Original Article

Hormone Replacement Therapy and Risk of Severe Asthma Exacerbation in Perimenopausal and Postmenopausal Women: 17-Year National Cohort Study

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What is already known about the topic? Evidence on the impact of use of hormonal replacement therapy (HRT) on clinical outcomes of asthma in perimenopausal and postmenopausal women with asthma is lacking.

What does this article add to our knowledge? Use of HRT in the long term may increase the risk of severe asthma exacerbation in perimenopausal and postmenopausal women.

How does this study impact current management guidelines? Although current findings do not suggest changes in management of asthma in perimenopausal and postmenopausal women, studies uncovering the mechanisms through which HRT impact on clinical outcomes of asthma are required.

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Abbreviations used
BMI- Body mass index
BSO- Bilateral salpingo-oophorectomy
CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
ER- Estrogen receptor
HRT- Hormonal replacement therapy
IMD- Index of multiple deprivation
OPCRD- Optimum Patient Care Research Database
QOF- Quality and Outcomes Framework
RECORD- Reporting of studies Conducted using Observational Routinely-collected Data
STROBE- Strengthening the Reporting of Observational Studies in Epidemiology

BACKGROUND: The impact of hormone replacement therapy (HRT) on clinical outcomes in menopausal women is uncertain.
OBJECTIVE: To investigate the association between use of HRT and severe asthma exacerbation in perimenopausal and postmenopausal women with asthma.
METHODS: We used the Optimum Patient Care Research Database, a population-based longitudinal primary care database in the United Kingdom, to construct a 17-year (January 1, 2000, to December 31, 2016) cohort of perimenopausal and postmenopausal (46-70 years, N = 31,656) women. We defined use of HRT, its subtypes, and duration of HRT use. Severe asthma exacerbation was defined as an asthma-related hospitalization, emergency department visits due to asthma, and/or prescription of oral corticosteroids. Analyses were undertaken using multilevel mixed-effects Poisson regression.
RESULTS: At baseline, 22% of women were using any HRT, 11% combined HRT, and 11% estrogen-only HRT. Previous, but not current, use of any (incidence rate ratio [IRR]: 1.24, 95% confidence interval [CI]: 1.22-1.26), combined (IRR: 1.28, 95% CI: 1.25-1.31), and estrogen-only HRT (IRR: 1.18, 95% CI: 1.14-1.21), and longer duration (1-2 years: IRR: 1.16, 95% CI: 1.13-1.19; 3-4 years: IRR: 1.43, 95% CI: 1.38-1.48; 5+ years: IRR: 1.32, 95% CI: 1.28-1.36) of HRT use were associated with increased risk of severe asthma exacerbation compared with nonuse. The risk estimates were greater among lean women (body mass index [BMI] <25 kg/m^2) than among heavier women (BMI 25-29.9 kg/m^2 and ≥30 kg/m^2) and higher among smokers than nonsmokers.
CONCLUSION: Use of HRT and subtypes, particularly previous, but not current, use and use for more than 2 years, is associated with an increased risk of severe asthma exacerbation in perimenopausal/postmenopausal women with established asthma. Lean women and smokers are at greater risk than heavier women and nonsmokers, respectively. **(J Allergy Clin Immunol Pract 2021;9:2751-60)**

Key words: *Asthma exacerbation; Combined hormone therapy; Estrogen-only therapy; Hormone replacement therapy; Menopause; Women; Cohort study*

Hormone replacement therapy (HRT), an umbrella term used for both estrogen-only and combined estrogen-progestogen hormone treatments, has long been used to mitigate the symptoms caused by menopause, a period of decline in the production of endogenous estrogen and progesterone hormones in perimenopausal and postmenopausal women.[1] Given the sex-related differences in asthma pathogenesis and clinical manifestation, largely attributed to the role of sex steroid hormones,[2-4] HRT has long been suspected to play a role in asthma in women.[5] For several decades, several studies have attempted to address this question, but the underlying evidence base is uncertain as findings from previous studies are conflicting.[6] Findings from our recent systematic review and meta-analysis showed that to date, there are no prospective cohort studies investigating the impact of use of HRT on clinical outcomes of asthma in perimenopausal and postmenopausal women with established asthma.[6] Previous studies, which have been cross-sectional and retrospective case-control studies, are hampered by their inability to establish temporality of association between HRT and clinical outcomes of asthma, self-selection bias, and ascertainment bias.[6] To overcome these limitations, there is a need to undertake long-term longitudinal cohort studies to investigate and clarify the impact of use of HRT on subsequent clinical outcomes of asthma in perimenopausal and postmenopausal women with established asthma.

The aim of the current study was to investigate the association of use of HRT, its subtypes, and duration of use with severe asthma exacerbation in perimenopausal and postmenopausal women with asthma. We also examined whether body mass index (BMI), cigarette smoking, and menopausal status (peri- and postmenopause) modified these associations.

METHODS

Ethics approvals and permissions

The Anonymised Data Ethics and Protocol Transparency Committee, responsible for approval of research using the Optimum Patient Care Research Database (OPCRD), gave approval for the current study (reference number: ADEPT1317). In addition, Optimum Patient Care has an existing ethics approval for the use of OPCRD for research purposes from the NHS Health Research Authority (REC Ref: 15/EM/150). All researchers involved in data analysis completed required information governance courses.

Protocol registration and publication

The study protocol was registered with the European Union electronic Register of Post-Authorization Studies (EUPAS22967) and also published in a peer-reviewed journal before the analyses were undertaken.[7]

Study design and population

OPCRD is a longitudinal anonymized primary care database, comprising 630 primary care practices across the United Kingdom with more than 6 million patients at the time of extracting data for the current study. The database is used to conduct epidemiological, clinical, and pharmaceutical studies (http://optimumpatientcare.org/opcrd/).[8,9] We established an open (meaning that cohort members can enter or leave the cohort anytime during follow-up) retrospective cohort of perimenopausal and postmenopausal women (46-70 years) who had any asthma event (including diagnosis, hospitalization, medication prescription) using previously established Read codes (available in this article's Online Repository at www.jaci-inpractice.org) starting from baseline on January 1, 2000. Participants entered the cohort from baseline or date of registration to a general

practice or the year of turning age 46 years and were followed up until December 31, 2016. Participants exited the cohort on the date of death, deregistration from a practice, year of turning 70 years, or December 31, 2016, whichever came first. In total, 31,656 perimenopausal and postmenopausal women were included in the study (Figure 1).

Ascertainment of hormonal contraceptives and HRT

We used the Read Clinical Classification System[10] (Read codes, available in this article's Online Repository at www.jaci-inpractice.org) to extract information on prescription of HRT. On the basis of the extracted information, we defined the following exposure categories for the use of HRT for each year of follow-up:

1. Previous (anytime in the past) and current (during that year) use versus nonuse
2. Previous and current use of subtypes of HRT (combined estrogen/progestogen, estrogen-only)
3. Duration of use: 1-2 years, 3-4 years, 5 years, or more versus nonuse.

Patients' use of HRT was individually ascertained for every year. In cases where a patient experienced severe asthma exacerbation, HRT use was only counted if the prescription for HRT preceded the asthma exacerbation event in that year.

Potential confounding variables

We selected potential confounding factors based on evidence from previous literature and demonstrated these using a directed acyclic graph (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Using relevant Read codes (available in this article's Online Repository at www.jaci-inpractice.org), we extracted information from the database and defined the following variables: gravidity, BMI, smoking, Charlson comorbidity index,[11] gynecological conditions that are potentially subject to hormonal manipulation—either through supplementation or inhibition—and those that potentially result from estrogen deficiency (endometriosis, polycystic ovary syndrome, acne, bilateral salpingo-oophorectomy [BSO], hysterectomy with BSO, hysterectomy without BSO, fibroids, and menstrual bleeding complaints identified under coding terms: menorrhagia, metrorrhagia; menometrorrhagia),[12] and index of multiple deprivation (IMD).[13] The IMD is a multidimensional measure used to categorize neighborhoods across the United Kingdom on the basis of material living conditions to determine resource allocation and service provision. Thus, although the IMD provides information on neighborhood relative deprivation, it gives an indirect indication of socioeconomic status of the neighborhood.[13] Age was derived using the date of birth. Baseline asthma severity was classified based on the Global Initiative for Asthma severity steps.

Study outcome

Our study outcome was the occurrence of severe asthma exacerbation (Read codes, available in this article's Online Repository at www.jaci-inpractice.org), which was defined according to the recommendation of the European Respiratory Society/American Thoracic Society[14] as asthma-related hospitalization, emergency department visits due to asthma, and/or prescription of oral corticosteroids. We counted the yearly number of asthma exacerbations, measured longitudinally during the 17-year follow-up on each patient. We considered severe asthma exacerbation occurring within a 14-day period as 1 event. This definition has been validated and used in previous studies using the OPCRD database.[15]

Statistical analyses

We used Pearson's χ^2 test to describe the distribution of the baseline study characteristics in relation to the use of HRT and severe asthma exacerbation (Table I). To study the association between HRT use and severe asthma exacerbation, we used multilevel mixed-effects Poisson regression. As the mean number of annual severe asthma exacerbation (0.26) and its variance (0.52) were not exactly the same, we initially implemented multilevel mixed-effects negative binomial regression to the data, but the models did not converge. For this reason, we used multilevel mixed-effects Poisson regression with QR decomposition, which provides an alternative to fitting models for Poisson distributed data. By using the QR decomposition of the variance-components matrix, this analysis approach aids improvement of the convergence of models when the variance components is close to the border of the parameter space.[16] In estimating the association between HRT and severe asthma exacerbation (but not in the descriptive analyses), women who experienced any asthma exacerbation at baseline (prevalent cases, n = 5172; see Figure 1 and Table I) were excluded from the analysis, allowing us to estimate a temporal association between baseline HRT and post-baseline severe asthma exacerbation (ie, new severe asthma exacerbation). The models, while accounting for variations across general practices, also took into account the nesting of patients within general practices; that is, the models included random effects for both patients and practices. Furthermore, the models accounted for the longitudinal nature of the data, so that each variable was allowed to take different values at each year of follow-up. We adjusted for the above-described potential confounding variables, which were included in the models using the categories given in Table I. Interactions of BMI and smoking with HRT were examined by including interaction terms in each adjusted model; the analyses were subsequently stratified by BMI or smoking if the interaction terms achieved P values of $<.20$. The analyses were in addition stratified by menopausal status (peri- and postmenopausal women). We evaluated the potential for residual confounding after the adjusted regression analyses by calculating the E values for the observed estimates of association between HRT use and severe asthma exacerbation.[17] The estimates of the E value indicate the minimum magnitude of association that an unmeasured confounder should have in relation to both respective exposures and outcome in order to negate the observed estimate of association between the respective exposures and the outcome.[17] Data management and editing were undertaken using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses were undertaken using and Stata 14 (Stata Statistical Software: Release 14; StataCorp LP, College Station, Tex).

Reporting

We followed the recommendations of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[18] and RECORD (Reporting of studies Conducted using Observational Routinely-collected Data)[19] in reporting the study results.

RESULTS

Characteristics of the study populations

The 17-year follow-up of the 31,656 women amounted to 366,678 person-years of follow-up time (Figure 1). At baseline (ie, the year a woman joined the study cohort), 22% of women

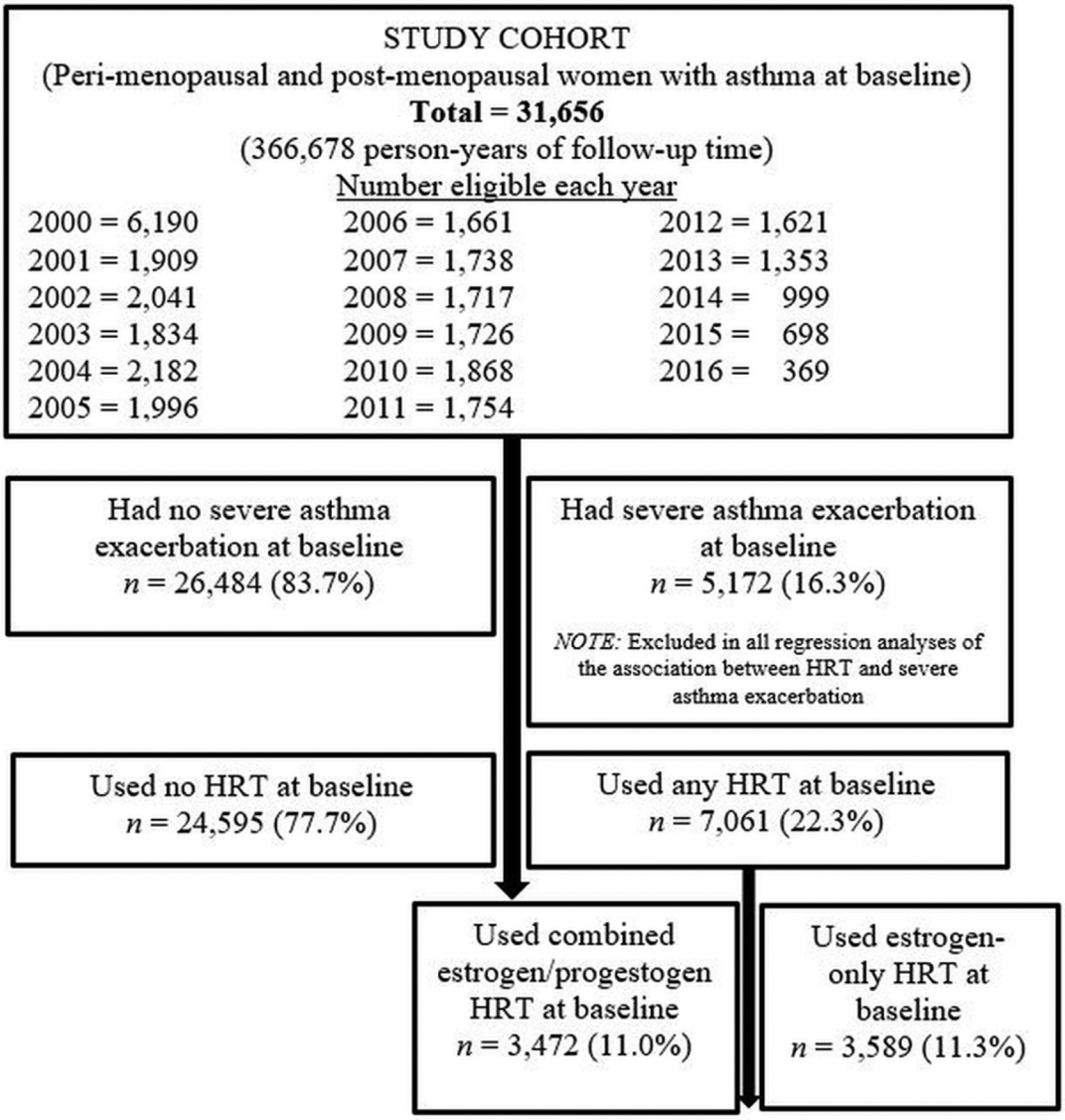

FIGURE 1. Flowchart of study cohort and baseline severe asthma exacerbation and HRT use. *HRT,* Hormone replacement therapy.

were using any HRT, 11% combined HRT, and 11% estrogen-only HRT. Use of any HRT, combined estrogen/progestogen HRT, and estrogen-only HRT was highest among women 51 to 55 years of age and then decreased afterward; higher in ex-/current smokers than nonsmokers; higher in those with BMI <25 kg/m^2 than in those with greater BMI; higher in women who had never been pregnant than those who had been; less in women with a comorbidity score of 1 to 3 than those with lower and higher scores; and relatively equally distributed between IMD quintiles (Table I). Use of any HRT and estrogen-only HRT was higher in women with a prior gynecological condition (ie, situations resulting in estrogen deficiency: BSO, hysterectomy with BSO; and also, management of perimenopausal menstrual bleeding complaints) than those without, but use of combined estrogen/progestogen HRT was higher in those without a prior gynecological condition than those with. Use of any HRT and combined estrogen/progestogen HRT was more common among perimenopausal women than among postmenopausal women, whereas use of combined estrogen-only HRT was more common among postmenopausal women than among perimenopausal women.

A total of 5172 (16%) of the women had experienced severe asthma exacerbation at baseline (Figure 1 and Table I). The annual mean number of severe asthma exacerbation at baseline was 0.26 (standard deviation, 0.71). Severe asthma exacerbation at baseline was highest in women aged 46 to 50 years than in other age groups; higher in ex-/current smokers than in nonsmokers; highest in obese than in nonobese women; highest in women who had 3 or more pregnancies than women who had fewer pregnancies; higher in women with a prior gynecological condition than those without; highest in women with a comorbidity score of 4 and above than those with lower scores; higher in peri- than in postmenopausal women; and relatively equally distributed between IMD quintiles and between baseline

TABLE I. Baseline characteristics by use of hormone replacement therapy (HRT) and severe asthma exacerbation at baseline

Baseline characteristics	Frequency N = 31,656 n (%)	Used any HRT n = 7061 (22.3%) n (%)	No HRT use n = 24,554 (77.6%) n (%)	Used combined HRT n = 3472 (11%) n (%)	Used estrogen-only HRT n = 3589 (11.3%) n (%)	Mean number of severe asthma exacerbation (standard deviation)	Had severe asthma exacerbation† n = 5172 (16%) n (%)
Age (y)							
46-50	14,677 (46.4)	2875 (19.6)	11,802 (80.4)	1649 (11.2)	1226 (8.3)	0.29 (0.75)	2763 (18.8)
51-55	6087 (19.2)	1818 (29.9)	4269 (70.1)	872 (14.3)	946 (15.5)	0.22 (0.66)	840 (13.8)
56-60	4722 (14.9)	1290 (27.3)	3432 (72.7)	558 (11.8)	732 (15.5)	0.24 (0.74)	679 (14.4)
61-65	3599 (11.4)	745 (20.7)	2854 (79.3)	278 (7.7)	467 (13.0)	0.22 (0,66)	508 (14.1)
66-70	2571 (8.1)	333 (12.9)	2238 (87.0)	115 (4.5)	218 (8.5)	0.23 (0.69)	382 (14.9)
Smoking status							
Nonsmoker	13,395 (42.3)	2701 (20.2)	10,694 (79.8)	1321 (9.9)	1380 (10.30)	0.21 (0.63)	1875 (14.0)
Ex-/current smoker	18,261 (57.7)	4360 (23.9)	13,901 (76.1)	2151 (11.8)	2209 (12.1)	0.29 (0.78)	3297 (18.0)
Body mass index (kg/m^2)							
<25	9210 (29.1)	2323 (25.2)	6887 (74.8)	1246 (13.5)	1077 (11.7)	0.22 (0.67)	1311 (14.2)
25-29.9	10,265 (32.4)	2410 (23.5)	7855 (76.5)	1102 (10.7)	1308 (12.7)	0.23 (0.67)	1517 (14.8)
≥30	12,181 (38.5)	2328 (19.1)	9853 (80.9)	1124 (9.2)	1204 (9.9)	0.31 (0.79)	2344 (19.2)
Gravidity							
None	19,805 (62.6)	4665 (23.5)	15,140 (76.4)	2290 (11.6)	2375 (12.0)	0.23 (0.69)	2891 (14.6)
One	4219 (13.3)	843 (20.0)	3376 (80.0)	412 (9.8)	431 (10.2)	0.29 (0.73)	794 (18.8)
Two	4142 (13.1)	842 (20.3)	3300 (79.7)	418 (10.1)	424 (10.2)	0.28 (0.73)	752 (18.2)
Three or more	3490 (11.0)	711 (20.4)	2779 (79.6)	352 (10.1)	359 (10.3)	0.34 (0.82)	735 (21.1)
Any gynecological condition*							
No	12,049 (38.1)	2323 (19.3)	9726 (80.7)	1612 (13.4)	711 (5.9)	0.22 (0.69)	1671 (13.9)
Yes	19,607 (61.9)	4738 (24.2)	14,869 (75.8)	1860 (9.5)	2878 (14.7)	0.28 (0.73)	3501 (17.9)
Charlson comorbidity index							
0	24,592 (77.7)	5653 (23.0)	18,939 (77.0)	2871 (11.7)	2782 (11.3)	0.23 (0.66)	3658 (14.9)
1-3	1189 (3.8)	201 (16.90)	988 (83.1)	87 (7.3)	114 (9.6)	0.31 (0.81)	230 (19.3)
4+	5875 (18.6)	1207 (20.5)	4668 (79.5)	514 (8.7)	693 (11.8)	0.37 (0.89)	1284 (21.9)
Index of multiple deprivation quintiles							
1st quintile (least deprived)	6126 (19.3)	1299 (21.2)	4827 (78.8)	667 (10.9)	632 (10.3)	0.26 (0.73)	1006 (16.4)
2nd quintile	5688 (18.0)	1132 (19.9)	4556 (80.1)	533 (9.4)	599 (10.5)	0.28 (0.77)	975 (17.1)
3rd quintile	6259 (19.8)	1507 (24.1)	4752 (75.9)	727 (11.6)	780 (12.5)	0.24 (0.66)	986 (15.7)
4th quintile	7060 (22.3)	1665 (23.6)	5395 (76.4)	817 (11.6)	848 (12.0)	0.25 (0.71)	1162 (16.5)
5th quintile (most deprived)	6523 (20.6)	1458 (22.3)	5065 (77.6)	728 (11.2)	730 (11.2)	0.25 (0.72)	1043 (16.0)
Menopausal status							
Perimenopause	18,366 (58.0)	4243 (23.1)	14,123 (76.9)	2413 (13.1)	1830 (10.0)	0.27 (0.73)	3230 (17.6)
Postmenopause	13,290 (42.0)	2818 (21.2)	10,472 (78.8)	1059 (8.0)	1759 (13.2)	0.23 (0.69)	1942 (14.6)
Used any HRT at baseline		–	–	–	–		
No	24,595 (77.7)					0.25 (0.71)	4017 (16.3)
Yes	7061 (22.3)					0.26 (0.75)	1155 (16.4)

*Defined as having any of the following conditions: endometriosis, polycystic ovary syndrome, menorrhagia, acne, metrorrhagia, bilateral salpingo-oophorectomy (BSO), hysterectomy BSO, hysterectomy, fibroids, and menometrorrhagia.
†Those with severe asthma exacerbation (n = 5172) at baseline were excluded in subsequent analyses investigating the association between HRT use and severe asthma exacerbations to estimate only new asthma exacerbation.

use and nonuse of HRT (Table I). Postbaseline severe asthma exacerbation was 11%, 13%, and 19% in women with the BMI of <25, 25 to 29.9, and ≥30 kg/m^2, respectively, among women who had not experienced any severe asthma exacerbation at baseline (data not shown).

Association between use of HRT and severe asthma exacerbation

Previous use of any HRT, combined estrogen/progestogen HRT, and estrogen-only HRT, compared with nonuse, was associated with an increased risk of severe asthma exacerbation (Figure 2). Whereas the current use of any HRT, compared with nonuse, was associated with a small increased risk of severe asthma exacerbation, the current use of combined estrogen/progestogen and estrogen-only HRT was not significantly associated with severe asthma exacerbation. Compared with non-HRT use, any duration of use was associated with an increased risk of exacerbation (Figure 2), but the risk was lowest for 1 to 2 years of use and highest for 3 to 4 years of use. Although the results were not substantially different between perimenopausal and postmenopausal women, previous use of estrogen-only HRT was associated with up to 24% (95% confidence interval [CI]: 16-29) but only 7% (95% CI: 3-12) increased risk of severe asthma exacerbation in perimenopausal and postmenopausal women, respectively (Figure 3). The estimated *E* values for the association between use of any HRT and severe asthma exacerbation ranged from 1.00 (for the current use of any HRT) to 2.21 (for 3-4 years of use of HRT), signifying that an unmeasured confounder requires a minimum risk ratio of 1.00 and a maximum of 2.21 to negate the observed association between HRT and severe asthma exacerbation after adjusting for all other confounding factors (data not shown). The least *E* values were observed for current HRT use and subtypes, indicating that whereas these results may be influenced by residual confounding, the results for previous HRT use and duration of HRT are less likely to be negated by residual confounding.

In stratified analyses by BMI, although there was an increased risk of severe asthma exacerbation with HRT use across the BMI groups, in most cases, the risk estimates were highest for women with BMI <25 kg/m^2, followed by those for women with BMI 25 to 29.9 kg/m^2, and less in obese women (BMI ≥30 kg/m^2) (Table II). In the stratified analyses by smoking status, only previous and current use of any HRT and estrogen-only HRT, but not combined estrogen/progestogen and duration of HRT use, were associated with an increased risk of severe asthma exacerbation among nonsmokers. However, among ex-/current smokers, use of any HRT, combined estrogen/progestogen, and estrogen-only HRT, previously and currently, and long-term HRT use, was clearly associated with an increased risk of severe asthma exacerbation (Table II).

DISCUSSION

In this national longitudinal cohort of perimenopausal and postmenopausal women with asthma who were followed for 17 years, we found that previous but not current use of any HRT, combined estrogen/progestogen HRT, and estrogen-only HRT and long-term use was associated with an increased risk of severe asthma exacerbation. These results were overall similar for peri- and postmenopausal women, but the risk estimates were greater for lean women than heavier women and greater for smokers than nonsmokers. Sensitivity analyses examining the impact of residual confounding on these results showed that, whereas the observations made with regard to current HRT use may be influenced by residual confounding, the results regarding previous and duration of HRT use were generally unlikely to be influenced of residual confounding.

OPCRD is one of the leading primary care databases in the United Kingdom dedicated to clinical and pharmacoepidemiologic studies with a well-characterized patient cohort that is largely representative of the UK primary care population. At the time of undertaking the current study, there were 6.3 million patients in the OPCRD database covering 630 general practices from across the United Kingdom. With the large sample size in the current study, we could address the question of the impact of HRT on severe asthma exacerbation by considering the role of both duration and subtypes of HRT, thus providing precise estimates of effect sizes of the associations. With a 17-year follow-up and in a longitudinal perspective, we were able to study the long-term impact of HRT on severe asthma exacerbation. The longitudinal framework also allowed us the opportunity to evaluate the time dependence of the impact of HRT on the outcome. On the basis of this, our analysis took into account the possibility that participants' use of HRT could change over the study follow-up period. Therefore, participants' HRT use status changed from nonusers in the years they did not use HRT to users in the years they used HRT. Given the challenge of immortal time bias, a common bias in pharmacoepidemiologic studies evaluating the effect of medical therapies on disease outcomes, the approach of allowing time dependences in the use of HRT is useful in minimizing the impact of immortal time bias.[20] All study variables were defined using the Read Clinical Classification System, which is a standardized system for documenting primary care events in the United Kingdom, thereby ensuring consistent recording of the study variables.[10]

Although it may be considered that the Quality and Outcomes Framework (QOF), a national initiative established in 2004 incentivizing primary care centers to maintain a register of patients with asthma for improvements in recording of clinical events, may have led to differential diagnosis of asthma during the study follow-up, 13 of the 17 years of follow-up of our study occurred after adoption of QOF.[21] Therefore, given that the majority of the study period occurred during the QOF program, any bias due to underdiagnosis of asthma would have been minimal. We defined severe asthma exacerbation after recommendation of the European Respiratory Society/American Thoracic Society,[14] and this definition has been previously defined within the OPCRD database.[15] However, provision of asthma action plans with oral corticosteroid scripts may possibly lead to overestimates in those having 1 severe asthma exacerbation. There is a possibility that some asthma cases might have been a result of misdiagnosis of chronic obstructive pulmonary disease (COPD). However, the Read codes we used for defining asthma have been previously validated in another comparable general practitioner database, which resulted in high accuracy.[22] Moreover, the concomitance between asthma and COPD based on Read codes has been estimated to be less than 15%.[23] Therefore, any potential misclassification of asthma in study as COPD will be minimal and is unlikely to change our conclusions from our study. Several other conditions, for example, endometriosis and fibroids, may be subject to hormonal manipulation—either through supplementation or inhibition—or may potentially result from estrogen deficiency, and thus may

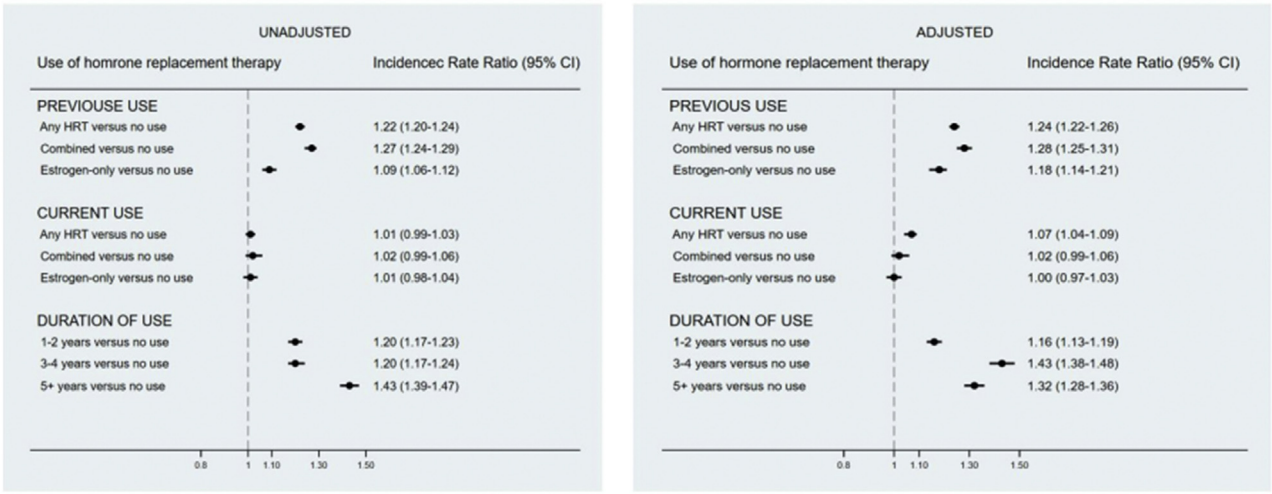

FIGURE 2. Unadjusted and adjusted associations between use of hormone replacement therapy (HRT) and severe asthma exacerbation in all women. Women with severe asthma exacerbation at baseline were excluded in these analyses to estimate the impact of HRT on new asthma exacerbation. *CI*, Confidence interval.

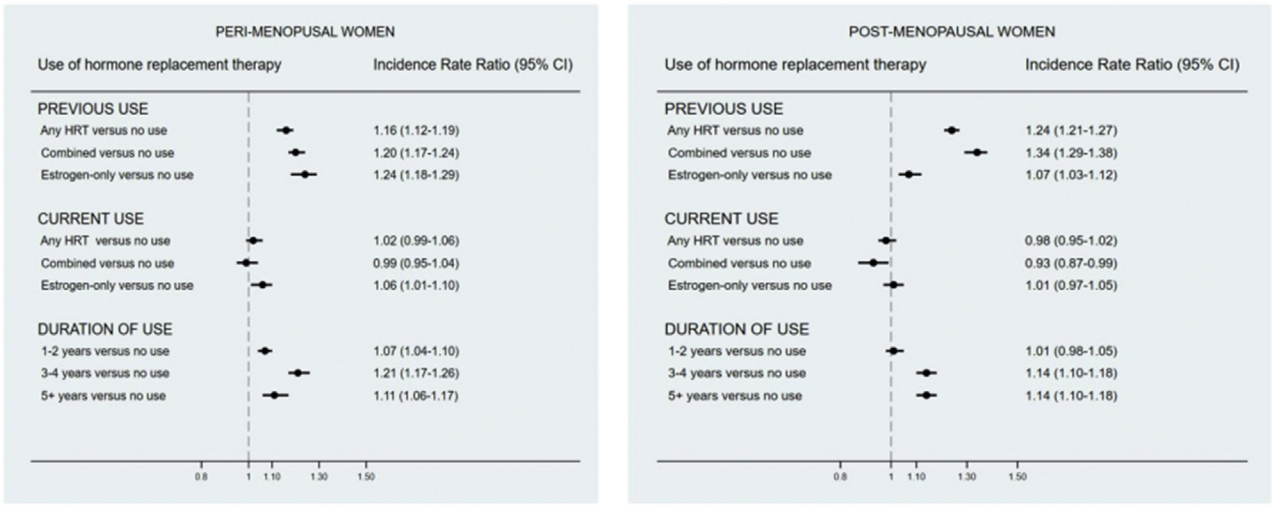

FIGURE 3. Adjusted associations between use of hormone replacement therapy (HRT) and severe asthma exacerbation by menopausal status. Women with severe asthma exacerbation at baseline (n = 5172) were excluded in these analyses to estimate the impact of HRT on new asthma exacerbation. *CI*, Confidence interval.

introduce confounding by indication. To minimize this, we identified a list of these conditions, including those that HRT may be used as a therapy and adjusted for these in our analyses. We defined perimenopausal and postmenopausal age, including cutoff for peri- and postmenopausal women, based only on the age of the women, because the age of menopause is not recorded in the database as an event and there was no additional information from the database to enhance these definitions. However, the chosen ages reflect the average ages of the menopausal events in the United Kingdom. Information on HRT was based only on medication prescription, and thus we could not establish whether the women actually used the prescribed medications, because we did not have information on medication dispensation.

Before embarking on the data analysis, we registered the analysis protocol for the current study, which was also published in a peer-reviewed journal, providing details of our analysis strategies.[7] This ensured the transparency of the current work, and any deviations from the protocol have been explained in the current manuscript. Registering and publishing the protocol before undertaking the analysis enhanced the transparency of our work. The protocol included a plan for propensity score analysis for adjusting for potential confounding factors,[4] but this could not be implemented as planned because we found no appropriate algorithm for propensity score analyses for multilevel models with time-varying covariates. In the absence of propensity score analysis, we performed conventional confounder adjustment by simultaneously adjusting for all the confounding factors in the

TABLE II. Association between use of hormone replacement therapy (HRT) and severe asthma exacerbation in perimenopausal and menopausal women, stratified by BMI and smoking*

	Stratified analyses by BMI Incidence rate ratio (95% CI)†,‡			Stratified analyses by smoking status Hazard ratio (95% CI)§,‖	
HRT use	**<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	**1.37 (1.32-1.42)**	**1.25 (1.21-1.30)**	**1.18 (1.15-1.22)**	**1.08 (1.04-1.11)**	**1.32 (1.29-1.35)**
Current use of any HRT					
None	1	1	1	1	1
Yes	**1.20 (1.15-1.25)**	**1.11 (1.06-1.16)**	0.98 (0.94-1.02)	**1.13 (1.08-1.18)**	**1.10 (1.07-1.14)**
Type of HRT (previous use)					
None	1	1	1	1	1
Estrogen only	**1.49 (1.41-1.58)**	**1.25 (1.18-1.32)**	**1.08 (1.03-1.14)**	**1.19 (1.13-1.26)**	**1.22 (1.17-1.26)**
Combined estrogen/progestogen	**1.34 (1.29-1.40)**	**1.25 (1.20-1.31)**	**1.34 (1.28-1.38)**	1.03 (0.99-1.07)	**1.43 (1.39-1.46)**
Type of HRT (current use)					
None	1	1	1	1	1
Estrogen only	**1.34 (1.27-1.41)**	**1.16 (1.10-1.22)**	1.01 (0.96-1.06)	**1.19 (1.13-1.25)**	**1.08 (1.05-1.13)**
Combined estrogen/progestogen	**1.06 (1.00-1.12)**	1.04 (0.97-1.11)	0.94 (0.88-1.00)	1.05 (0.98-1.12)	**1.14 (1.09-1.18)**
Duration of use of any HRT (y)					
None	1	1	1	1	1
1-2	**1.25 (1.20-1.31)**	**1.25 (1.20-1.30)**	0.98 (0.95-1.01)	0.97 (0.94-1.01)	**1.09 (1.07-1.12)**
3-4	**2.18 (2.06-2.30)**	1.02 (0.96-1.08)	**1.24 (1.19-1.29)**	0.95 (0.91-1.00)	**1.31 (1.27-1.36)**
5+	**1.53 (1.44-1.62)**	**1.42 (1.34-1.49)**	**1.35 (1.30-1.41)**	1.04 (0.99-1.10)	**1.39 (1.34-1.43)**

Bolded numbers indicate statistical significance at $P < 0.05$ threshold.

*All analyses were based on multilevel mixed-effects Poisson regression that accounted for clustering of patients within general practitioner practices. Women with severe asthma exacerbation at baseline (n = 5172) were excluded in these analyses to estimate the impact of HRT on new asthma exacerbation.

†Adjusted for asthma severity level at baseline, age, smoking, Charlson comorbidity index, gravidity, any gynecological condition, and index of multiple deprivation.

‡Stratified analyses performed after the interaction term between use of HRT and BMI gave $P < .20$.

§Adjusted for asthma severity level at baseline, age, Charlson comorbidity index, BMI, gravidity, any gynecological condition, and index of multiple deprivation.

‖Stratified analyses performed after the interaction term between use of HRT and smoking gave $P < .20$.

statistical models. To minimize the impact of residual confounding on the effect estimates, we calculated the *E* value, which provides evidence that our results regarding previous HRT use were not substantially influenced by residual confounding, whereas results for current HRT use seemed to have been influenced by residual confounding. Our plan to investigate the role of routes of administration of HRT (oral, transdermal, subcutaneous, intramuscular, or local intrauterine) was not possible, because this information was not consistently recorded in the database. In the context of coronary heart disease and overall mortality, the timing hypothesis has been highlighted, indicating that the timing of use of HRT in proximity to the timing of onset of menopause seems to be critical and thus provides a window of opportunity for primary prevention.[24] However, although to our knowledge no previous study has evaluated this hypothesis in the context of asthma, we did not have the required data to define this aspect in the current study.

Of the 7 studies[25-31] identified in our previous systematic review[6] to have investigated the association between HRT and clinical outcomes of asthma in perimenopausal and postmenopausal women, 4 were cross-sectional studies,[25-28] whereas 3 were very small retrospective case-control studies.[29-31] The design of the studies, which was graded as weak in that systematic review, does not allow establishment of temporality in the association between HRT and clinical outcomes of asthma; thus the previous studies are of poorer quality and not comparable with the current study.[6] Assessment of HRT and study outcomes, based on self-report in most of the previous studies, exposed the studies to greater risk of ascertainment bias. To date, the current study, with long-term follow-up and longitudinal design, is the most robustly undertaken to address the question of the role of HRT in clinical outcomes of asthma in perimenopausal and postmenopausal women. Our results indicate that use of HRT and subtypes, particularly previous rather than current use, was associated with an increased risk of severe asthma exacerbation, both in peri- and postmenopausal women. Furthermore, we found that long-term rather than short-term HRT use was associated with an increased risk of severe asthma exacerbation. The increased risk of HRT use on severe asthma exacerbation was greatest in women with BMI <25 kg/m^2 and least in those with BMI ≥30 kg/m^2, as well greater in ex-/current smokers than in nonsmokers.

The proposed impact of HRT on asthma is complex, as HRT has been shown to exert both anti-inflammatory and proinflammatory effects on innate[32,33] and adaptive immunity.[34] The role of HRT in inflammation is attributed primarily to the effects of estrogen through the activities of estrogen receptors (ERs), ERα and ERβ, both of which are expressed on immune cells, but are also present in the lung; they regulate cells and pathways in both the innate and adaptive immune system.[33] Monocytes in premenopausal women are reported to have lower amounts of ERα RNA than monocytes isolated from males and postmenopausal women, suggesting that higher estradiol levels correlate with reduced ERα expression.[35] ERα and ERβ RNA levels however did not differ in male and female B and T lymphocytes, or in lymphocytes of peri- and postmenopausal women.[35] A preponderance of one or other ER is suggested to modify the effects of estrogen,[36]

and an imbalance of their expression has been shown between asthmatic and healthy airways.[36] However, the molecular mechanisms that may result in sex differences in ER expression in particular immune cells remain to be defined. Further mechanistic studies are required to better understand the biology underpinning the influence of HRT on clinical outcomes in perimenopausal and postmenopausal women with established asthma and also to understand whether the route of steroid replacement delivery plays a role. Overall, our results indicate that previous and long-term, but not current, HRT use are crucial, perhaps indicating that withdrawal of HRT use among those with long-term exposures may constitute a preventative measure for severe asthma exacerbations. It is, however, unclear whether the increased number of exacerbations given previous or long-term HRT use is a one-off risk, possibly coincident with a sudden decline in estrogen, or represents a continuing effect.

The interaction between HRT and BMI in relation to asthma has been hypothesized to perhaps be an indication of a common pathway for the impact of HRT and BMI on asthma.[36] Although BMI is closely linked to insulin resistance,[37,38] there is evidence that insulin resistance is also closely involved in local estrogen production.[39,40] In women with low BMI, insulin resistance is low and this may portend a proinflammatory effect of HRT, but in women with high BMI, there appears a counterbalance between estrogen and insulin resistance, whereby the effect of HRT on asthma may be minimal.[41] These propositions may explain our current observations in which the impact of HRT on risk of severe asthma exacerbation was greatest for lean women and lowest for heavier women. A possible explanation for our findings may be that low levels of estrogen (and symptoms thereof) at onset of menopause prompt the use of HRT. During the period of use of HRT, the woman is somewhat protected from asthma exacerbations. However, when discontinuing treatment, which is recommended after 1 to 5 years, and being nonobese, the levels of estrogen drop, potentially increasing women's risk of asthma exacerbations. Concerning the differential effect of HRT on severe asthma exacerbation between nonsmokers and smokers, the potential underlying mechanism is unclear, and thus requires further studies for confirmation as well as mechanistic investigations to highlight the biological pathways through which these results are tenable.

CONCLUSIONS

Our results demonstrate that the use of HRT and subtypes by perimenopausal and postmenopausal women with established asthma, particularly previous HRT use and long-term use but not current use, is associated with an increased risk of severe asthma exacerbation. Lean women and smokers were at greatest risk than heavier women and smokers, respectively. There is a need to confirm the current findings by further longitudinal studies. In such studies, identification of new users of HRT will enhance establishment of a casual relationship between HRT and clinical outcomes of asthma. Furthermore, mechanistic studies investigating the biologic processes underlying the impact of HRT on clinical outcomes of asthma in perimenopausal and postmenopausal women are required.

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BIN and AS: conceived idea for the study; BIN, AS, CRS, and CMH: designed the study; BIN, AS, RP, DP, INS, and FA: data collection; BIN, RP, HT, AS, and SAS: data analyses; DR and DP: clinical/primary care expertise on asthma and OPCRD-related expertise; SM: primary care coding expertise; HC: expertise on sex steroids; BIN and AS: drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version.

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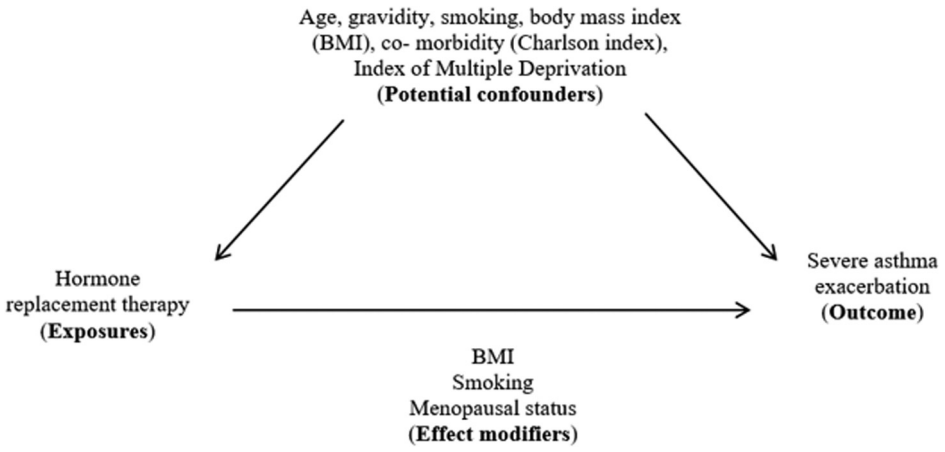

FIGURE E1. Direct acyclic graph showing the association of use of hormone replacement therapy with severe asthma exacerbations in women, with effect modification of body mass index, smoking, and menopausal status.