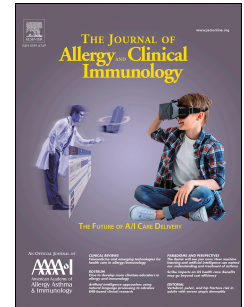


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Hormone Replacement Therapy and Asthma Onset in Menopausal Women: National Cohort Study

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Conflicts of interests: The authors declare no conflict of interest related to this work.

Abstract

Background: There is uncertainty about the role of hormonal replacement therapy (HRT) in development of asthma.

Objective: We investigated whether use of HRT and duration of use was associated with risk of developing asthma in peri- and post-menopausal women.

Methods: We constructed a 17-year (1/1/2000 – 12/31/2016) open cohort of 353,173 women (46-70 years old) from the Optimum Patient Care Database, a longitudinal primary care database from across UK. HRT use, subtypes, and duration of use; confounding variables; and asthma onset were defined using the Read Clinical Classification System. We fitted multilevel Cox regression models to estimate hazard ratios (HR) with 95% confidence intervals (CIs).

Results: During 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 to non-use 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), and combined estrogen/progestogen (HR 0.82; 95%CI 0.76-0.88) HRT were 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/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; 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 developing late onset asthma in menopausal women. Further cohort studies are needed to confirm these findings.

Abstract Words: 249

Key Messages

- Our national, longitudinal study found that hormone replacement therapy was 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.

Capsule Summary

This national, longitudinal study found that current and previous use of estrogen-only and combined estrogen/progestogen hormone replacement therapy was associated with clinically-important reductions in the development of asthma in menopausal women.

Key words: asthma, estrogens, epidemiology, estradiol, progestogen

List of Abbreviations

hormonal replacement therapy (HRT)
 body mass index (BMI)
 Anonymized Data Ethics and Protocol Transparency Committee (ADEPT)
 Optimum Patient Care Research Database (OPCRD)
 directed acyclic graph (DAG)
 bilateral salpingo-oophorectomy [BSO]
 Index of Multiple Deprivation (IMD)
 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
 Reporting of studies Conducted using Observational Routinely-collected Data (RECORD)
 general practitioner (GP)
 Quality and Outcomes Framework (QOF)
 estrogen receptors (ERs)
 airway smooth muscle cells (ASM)
 Optimum Patient Care (OPC)
 Observational and Pragmatic Research Institute Pte Ltd (OPRI)

Introduction

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 and current use of hormone replacement therapy (HRT), compared to non-use, were associated with an increased risk of developing asthma in menopausal women (1). In contrast, some studies showed that HRT use led to improved lung function in post-menopausal 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. There is in particular 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 developing 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

The study was approved by the Anonymized Data Ethics and Protocol Transparency Committee (reference number: ADEPT1317), which grants project-specific approvals for use of Optimum Patient Care Research Database (OPCRD) data. Optimum Patient Care has an existing NHS Health Research Authority ethics approval for use of OPCRD for research (REC Ref: 15/EM/150). All researchers involved in 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 undertaking the analyses (7).

Study design and population

The study data were derived from OPCRD – a bespoke, longitudinal, de-identified primary care database from across the UK– which is used to conduct epidemiologic, pharmaceutical and clinical studies (<https://opcrd.co.uk/>) (8,9). At the time of this study, OPCRD consisted of data from 630 primary care practices, which represented over 6.5 million patients. All individuals resident in UK (including children) are registered with primary care. We constructed an open retrospective cohort of peri- and post-menopausal women (aged 45-70 years) from the database. Participants were followed from baseline starting from January 1, 2000 or date of registration to a general practice or the year of turning age 45 years until December 31, 2016. Exit date was defined as date of first record of an asthma event, death, deregistration from a practice, the year of turning 70 years old, or end of follow up (December 31, 2016), whichever came first. Participants without asthma at baseline or five years prior to 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 (Read codes; Online Supplement 1) (10), we defined the following exposures:

1. Previous (anytime in the past) and current (during that study year) use of any HRT versus non-use;
2. Previous and current use of subtypes of HRT (estrogen-only, combined estrogen/progestogen) versus non-use;
3. Duration of HRT use (treated as a persistent variable): 1-2 years; 3-4 years; 5 years or more versus non-use;
4. Menopausal status: peri-menopausal (46–55 years) versus post-menopausal (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 (DAG) was used to select potential confounding factors adjusted in our analysis (Figure 1). Confounding factors were extracted using the relevant Read codes (Supplement 2) and included age, gravidity, BMI, smoking, Charlson Comorbidity Index (11), any gynecologic condition (endometriosis, polycystic ovary syndrome, acne, bilateral salpingo-oophorectomy [BSO], hysterectomy BSO, hysterectomy, fibroids, or menstrual bleeding complaints identified under coding terms: menorrhagia, metrorrhagia, menometrorrhagia) (12), and Index of Multiple Deprivation (IMD) (13).

Outcome

Asthma onset was defined as the first ever GP-recorded asthma event defined using primary care codes associated with asthma diagnosis occurring any time after the baseline date. To ensure that only patients who do not have asthma at the start of the follow-up are 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 prior to the baseline date. The relevant Read codes are provided in Online Supplement 3.

Statistical analyses

We used the Pearson's 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 (risk of remaining asthma-free, see online supplement 6 for additional details) by HRT categories (type, 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 time-varying nature of exposure and confounders, as well as

clustering of patients from the same practice. Adjusted analyses included all factors described above. 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 < 0.20 were stratified for BMI or smoking. Data management and editing were undertaken using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses were undertaken using Stata 14 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Reporting

This manuscript paper is reported 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 1 and **Error! Reference source not found.** provide the baseline characteristics of the population. Of the 353,173 women at-risk of asthma included in the study, 16% used any HRT, 9% used combined estrogen/progestogen HRT, and 7% used estrogen-only HRT at baseline. Use of any HRT, estrogen-only HRT, and combined estrogen/progestogen HRT, was highest among women 51-55 years of age compared to other age groups; higher in ex/current smokers than non-smokers (which was a surprising finding); highest in those with BMI <25kg/m² versus women with a higher BMI score; higher in women who had never been pregnant versus those with a recorded pregnancy; lowest in women with co-morbidity score of 1-3 versus those with fewer and or a greater number of comorbidities, with no differences found between IMD quintiles. Whilst use of any HRT was similar between pre- and post-menopausal women, use of combined estrogen/progestogen HRT was more common in peri-menopausal women than in post-menopausal women, while use of estrogen-only HRT was more common in post-menopausal than in peri-menopausal women. Use of any HRT and estrogen-only HRT was higher in women with a prior gynecological condition than those without, while the reverse was found for combined estrogen/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 (95%CI 5.5-5.8) per 1,000 person-years. The incidence rate of asthma increased with increasing age; was similar between pre- and post-menopausal women;

higher in ex/current smokers than non-smokers; increased with increasing BMI; decreased with increasing number of pregnancies; was lower in women with prior gynecological conditions than those without; was similar across the Charlson Comorbidity Index; and decreased with increasing quintiles of IMD (Table 1).

Associations of HRT and menopause with asthma onset

Previous use of any HRT, estrogen-only HRT, and combined estrogen/progestogen HRT were associated with up to 18% (95%CI 24-12) reduced risk of developing new onset asthma when compared with non-HRT use (Table 2). Similarly, current use of any HRT, estrogen-only HRT, and combined estrogen/progestogen HRT was associated with up to 22% (95%CI 30-13) reduced risk of developing asthma than non-HRT use. We observed a dose-response association (Kandall's tau statistic = -1, p-value=0.089) between duration of HRT use and risk of asthma onset: women with 1-2 years of HRT use had 7% (95%CI 13-1), women with 3-4 years of use had 23% (95%CI 30-16), and those with five or more years of use had 29% (95%CI 36-22) lower risk than women who did not use HRT. Post-menopausal women, compared to peri-menopausal 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 peri-menopausal than in post-menopausal women (Table 2). In stratified analyses by BMI and smoking, we found statistically significant associations only with current use of any HRT and its subtypes and asthma onset (most likely because stratified analyses lacked sufficient power to detect significant effect), but the effect estimates were generally similar across the categories of BMI and smoking (Table 3). Kaplan-Meier survival curves confirmed that the risk of remaining asthma free was lower in women who used HRT than those who did not use it (**Error! Reference source not found.**). Figure 4Figure 5 summarize Table 2Table 3 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

Current use of any HRT, estrogen-only HRT, and estrogen/progestogen combined HRT, was associated with a decreased risk of developing new-onset asthma amongst peri- and post-menopausal women. However, previous use of HRT was associated with a reduced risk of asthma only in all women, but not when 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 women who used it for shorter periods. This effect, however, becomes insignificant when patients are stratified by age, BMI and smoking possibly due to lack of sufficient power to detect significant effect after stratification. Compared to peri-menopausal women, post-menopausal women were at lower risk of developing asthma.

Strengths and limitations of the study

The key strengths of this study were that it is so far the largest longitudinal cohort study on the topic, had a long follow-up period (17 years), and based on a real-life, nationwide primary care dataset. 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 sub-groups of women, e.g., smoking status and BMI with considerable precision. OPCRd included longitudinal encounters of 6.3 million well-characterized patients registered with 630 general practices from across the U.K. This database is representative of the U.K.-wide primary care population; thus findings have direct generalizability to the wider U.K. population. The long-term follow-up meant 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 U.K., to identify and define all variables used in the study (10). Based on general practitioner (GP)-recorded parameters, as opposed to 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 defining participants as either users or non-users 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 non-users in the years they did not use HRT and only counted as users in the years they used HRT. This approach meant we minimized immortal time bias, a common bias in pharmaco-epidemiologic 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 U.K. primary care to develop a register of asthma patients, came into existence in 2004 (25). The QOF included regular registry audits and consequently led to improvement in GPs' recording of clinical events (26). Most of the follow-up period in our study (13 out of 17 years) was after the adoption of the QOF thereby minimizing bias due to asthma under-diagnosis (see online supplement 5 for sensitivity analysis that excluded all patients who joined the study before the QOF was introduced). Furthermore, to ensure that only at-risk women (who did not have asthma at the start of follow-up) were included in the study, we employed a 5-year look back period that assumed that women with asthma would have had at least one contact with primary care during the five years preceding the start of follow-up. It is however possible that a minority of patients who, despite being diagnosed with asthma, had no primary care contact during the five years preceding the start of follow-up, thus may be 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 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 cut-off years we used to define peri- and post-menopausal women were based on the average age of these events in the U.K. Furthermore, we have assumed that any prescriptions of HRT were used according to GP's prescription, which may not always be the case. We were unable to adjust for ethnicity as this information was missing in over 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 multi-categorical nature of the study exposures within multi-level models) and therefore, we performed a conventional confounding adjustment. It is possible that some residual confounding remains even after controlling for various confounders; however our evaluation of unmeasured confounders indicate that this may be an unlikely explanation for our findings. Furthermore, our original protocol included an analysis including the route of HRT administration (oral, transdermal, subcutaneous, intramuscular, or local intrauterine). However, after acquiring the data, 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 based on GP-recorded diagnosis, it is possible that some of these cases might be a misdiagnosis for COPD. 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 COPD 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

While some previous studies have generally shown an increased risk of asthma onset with the use of HRT (15,18,19)(20) (21–23), contrary findings have also been reported (1) (2,3) (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 shorter duration of use, were associated with an increased risk of new-onset asthma in post-menopausal women. The French E3N cohort study found statistically significant increased risk of new-onset asthma with use of estrogen-only HRT, but not with combined estrogen/progestogen HRT; they also showed no clear association of past, recent, and duration of use with risk of asthma in post-menopausal women (1). Another prospective cohort study found that use of any HRT, subtypes, and long duration of use were associated with increased risk of new-onset asthma (19). The findings are in contrast to 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. Whilst the previous cohort studies included only post-menopausal women, our study included both peri- and post-menopausal women, yet our findings were similar in both peri- and post-menopausal 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 (i.e. maintained for the purpose of routine care) based on GP-recorded HRT prescription and asthma diagnosis. Only two previous cohort studies used HRT as a time-dependent exposure, but even in those studies, information on HRT use from biennial surveys was only updated every two 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 post-menopausal women were at a lower risk of developing asthma than peri-menopausal women (20). When stratified by smoking status, the French E3N study found that risk was specific to non-smokers only (1). Our results, however, showed similar risks amongst smokers and non-smokers and across the categories of BMI.

Interpretation and possible mechanisms of action

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

Several studies have demonstrated that both progesterone and estrogen increase T regulatory (Treg) cell frequency and/or function, which is predicted to contribute to protective effects of HRT and beneficially impact asthma outcomes (34). In contrast, estrogen and progesterone have been variously reported to inhibit and enhance Th1, Th2 and Th17 effector responses (34,39–41). These studies highlight the complexity of sex hormone effects on structural, innate and adaptive immune cells, and the influence of an inflammatory milieu, receptor signaling and hormone concentration. The findings from the current study, which contrast three cohort studies earlier described, provide strong evidence demonstrating that use of HRT and its subtypes, previously and currently and long-term is associated with a clinically significant reduced risk of developing asthma in menopausal women. It is unclear whether these contradictory findings are result of complex roles of HRT. Perhaps, they indicate presence of a number of mechanisms by which HRT can influence asthma outcomes and highlight the need for further detailed and longitudinal mechanistic studies alongside observational studies.

Conclusion

Our study found that past and current use of HRT and its subtypes was 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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Author contribution

Conceived idea for the study (BN, AS); designed the study (BN, AS, CRS, CMH); data collection (BN, AS, RP, DP, INS, FA); data analyses (BN, RP, HT, AS, SAS); clinical/primary care expertise on asthma and OPCRd-related expertise (DR, DP); expertise on sex steroids (HC); drafted the manuscript (SAS, BN, AS); all authors critically revised the manuscript for intellectual content and approved the final version. AS was the PI on this study.

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Figures and Tables

Figure 1: Direct acyclic graph showing the association between use of HRT and asthma onset in females, with effect modification by body mass index and smoking

Figure 2: Flowchart of study cohort and baseline use of hormonal replacement therapy (HRT)

Figure 3: Kaplan-Meier curves comparing current users and non-users of HRT among menopausal women (a) comparing risk of remaining free of asthma between users and non-users of any HRT (b) comparing risk of remaining free of asthma by types of HRT (color required)

Figure 4 Association between use of hormone replacement therapy (HRT) and onset of asthma in all women

Figure 5 Association between use of hormone replacement therapy (HRT) and onset of asthma by menopausal status

Table 1: Baseline characteristics by use of hormone replacement therapy (HRT) and study outcomes in menopausal women (46-70 years) without asthma

	Frequency N = 353,173 n (%)	Used any HRT n=57,104 (16%) % (95% CI) ²	Used estrogen/progest ogen combined HRT n=31,281 (9%) % (95% CI) ²	Used estrogen- only HRT n=25,823 (7%) % (95% CI) ²	Asthma incidence during follow-up n = 7,614 Incidence rate (95% CI) per 1000 person-years
Age, years					
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					
Peri-menopause (46-55 years)	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)
	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)
Post-menopause (56-70 years)					
Smoking status					
Non-smoker	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/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)

Body mass index, 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					
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)
One	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)
Two	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)
Three or more	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 gynecological condition ¹	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)
No	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)
Yes					
Charlson Comorbidity Index	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)
0	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)
1-3	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)
4+					
Index of Multiple Deprivation quintiles	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)
1 st quintile (least deprived)	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)
2 nd 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)
3 rd 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)
4 th quintile	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)
5 th quintile (most deprived)					

¹Defined as having any of the following conditions: endometriosis, polycystic ovary syndrome, menorrhagia, acne, metrorrhagia, bilateral salpingo-oophorectomy (BSO), hysterectomy BSO, hysterectomy, fibroids, and menometrorrhagia

²Difference between groups of background variables were statistically significant ($P < 0.001$)

519
520Table 2 Association between use of hormone replacement therapy (HRT) and onset of asthma in all women and by menopausal status¹

HRT use	Asthma onset			
	All menopausal women		Peri-menopausal women	Post-menopausal women
	Unadjusted	Adjusted	Adjusted	Adjusted
	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio
	(95% CI) ²	(95% CI) ²	(95% CI) ²	(95% CI) ²
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, years				
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				
Peri-menopause (46-55 years)	1	1	Not applicable	Not applicable
Post-menopause (56-70 years)	0.91 (0.87-0.96)	0.88 (0.83-0.92)		

521
522
523¹All analysis were based on multilevel Cox regression that accounted for clustering of patients within GP practices²Adjusted for age, smoking, Charlson co-morbidity index, BMI, gravidity, any gynecological condition, and index of multiple deprivation ³Both unadjusted and adjusted models were adjusted for use of HRT

524

525 *Table 3 Association between use of hormone replacement therapy (HRT) and onset of asthma in menopausal women and by BMI*
 526 *and smoking¹*

HRT use	Asthma onset				
	Stratified analyses by BMI			Stratified analyses by smoking status	
	Hazard Ratio (95% CI) ^{2,3}			Hazard Ratio (95% CI) ^{2,4}	
	<25 kg/m ²	25-29.9 kg/m ²	≥30 kg/m ²	Non-smokers	Smokers
Previous use of any HRT	1	1	1	1	1
None	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)
Yes					
Current use of any HRT	1	1	1	1	1
None	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)
Yes					
Type of HRT (previous use)	1	1	1	1	1
None	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)
Estrogen only	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)
Combined estrogen/progestogen					
Type of HRT (current use)	1	1	1	1	1
None	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)
Estrogen only	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)
Combined estrogen/progestogen					
Duration of use of any HRT, years	1	1	1	1	1
None	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)
1-2	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)
3-4	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)
5+					

Peri-menopause ⁶ (46-55 years)	1	1	1	1	1
Post-menopause ⁶ (56-70 years)	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)

¹All analysis were based on multilevel Cox regression that accounted for clustering of patients within GP practices

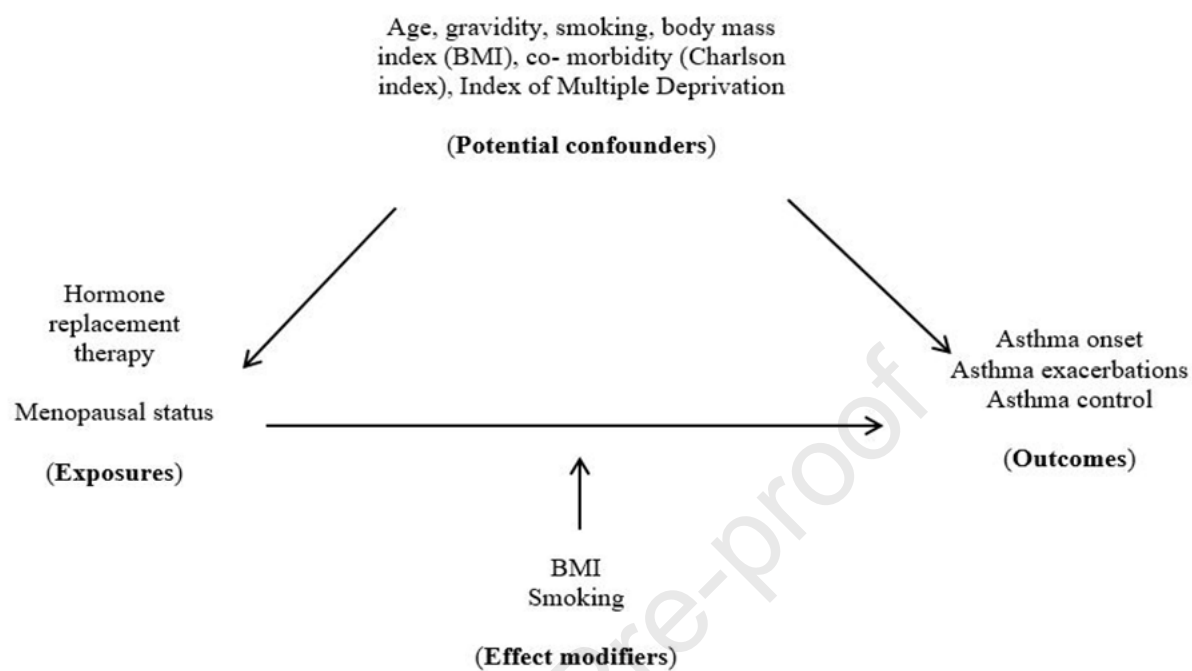
²Adjusted for age, smoking, Charlson co-morbidity index, BMI, gravidity, any gynecological condition, and index of multiple deprivation

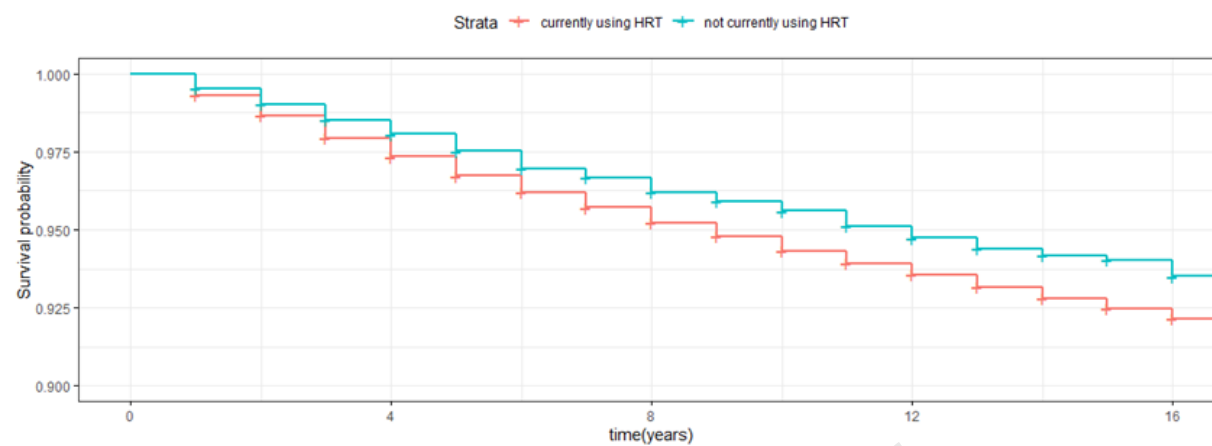
³Stratified analyses performed after interaction term between use of HRT and BMI gave $p < 0.20$

⁴Stratified analyses performed after interaction term between use of HRT and smoking gave $p < 0.20$

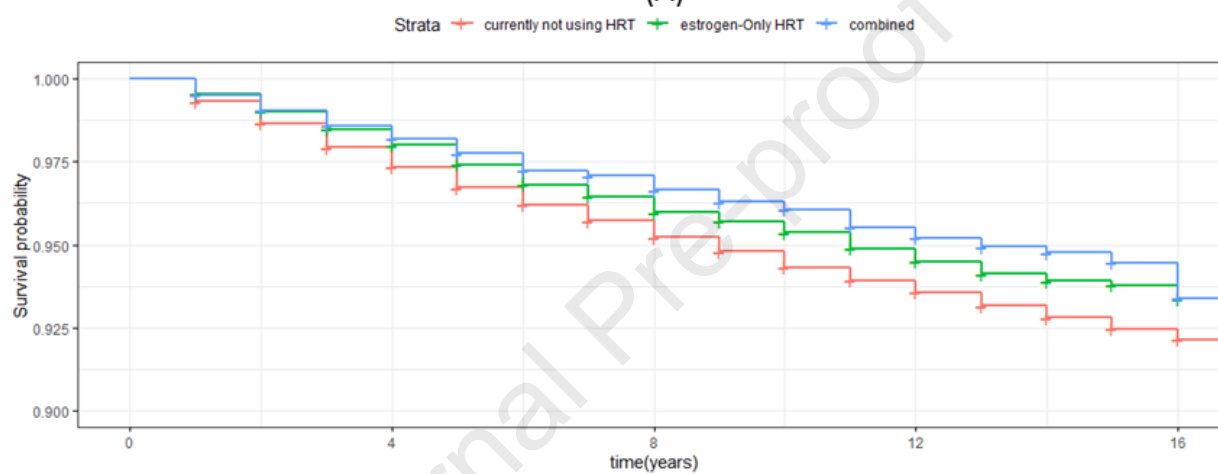
⁵Both unadjusted and adjusted models were adjusted for use of HR

⁶Menopausal status at baseline





(A)



(B)

