI = 0.64-0.78]) was associated with a dose-response reduced risk of asthma onset.
Conclusion: We found that HRT was associated with a reduced risk of development of late onset asthma in menopausal women. Further cohort studies are needed to confirm these findings. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

Key words: *Asthma, estrogens, epidemiology, estradiol, progestogen*

Sex steroid hormones are believed to contribute to the observed notable sex-related differences in the development and clinical manifestation of asthma.[1] Over several decades, several epidemiologic studies have investigated the role of both endogenous and exogenous sex steroids in the development of asthma in women, but the underlying evidence remains uncertain. In our recent systematic review, most previous studies (which were predominantly cross-sectional) showed that ever-use and current use of hormone replacement therapy (HRT), compared with nonuse, were associated with an increased risk of development of asthma in menopausal women.[1] In contrast, some studies showed that HRT use led to improved lung function in postmenopausal women.[2,3] Previous studies have also shown that obesity and cigarette smoking may modify the association between HRT and asthma.[4,5]

The cross-sectional design of most previous studies impedes clear evaluation of any potential causal association between the use of HRT and asthma. Additionally, ascertainment of HRT and asthma, based on self-report (as was the case in the majority of studies), highlights the importance of recall and information bias in influencing the reported findings.[6] In the light of these important methodologic shortcomings, the role of HRT in the development of asthma in menopausal women remains unclear. In particular, there is a need to undertake more robust longitudinal studies that will help clarify the underlying evidence base. In the current study, we investigated the association of HRT use, its subtypes, and duration of use with the risk of development of asthma in menopausal women. We also examined whether these associations were modified by body mass index (BMI) and cigarette smoking.

METHODS

Ethics approvals and permissions

This study was approved by the Anonymized Data Ethics and Protocol Transparency Committee (reference no. ADEPT1317), which grants project-specific approvals for use of data from the the Optimum Patient Care Research Database (OPCRD). Optimum Patient Care has an existing National Health

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Abbreviations used
BMI: Body mass index
ER: Estrogen receptor
GP: General practitioner
HRT: Hormonal replacement therapy
IMD: Index of Multiple Deprivation
OPCRD: Optimum Patient Care Research Database
QOF: Quality and Outcomes Framework

Service Health Research Authority ethics approval for use of the OPCRD for research (NHS Research Ethics Committee reference no. 15/EM/150). All researchers involved in the data analysis completed required information governance courses before working on the data.

Protocol registration and publication

The study protocol was registered with the European Union Electronic Register of Post-Authorization Studies (EUPAS22967). In addition, the protocol was peer-reviewed and published before the analyses were undertaken.[7]

Study design and population

The study data were derived from OPCRD, which is a bespoke, longitudinal, de-identified primary care database from across the United Kingdom that is used to conduct epidemiologic, pharmaceutical, and clinical studies (https://opcrd.co.uk/).[8,9] At the time of this study, the OPCRD consisted of data from 630 primary care practices that represented more than 6.5 million patients. All individuals resident in the United Kingdom (including children) are registered with primary care. We constructed an open retrospective cohort of perimenopausal and postmenopausal women (aged 45-70 years) from the database. Participants were followed from baseline (starting from January 1, 2000), the date of their registration to a general practice, or the year in which they reached the age of 45 years until December 31, 2016. Exit date was defined as the date of the first record of an asthma event, death, deregistration from a practice, the year of in which the participant reached the age of 70 years, or the end of follow-up (December 31, 2016), whichever came first. Participants without asthma at baseline or 5 years before the baseline date were included and followed up. In total, 353,173 women met the inclusion criteria.

Ascertainment and definition of study exposures

Using the Read Clinical Classification System (for the Read codes, see Supplement 1 in the Online Repository at www.jacionline.org),[10] we defined the following exposures: (1) previous (anytime in the past) and current (during that study year) use of any HRT versus nonuse; (2) previous and current use of subtypes of HRT (estrogen-only or combined estrogen and progestogen) versus nonuse; (3) duration of HRT use (treated as a persistent variable) of 1 to 2 years, 3 to 4 years, and 5 years or more versus nonuse; and (4) menopausal status of perimenopausal (age 46-55 years) versus postmenopausal (age 56-70 years). HRT use was counted only if it occurred before the outcome and was ascertained for each year of follow-up.

Potential confounding variables

A directed acyclic graph was used to select potential confounding factors adjusted in our analysis (Fig 1). Confounding factors were extracted by using the relevant Read codes (see Supplement 2 in the Online Repository at www.jacionline.org) and included age, gravidity, BMI, smoking, Charlson Comorbidity Index score,[11] any gynecologic condition (endometriosis, polycystic ovary syndrome, acne, bilateral salpingo-oophorectomy, hysterectomy bilateral salpingo-oophorectomy, hysterectomy, fibroids, or menstrual bleeding complaints identified under the coding terms menorrhagia, metrorrhagia, and menometrorrhagia),[12] and Index of Multiple Deprivation (IMD) quintile.[13]

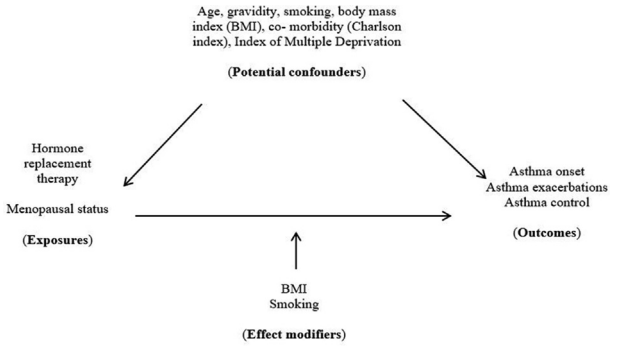

FIG 1. Direct acyclic graph showing the association between use of HRT and asthma onset in females, with effect modification by BMI and smoking.

Outcome

Asthma onset was defined as the first ever general practitioner (GP)-recorded asthma event defined by using the primary care codes associated with asthma diagnosis occurring any time after the baseline date. To ensure that only patients who did not have asthma at the start of the follow-up were included in the cohort, a broader definition of asthma (defined as occurrence of either asthma diagnosis or asthma-related hospitalization, exacerbation, or medication prescription) was used to exclude patients who may have asthma before the baseline date. The relevant Read codes are provided in Supplement 3 (in the Online Repository at www.jacionline.org).

Statistical analyses

We used the Pearson chi-square test and differences in means to describe the distribution of the baseline study characteristics, use of HRT, and incidence of asthma. We used extended Kaplan-Meier curves[14] to describe survival functions (for additional details regarding the risk of remaining asthma-free, see Supplement 6 in the Online Repository at www.jacionline.org) by HRT categories (type and duration). Multilevel mixed-effects extended Cox regression was used to study the association of HRT use and menopausal status with risk of asthma onset. This allowed us to account for the time-varying nature of exposure and confounders, as well as for the clustering of patients from the same practice. Adjusted analyses included all of the aforementioned factors. To evaluate any potential for residual confounding, we calculated the E-values[15] for the observed estimates of association of HRT use and menopausal status with asthma onset. We included interaction terms for smoking and BMI in each adjusted model to evaluate the interactions between HRT use and these factors in relation to asthma onset. Models in which interaction term achieved a P value less than .20 were stratified for BMI or smoking. Data management and editing were undertaken by using R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses were undertaken using Stata 14 software (Stata Statistical Software, release 14 [StataCorp LP, College Station, Tex]).

Reporting

This article has been written following the recommendations of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[16] and RECORD (Reporting of studies Conducted Using Observational Routinely Collected Data).[17]

RESULTS

Baseline characteristics of the study populations

Table I and Fig 2 provide the baseline characteristics of the population. Of the 353,173 women at risk of asthma who were included in the study, 16% used any HRT, 9% used combined estrogen and progestogen HRT, and 7% used estrogen-only HRT at

TABLE I. Baseline characteristics of menopausal women (aged 46-70 years) without asthma by use of HRT and study outcomes

Characteristic	Frequency (N = 353,173), no. (%)	Used any HRT (n = 57,104 [16%]), % (95% CI)*	Used estrogen + progestogen combined HRT (n = 31,281 [9%]), % (95% CI)*	Used estrogen-only HRT (n = 25,823 [7%]), % (95% CI)*	Asthma incidence during follow-up (n = 7,614), incidence rate per 1000 person years (95% CI)
Age (y)					
46-50	114,544 (32.4)	10.6 (10.4-10.7)	5.7 (5.6-5.8)	4.9 (4.7-5.0)	5.00 (4.83-5.17)
51-55	71,582 (20.3)	24.1 (23.8-24.5)	14.9 (14.6-15.1)	9.2 (9.0-9.5)	6.09 (5.81-6.38)
56-60	61,055 (17.3)	23.5 (23.1-23.8)	13.3 (13.0-13.6)	10.2 (9.9-10.4)	6.30 (5.97-6.65)
61-65	54,043 (15.3)	15.8 (15.5-16.1)	7.4 (7.2-7.6)	8.3 (8.1-8.6)	6.65 (6.23-7.11)
66-70	51,949 (14.7)	9.3 (9.1-9.6)	3.7 (3.6-3.9)	5.6 (5.4-5.8)	6.44 (5.89-7.05)
Menopausal status, no. (%)					
Perimenopausal (age 46-55 y)	193,816 (54.9)	16.3 (16.2-16.5)	9.6 (9.5-9.7)	6.7 (6.6-6.8)	5.61 (5.44-5.80)
Postmenopausal (age 56-70 y)	159,357 (45.1)	16.0 (15.8-16.1)	7.9 (7.8-8.1)	8.0 (7.9-8.1)	5.74 (5.57-5.93)
Smoking status, no. (%)					
Nonsmoker	175,235 (49.6)	14.6 (14.4-14.8)	7.7 (7.6-7.8)	6.9 (6.8-7.0)	5.05 (4.88-5.22)
Ex-smoker or current smoker	177,938 (50.4)	17.7 (17.5-17.9)	10.0 (9.9-10.1)	7.7 (7.6-7.8)	6.28 (6.09-6.47)
BMI, kg/m^2					
<25	139,415 (39.5)	17.6 (17.4-17.8)	10.3 (10.1-10.4)	7.3 (7.2-7.5)	4.12 (3.94-4.30)
25-29.9	121,825 (34.5)	17.0 (16.8-17.2)	9.2 (9.0-9.3)	7.9 (7.7-8.0)	5.58 (5.37-5.80)
≥30	91,933 (26.0)	12.8 (12.5-13.0)	6.3 (6.1-6.4)	6.5 (6.4-6.7)	7.85 (7.57-8.14)
Gravidity, no. (%)					
None	241,719 (68.4)	16.9 (16.7-17.0)	9.2 (9.1-9.3)	7.7 (7.6-7.8)	6.17 (6.00-6.34)
1	40,811 (11.6)	14.9 (14.6-15.3)	8.5 (8.2-8.7)	6.4 (6.2-6.7)	5.00 (4.68-5.33)
2	41,096 (11.6)	15.0 (14.7-15.3)	8.4 (8.1-8.6)	6.6 (6.4-6.9)	4.86 (4.56-5.17)
≥3	29,547 (8.4)	13.5 (13.1-13.9)	7.3 (7.0-7.6)	6.2 (5.9-6.5)	4.90 (4.55-5.27)
Any gynecologic condition†					
No	251,959 (71.3)	14.9 (14.7-15.0)	10.0 (9.9-10.1)	4.9 (4.8-5.0)	6.02 (5.79-6.26)
Yes	101,214 (28.7)	19.4 (19.1-19.6)	6.0 (5.9-6.1)	13.4 (13.1-13.6)	5.53 (5.38-5.68)
Charlson Comorbidity Index, no. (%)					
0	303,205 (85.8)	16.5 (16.4-16.6)	9.2 (9.1-9.3)	7.3 (7.2-7.4)	5.58 (5.44-5.72)
1-3	11,129 (3.2)	11.6 (11.0-12.2)	5.5 (5.1-6.0)	6.0 (5.6-6.5)	5.58 (4.94-6.30)
≥4	38,839 (11.0)	14.7 (14.3-15.0)	7.2 (7.0-7.5)	7.5 (7.2-7.7)	6.22 (5.89-6.57)
IMD quintile, no. (%)					
First quintile (least deprived)	82,551 (23.4)	14.4 (14.1-14.6)	8.0 (7.8-8.2)	6.4 (6.2-6.5)	6.42 (6.14-6.71)
Second quintile	68,280 (19.3)	16.3 (16.1-16.6)	8.6 (8.4-8.9)	7.7 (7.5-7.9)	6.26 (5.96-6.57)
Third quintile	71,168 (20.1)	18.3 (18.0-18.6)	10.1 (9.8-10.3)	8.2 (8.0-8.4)	5.64 (5.36-5.94)
Fourth quintile	68,152 (19.3)	15.7 (15.4-16.0)	8.5 (8.3-8.7)	7.2 (7.0-7.3)	5.44 (5.17-5.73)
Fifth quintile (most deprived)	63,022 (17.8)	16.4 (16.1-16.7)	9.1 (8.9-9.3)	7.3 (7.1-7.5)	4.50 (4.24-4.77)

*Defined as having any of the following conditions: endometriosis, polycystic ovary syndrome, menorrhagia, acne, metrorrhagia, bilateral salpingo-oophorectomy, hysterectomy bilateral salpingo-oophorectomy, hysterectomy, fibroids, and menometrorrhagia.
†The differences between groups of background variables were statistically significant ($P < .001$).

baseline. Use of any HRT, estrogen-only HRT, or combined estrogen and progestogen HRT was highest among women 51 to 55 years of age compared with that in other age groups; it was higher in ex-smokers or current smokers than in nonsmokers (which was a surprising finding), highest in those with a BMI less than 25 kg/m^2 versus in women with a higher BMI score, higher in women who had never been pregnant versus in those with a recorded pregnancy; and lowest in women with a comorbidity score of 1 to 3 versus in those with fewer and or a greater number of comorbidities, with no differences found between IMD quintiles. Although use of any HRT was similar between premenopausal and postmenopausal women, use of combined estrogen and progestogen HRT was more common in perimenopausal women than in postmenopausal women whereas use of estrogen-only HRT was more common in postmenopausal than in perimenopausal women. Use of any HRT and estrogen-only HRT was higher in women with a prior gynecologic condition than in those without such a condition, whereas the reverse was found for combined estrogen and progestogen HRT.

During the 17 years of follow-up (1,340,423 person years), 7,614 new asthma cases were observed, giving an incidence rate of 5.7 cases (95% CI = 5.5-5.8) per 1000 person years. The incidence rate of asthma increased with increasing age; it was similar between premenopausal and postmenopausal women, higher in ex-smokers and current smokers than in nonsmokers, increased with increasing BMI, decreased with increasing

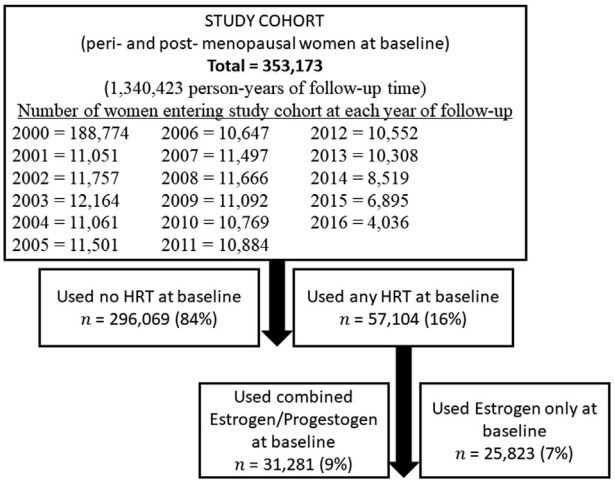

FIG 2. Flowchart of the study cohort and baseline use of HRT.

number of pregnancies, lower in women with prior gynecologic conditions than in those without such a condition; similar across the range of Charlson Comorbidity Index scores, and decreased with increasing IMD quintiles (Table I).

Associations of HRT and menopause with asthma onset

Previous use of any HRT, estrogen-only HRT, and combined estrogen and progestogen HRT were associated with up to an 18% (95% CI = 24-12) reduction in risk of development of new-onset asthma when compared with the risk among women who did not use HRT (Table II). Similarly, current use of any HRT, estrogen-only HRT, and combined estrogen and progestogen HRT was associated with up to a 22% (95% CI = 30-13) reduced risk of development of asthma than among those who did not use HRT. We observed a dose-response association (Kandall τ statistic = –1 [P = .089]) between duration of HRT use and risk of asthma onset: women with 1 to 2 years of HRT use had a 7% (95% CI = 13-1) lower risk than women who did not use HRT, women with 3 or 4 years of use had a 23% lower risk (95% CI = 30-16), and those with 5 or more years of use had a 29% (95% CI = 36-22) lower risk. Postmenopausal women, compared with perimenopausal women, had a 12% (95% CI = 17-8) reduced risk of asthma onset. Stratified by menopausal status, we found statistically significant associations only with current use of HRT and its subtypes, and in these cases, the reduction in asthma onset was slightly greater in perimenopausal than in postmenopausal women (Table II). In analyses stratified by BMI and smoking, we found statistically significant associations only with current use of any HRT and it subtypes and asthma onset (most likely because stratified analyses lacked sufficient power to detect significant effect); however, the effect estimates were generally similar across the categories of BMI and smoking (Table III). Kaplan-Meier survival curves confirmed that the risk of remaining asthma-free was lower in women who used HRT than in those who did not use it (Fig 3, see Supplement 4 in the Online Repository at www.jacionline.org for Kaplan-Meier survival curve stratified by menopausal status). Figs 4 and 5 summarize Tables II and III, illustrating the hazard ratios obtained in a forest plot.

The E-values for the association of use of any HRT, use of HRT subtypes, and duration of use with asthma onset ranged from 1.36 (for the effect of 1-2 years of HRT use) to 2.17 (for the effect of ≥5 years of HRT use), signifying that an unmeasured confounder would require a minimum effect measure of 1.36 and a maximum of 2.17 beyond the adjusted confounders to negate the observed risk estimates.

DISCUSSION

Summary of key findings

Use of any HRT, estrogen-only HRT, or combined estrogen and progestogen HRT, was associated with a decreased risk of development of new-onset asthma among perimenopausal and postmenopausal women. However, use of HRT was associated with a reduced risk of asthma only in all women, but not when the women were stratified by menopausal status. Duration of HRT use was associated with a decreased risk of asthma onset in a dose-response manner, so that women who used HRT for longer periods had greater protection than did women who used it for shorter periods. This effect becomes insignificant, however, when patients are stratified by age, BMI, and smoking, possibly because of lack of sufficient power to detect significant effect after stratification. Compared with perimenopausal women, postmenopausal women were at lower risk of development of asthma.

Strengths and limitations of the study

The key strengths of this study were that thus far, it is the largest longitudinal cohort study on the topic; it had a long follow-up period (17 years); and it is based on a real-life, nationwide primary care data set. With the large sample size, we were able to investigate the associations between both subtypes and duration of HRT use on the risk of asthma onset in different subgroups of women (eg, subgroups based on smoking status and BMI) with considerable precision. The OPCRD included longitudinal encounters of 6.3 million well-characterized patients registered with 630 general practices from across the United Kingdom. This database is representative of the United Kingdom–wide primary care population; thus, findings have direct generalizability to the wider UK population. The long-term follow-up meant that we could study the longer-term impact of HRT on asthma onset.

This work used the Read coding system, which is a standardized system for recording primary care diagnoses and clinical encounters across the United Kingdom, to identify and define all variables used in the study. On the basis of GP-recorded parameters, as opposed to the self-administered subjective assessments used in most previous studies,[1,18-23] we had consistent measurement of the study exposures, potential confounders, and outcome. The longitudinal framework of the OPCRD database enabled us to undertake time-dependent multilevel survival analysis. In this type of analysis, instead of forcing us to define participants as either users or nonusers of HRT throughout the follow-up of the study, the time-dependent approach allowed us to take account of the possibility that the status of participants regarding use of HRT could change over the study period. Thus, participants were counted as nonusers in the years during which they did not use HRT and were counted as users only in the years during which they used HRT. This approach meant that we minimized immortal time bias, which is a common bias

TABLE II. Association between use of HRT and onset of asthma in all women and by menopausal status

	Asthma onset			
	All menopausal women		Perimenopausal women	Postmenopausal women
HRT use	Unadjusted hazard ratio (95% CI)*	Adjusted hazard ratio (95% CI)*	Adjusted hazard ratio (95% CI)*	Adjusted hazard ratio (95% CI)*
Previous use of any HRT				
None	1	1	1	1
Yes	**0.82 (0.78-0.86)**	**0.83 (0.79-0.88)**	**0.84 (0.78-0.91)**	**0.86 (0.80-0.92)**
Current use of any HRT				
None	1	1	1	1
Yes	**0.75 (0.70-0.80)**	**0.79 (0.74-0.85)**	**0.68 (0.61-0.75)**	**0.86 (0.79-0.95)**
Type of HRT (previous use)				
None	1	1	1	1
Estrogen only	**0.87 (0.82-0.93)**	**0.89 (0.84-0.95)**	0.98 (0.88-1.08)	**0.89 (0.82-0.97)**
Combined estrogen + progestogen	**0.82 (0.77-0.88)**	**0.82 (0.76-0.88)**	**0.78 (0.70-0.87)**	**0.88 (0.80-0.97)**
Type of HRT (current use)				
None	1	1	1	1
Estrogen only	**0.74 (0.68-0.81)**	**0.80 (0.73-0.87)**	**0.73 (0.64-0.83)**	**0.84 (0.74-0.94)**
Combined estrogen + progestogen	**0.76 (0.69-0.85)**	**0.78 (0.70-0.87)**	**0.61 (0.53-0.71)**	**0.93 (0.80-1.08)**
Duration of use of any HRT (y)				
None	1	1	1	1
1-2	**0.91 (0.86-0.97)**	**0.93 (0.87-0.99)**	0.92 (0.83-1.01)	0.96 (0.87-1.05)
3-4	**0.75 (0.69-0.82)**	**0.77 (0.70-0.84)**	**0.76 (0.66-0.88)**	**0.76 (0.68-0.85)**
≥5	**0.70 (0.64-0.77)**	**0.71 (0.64-0.78)**	**0.71 (0.59-0.86)**	**0.80 (0.72-0.90)**
Menopausal status at baseline				
Perimenopause (age 46-55 y)	1	1	Not applicable	Not applicable
Postmenopauseal (age 56-70 y)	**0.91 (0.87-0.96)**	**0.88 (83-0.92)**		

All analysis were based on a multilevel Cox regression that accounted for clustering of patients within GP practices. Both unadjusted and adjusted models were adjusted for use of HRT. Boldface indicates statistical significance.

*Adjusted for age, smoking, Charlson Comorbidity Index score, BMI, gravidity, any gynecologic condition, and IMD quintile.

in pharmacoepidemiologic studies evaluating the effect of medical therapies on disease outcomes.[24]

The Quality and Outcomes Framework (QOF), a national initiative and the first of its kind in the world that provided incentives to encourage UK primary care to develop a register of patients with asthma, came into existence in 2004.[25] The QOF included regular registry audits and consequently led to improvement in a GPs' recording of clinical events.[26] Most of the follow-up period in our study (13 of 17 years) was after adoption of the QOF, thereby minimizing bias due to asthma underdiagnosis (see Supplement 5 in the Online Repository at www.jacionline.org for a sensitivity analysis that excluded all patients who joined the study before the QOF was introduced). Furthermore, to ensure that only at-risk women (ie, those who did not have asthma at the start of follow-up) were included in the study, we used a 5-year look-back period under the assumption that women with asthma would have had at least 1 contact with primary care during the 5 years preceding the start of follow-up. It is possible, however, that a minority of patients who despite being diagnosed with asthma, had no primary care contact during the 5 years preceding the start of follow-up and thus may have been incorrectly classified as asthma-free. The risk of confounding by indication was minimized through identification of a comprehensive list of conditions for which HRT is also used, and we adjusted for these conditions in our analyses.

A potential limitation is that the menopausal status of females was based only on the ages of women, which was the only information available from the database for this purpose. Nevertheless, the cutoff years we used to define perimenopausal and postmenopausal women were based on the average age of occurrence of these events in the United Kingdom. Furthermore, we have assumed that any prescriptions of HRT were used according to a GP's prescription, which may not always be the case. We were unable to adjust for ethnicity, as this information was missing in more than 70% of cases. We had originally planned to carry out propensity score matching analysis to reduce the bias due to the confounding variables. We were, however, unable to design an appropriate statistical model (given the time-varying and multicategoric nature of the study exposures within multilevel models), and therefore, we performed a conventional confounding adjustment. It is possible that some residual confounding has remained even after controlling for various confounders; however, our evaluation of unmeasured confounders indicates that this may be an unlikely explanation for our findings. Furthermore, our original protocol contained an analysis that included the route of HRT administration (oral,

TABLE III. Association between use of HRT and onset of asthma in menopausal women and by BMI and smoking

	Asthma onset				
	Stratified analyses by BMI, hazard ratio (95% CI)*,†			Stratified analyses by smoking status, hazard ratio (95% CI)*,‡	
HRT use by BMI	<25 kg/m^2	25-29.9 kg/m^2	≥30 kg/m^2	Nonsmokers	Smokers
Previous use of any HRT					
None	1	1	1	1	1
Yes	0.98 (0.88-1.08)	0.94 (0.86-1.02)	0.99 (0.91-1.08)	1.01 (0.94-1.10)	0.94 (0.87-1.01)
Current use of any HRT					
None	1	1	1	1	1
Yes	**0.76 (0.67-0.87)**	**0.72 (0.64-0.81)**	**0.72 (0.63-0.81)**	**0.75 (0.67-0.83)**	**0.72 (0.66-0.80)**
Type of HRT (previous use)					
None	1	1	1	1	1
Estrogen only	1.02 (0.91-1.15)	1.03 (0.93-1.15)	1.00 (0.90-1.11)	1.07 (0.97-1.18)	0.99 (0.90-1.06)
Combined estrogen + progestogen	0.99 (0.86-1.15)	**0.85 (0.76-0.96)**	1.00 (0.88-1.12)	1.00 (0.89-1.13)	0.91 (0.82-1.00)
Type of HRT (current use)					
None	1	1	1	1	1
Estrogen only	**0.79 (0.68-0.93)**	**0.78 (0.67-0.90)**	**0.70 (0.60-0.82)**	**0.74 (0.65-0.85)**	**0.76 (0.67-0.87)**
Combined estrogen + progestogen	**0.73 (0.59-0.90)**	**0.64 (0.53-0.77)**	**0.74 (0.62-0.90)**	**0.76 (0.63-0.91)**	**0.67 (0.59-0.76)**
Duration of use of any HRT, y					
None	1	1	1	1	1
1-2	1.00 (0.89-1.13)	0.90 (0.80-1.00)	0.96 (0.86-1.08)	1.01 (0.91-1.12)	0.91 (0.83-1.00)
3-4	0.86 (0.72-1.03)	0.91 (0.78-1.05)	0.98 (0.85-1.14)	0.99 (0.86-1.15)	0.88 (0.78-0.99)
≥ 5	1.04 (0.86-1.25)	1.12 (0.95-1.32)	1.08 (0.92-1.26)	1.04 (0.88-1.23)	1.10 (0.97-1.24)
Perimenopausal (age 46-55 y)§	1	1	1	1	1
Postmenopausal (age 56-70 y)§	0.98 (0.88-1.10)	1.05 (0.95-1.15)	1.01 (0.93-1.10)	1.02 (0.94-1.11)	1.02 (0.94-1.10)

All analysis were based on a multilevel Cox regression that accounted for clustering of patients within GP practices. Boldface indicates statistical significance.
*Adjusted for age, smoking, Charlson Comorbidity Index score, BMI, gravidity, any gynecologic condition, and IMD quintile.
†Stratified analyses performed after interaction term between use of HRT and BMI gave $P < .20$.
‡Stratified analyses performed after interaction term between use of HRT and smoking gave $P < .20$.
§Menopausal status at baseline.

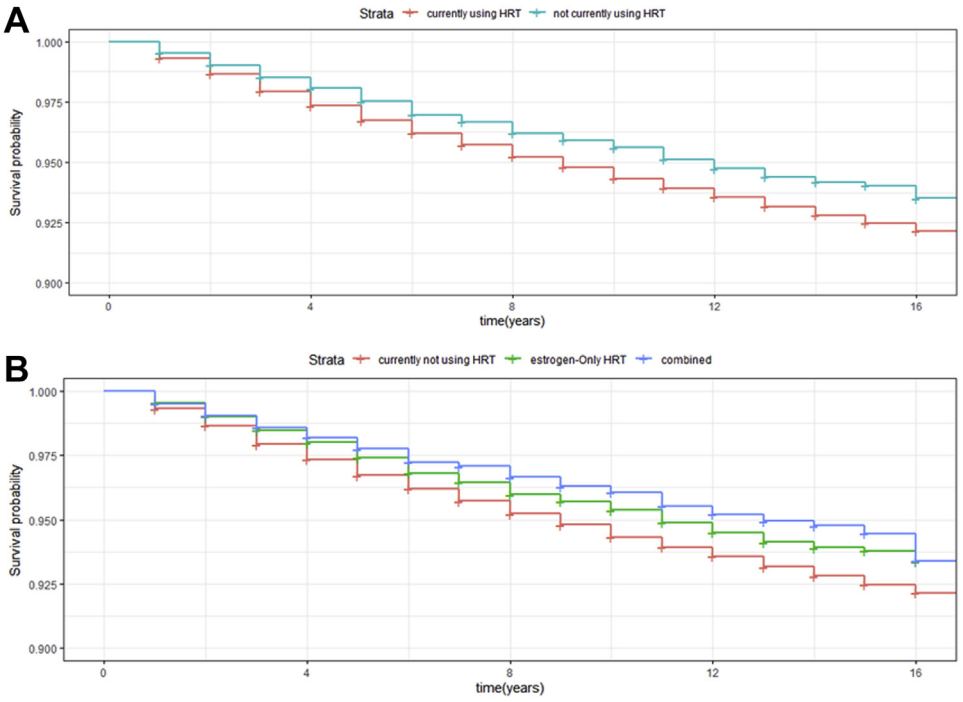

FIG 3. Kaplan-Meier curves comparing current users and nonusers of HRT among menopausal women. **A**, Difference in risk of remaining free of asthma between users and nonusers of any HRT. **B**. Comparison of the risk of remaining free of asthma by type of HRT.

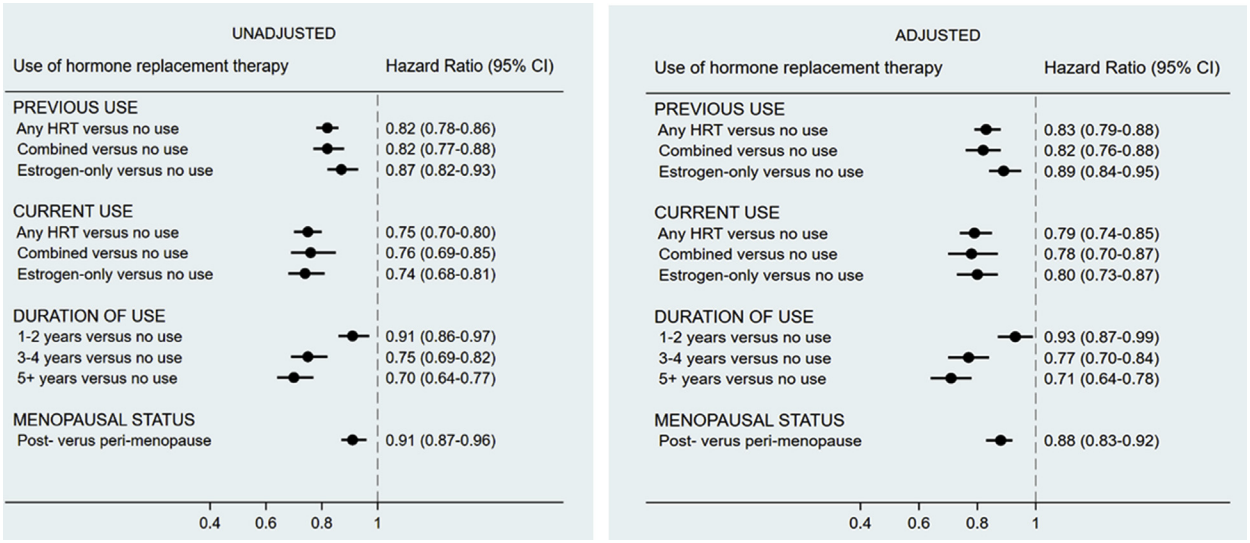

FIG 4. Association between use of HRT and onset of asthma in all women.

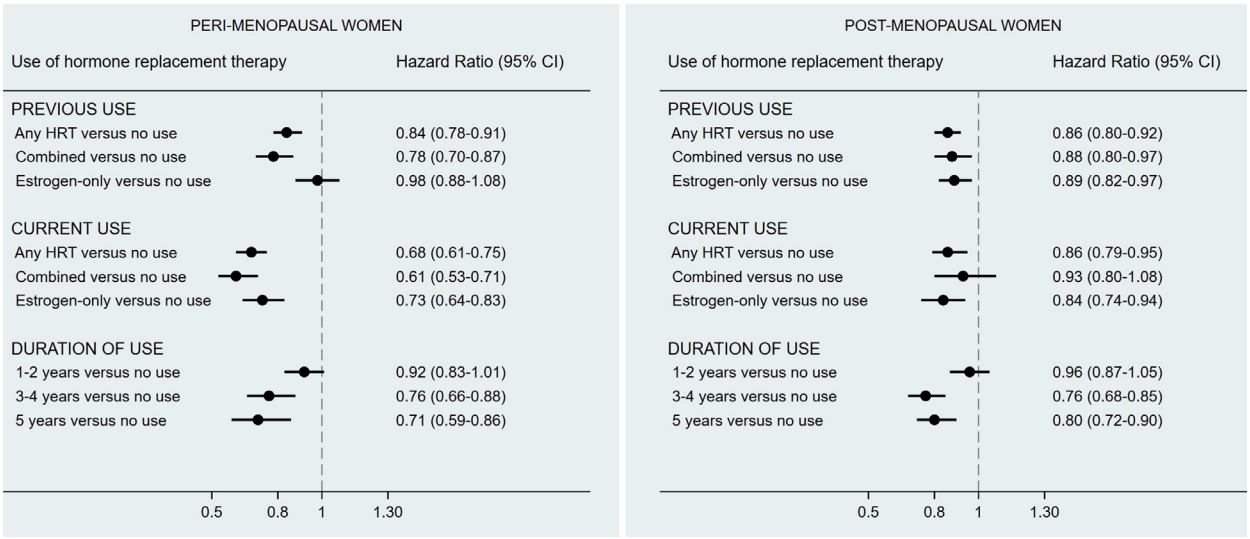

FIG 5. Association between use of HRT and onset of asthma by menopausal status.

transdermal, subcutaneous, intramuscular, or local intrauterine). However, after the data had been acquired, this information was found to be inconsistently recorded in the database, and therefore we did not proceed with this analysis.

Lastly, although we defined asthma onset on the basis of GP-recorded diagnosis, it is possible that some of these cases might be a misdiagnosis for chronic obstructive pulmonary disease. However, given that the Read codes for asthma diagnosis have been validated previously in a comparable database with high accuracy[27] and the concomitance of asthma and chronic obstructive pulmonary disease based on Read codes is less than 15%,[28] we believe such cases to be minimal if present and unlikely to change our conclusions.

Comparison of findings with previous literature

Although some previous studies have generally shown an increased risk of asthma onset with the use of HRT,[15,18-23] contrary findings have also been reported.[1-3,29-31] Most previous studies were cross-sectional.[21-23] Three studies identified in our systematic review were prospective cohort studies.[1,18-20] The Nurses' Health Study[18,20] reported that previous and current use of HRT and subtypes, including HRT use for more than 10 years but not a shorter duration of use, were associated with an increased risk of new-onset asthma in postmenopausal women. The French E3N cohort study found a statistically significant increased risk of new-onset asthma with use of estrogen-only HRT, but not with use of combined estrogen and progestogen

HRT; they also showed no clear association of past use, recent use, or duration of use with risk of asthma in postmenopausal women.[1] Another prospective cohort study found that use of any HRT, HRT subtypes, and long duration of use were associated with increased risk of new-onset asthma.[19] The findings are in contrast to the findings in our study, in which we showed that current HRT use, its subtypes, and long duration of use were associated with a decreased risk of new-onset asthma. Whereas the previous cohort studies included only postmenopausal women, our study included both perimenopausal and postmenopausal women; yet our findings were similar in both perimenopausal and postmenopausal women when analyzed separately. The assessment of HRT and/or asthma was based on subjective self-reported questionnaires in previous studies, giving a potential for information and recall bias. Our study, apart from being the largest longitudinal cohort study on the topic to date, used real-life primary care records (ie, records maintained for the purpose of routine care) based on GP-recorded HRT prescription and asthma diagnosis. Only 2 previous cohort studies used HRT as a time-dependent exposure, but even in those studies, information on HRT use from biennial surveys was updated only every 2 years.[1,18,20] In our study, we were able to update information on HRT use yearly throughout the follow-up period (from the prescribing record), which then provides more precise information on HRT. Similar to our findings, results from the Nurses' Health Study showed that postmenopausal women were at a lower risk of development of asthma than perimenopausal women were.[20] When participants were stratified by smoking status, the French E3N study found that risk was specific to nonsmokers only.[1] Our results, however, showed similar risks among smokers and nonsmokers and across the categories of BMI.

Interpretation and possible mechanisms of action

HRT is proposed to exert both anti-inflammatory and proinflammatory effects on innate[32,33] and adaptive immune pathways,[34] highlighting a potentially complex role in asthma pathogenesis. The estrogen receptors (ERs), ERα and ERβ, are widely expressed on immune cells, and both are present in the lung.[32,35] Estrogen signaling appears context and dose dependent. For example, ERα has been shown to promote proinflammatory cytokine synthesis in response to Toll-like receptor ligation in dendritic cells and macrophages, whereas higher levels may promote anti-inflammatory responses.[33] An imbalance of ERα and ERβ expression has been reported in the airways of individuals with asthma versus in healthy airways[36] that may also influence the nature of responses. Recent reports describe differential effects of signaling via ERα and ERβ, with signaling of airway smooth muscle cells via ERβ being protective. This included regulation of airway smooth muscle cell contractility to relax airways[35] and downregulation of AHR and airway remodeling by ERβ signaling.[37] Elegant studies comparing intranasal allergen challenge in wild-type, ERα knockout mice, and ERβ knockout mice demonstrate exacerbated airway hyperresponsiveness, immune cell infiltration, and remodeling in ERβ knockout mice, which were most prominent in female mice.[38]

Several studies have demonstrated that both progesterone and estrogen increase regulatory T–cell frequency and/or function, which is predicted to contribute to protective effects of HRT and beneficially affect asthma outcomes.[34] In contrast, estrogen and progesterone have been variously reported to inhibit and enhance T_H1, T_H2, and T_H17 effector cell responses.[34,39-41] These studies highlight the complexity of sex hormone effects on structural, innate, and adaptive immune cells, as well as the influence of an inflammatory milieu, receptor signaling, and hormone concentration. The findings from the current study, which contrast those of 3 cohort studies described earlier, provide strong evidence demonstrating that use of HRT and its subtypes previously, currently, and long-term is associated with a clinically significant reduced risk of development of asthma in menopausal women. Whether these contradictory findings are the result of complex roles of HRT is unclear. Perhaps, they indicate the presence of a number of mechanisms by which HRT can influence asthma outcomes, and they highlight the need for further detailed and longitudinal mechanistic studies alongside observational studies.

Conclusion

Our study found that past use and current use of HRT and its subtypes are associated with a reduced risk of development of new-onset asthma in menopausal women. Further prospective cohort studies are now required to confirm these findings. There is also a need for mechanistic studies to elucidate the specific pathways through which HRT may influence inflammation leading to asthma pathogenesis.

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Key messages

- **Our national, longitudinal study found that HRT is associated with reduced risk of clinically important reductions in the development of asthma in menopausal women.**
- **These findings now need to be validated in other populations, and there is also the need for mechanistic studies to investigate the possible protective role of menopausal hormone therapy in the pathogenesis of asthma in women.**

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