Inhaled anti-asthma therapies following hormone therapy in women: a nationwide cohort study

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Shareable abstract (@ERSpublications)
In women with asthma, use of exogenous female sex hormones in menopause does not significantly change the use of inhaled anti-asthma medications. However, data suggest there could be beneficial effects of progestogens and detrimental effects of oestrogens. https://bit.ly/31TgGTK

Cite this article as: Hansen ESH, Aasbjerg K, Moeller AL, *et al.* Inhaled anti-asthma therapies following hormone therapy in women: a nationwide cohort study. *ERJ Open Res* 2022; 8: 00611-2021 [DOI: 10.1183/23120541.00611-2021].

Abstract

Research question Does menopausal hormone therapy (HT) with exogenous oestrogens and progestogens change the use of inhaled anti-asthma medications in women with asthma?

Methods In a population-based matched cohort study using the Danish registries, we included women with asthma aged 45–65 years from 1 June 1995 to 30 June 2018. We investigated whether HT with oestrogen and/or progestogens was associated with changes in use of inhaled anti-asthma therapies in the 12 months following initiation. We used exposure density matching to match exposed subjects with unexposed subjects on age, household income and level of education. An exposed subject was defined as receiving HT. We calculated mean dose of medications and odds ratios of increases in the 12 months following HT initiation.

Results We included 139 483 women with asthma, of whom 116 014 (83.2%) were unexposed subjects and 23 469 (16.8%) exposed subjects. Mean±SD age was 53.0±5.2 years. Initiation of HT was not consistently associated with increased mean doses of inhaled corticosteroids (ICS), or long- and short-acting β_2-agonists. Women receiving systemic oestrogens had increased odds ratios of large increases (>100 µg) in ICS at 6 months (OR 1.09; 95% CI 1.04–1.13; p<0.001) and 9 months (OR 1.07; 95% CI 1.03–1.12; p<0.001). Progestogens were protective against increases in ICS at 6 and 9 months (OR 0.87; 95% CI 0.82–0.93; p<0.001; and OR 0.86; 95% CI 0.81–0.91; p<0.001).

Conclusion Initiation of HT did not change the use of inhaled medications in asthma. However, detrimental effects of oestrogen, as well as beneficial effects of progestogens, cannot be excluded.

Introduction

Menopausal hormone therapy (HT) with exogenous female sex hormones has been shown to alter the incidence of asthma [1–4]. However, little is known about whether initiation of HT affects asthma in women already in treatment for asthma. A study consisting of a small sample of menopausal women found use of inhaled corticosteroids (ICS) to decrease during treatment with HT [5]. As HT affects the incidence of asthma, it is reasonable to assume that HT could modulate ongoing asthma disease. According to the present treatment guidelines from the Global Initiative for Asthma, asthma is managed "step-by-step", with increasing doses of ICS and long-acting β_2-agonists (LABA) until the patient experiences asthma control [6]. Thus, if HT impacts asthma negatively, with increasing level of symptoms, we expect that physicians will prescribe increased amounts of ICS and LABA [6]. Known adverse events to HT range from nausea and headache to hormone-dependent malignancies and possibly fatal thromboembolic incidents [7, 8].

Pulmonary side-effects, on the other hand, such as new asthma or asthma deterioration, are rarely reported in the literature. Therefore, in Danish women with asthma, we sought to investigate whether use of inhaled medications for asthma changed following initiation of HT.

Methods

We performed a matched cohort study nested in a nationwide open cohort of Danish women with asthma aged 45 to 65 years between 1 June 1995 and 30 June 2018. The study was reported by the STROBE guidelines [9]. Our aim was to determine whether current use of menopausal HT was associated with change in use of inhaled anti-asthma medications such as ICS, LABA and short-acting β_2-agonists (SABA).

Study population

Asthma was defined as either a diagnosis of asthma (coded according to the International Classification of Diseases, 10th revision (ICD-10); J45), or if a woman had filled at least two prescriptions of ICS within 2 years. A woman was included in the cohort at her asthma diagnosis date, or at her 45th birthday, whichever was the latest.

We censored participants before the end of the study period or before the age of 66 years, if they died, emigrated or developed COPD. A diagnosis of COPD was based on ICD-10 J44, or if they had received a medication regimen typical for COPD such as long-acting muscarinic antagonist (LAMA) and/or LABA as the only or first-line treatment.

Data sources

Data were extracted from the Danish registries. The Danish Register of Medicinal Product Statistics includes information on all prescription fills from Danish pharmacies since 1995 by use of the Anatomical Therapeutic Chemical Classification System (ATC codes) [10]. The Danish National Patient Registry contains information on all hospital admissions in Denmark since 1978 with indexing by ICD-10 as described by the World Health Organization [11, 12]. Information about household income, education level, age and sex was retrieved from the Danish Population Register. In Denmark register-based studies that are conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law. The first author vouches for the integrity of the data and the accuracy of the analysis.

Matching and definitions of exposed and unexposed women

Our main exposure was menopausal HT and so we matched women with asthma who received HT (exposed subjects) with women with asthma who did not receive HT (unexposed subjects). We used exposure density matching to match one exposed subject to five unexposed subjects [13, 14]. Exposed and unexposed subjects were matched on age, household income and education level [15, 16]. The index date for exposed and unexposed subjects was the date of initiation of HT for the exposed subject. Women were excluded if they had received HT within 1 year prior to their 45th birthday. It was a condition that the women with asthma had their asthma diagnosis prior to the index date. The number of women with asthma who received HT determined the study size.

Definition of the exposure to HT

For systemic vasomotor symptoms of menopause, women are currently recommended combined systemic use of oestrogens and progestogens or oestrogen-only therapy if previously hysterectomised, because the sole purpose of progestogen is the protection of the endometrium against abnormal proliferation [17]. Progestogen-only therapy is typically used for perimenopausal abnormal menstrual bleeding symptoms. Our primary focus was menopausal HT, but as we were interested in investigating the different effects of all currently and previously prescribed female sex hormones in this age group, we included all types of exogenous female sex hormones, including perimenopausal progestogen-only therapy.

We defined treatment with HT as treatment with ATC G03C (oestrogens, systemic and local), G03D (progestogens) or G03F (progestogens and oestrogens in combination) within 1 year or prescription of G02BA03 (progestogens, intrauterine device) [18]. We registered which type of HT was used as initial treatment. Monotherapy with oestrogen was defined as filled prescriptions of G03C without concurrent prescriptions of G03D or G02BA03. Combination HT with oestrogen and progestogens was defined as filled prescriptions of G03F or as filled prescriptions of G03C with concurrent prescriptions of G03D or G02BA03. Lastly, monotherapy with progestogen was defined as filled prescriptions of G03D or G02BA03 without concurrent prescriptions of G03C or G03F. Substances were analysed collectively and independently by substance. To account and adjust for changes in prescription patterns due to

discontinuation of HT, we defined discontinuation of HT as a pause in treatment of ⩾60 days, with the discontinuation date being set to the last day of the last treatment period.

Inhaled anti-asthma medications

Main outcomes of interest were changes in mean daily doses of ICS, LABA and SABA in the 12 months following the index date. Mean daily dose at the index date (baseline) was calculated by including all doses 180 days prior to the index date. All forms of ICS were converted to a budesonide equivalent. The estimations of budesonide equivalents and all investigated ATC codes are provided in supplementary tables S1 and S2.

As LABA come in different substances and sizes and no apparent equivalents are available, doses of LABA were calculated for each substance (formoterol, indacaterol, salmeterol and vilanterol). The same was done for SABA (terbutaline and salbutamol).

Statistical considerations

Baseline characteristics were reported as frequencies or means with SD, and compared with Student's t-test for continuous variables and chi-squared test for frequency distributions.

Mean daily amounts of ICS were calculated as daily budesonide equivalent doses in microgrammes and were returned in date intervals. For each month following HT initiation, we calculated the change in mean use of ICS, LABA and SABA for the last 30 days and compared the groups with their respective baseline value using a paired two-sided Student's t-test.

To investigate whether one group was more likely to increase their dosage of inhaled medication following the index date, we calculated odds ratios of being on an increased dose at 3, 6, 9 and 12 months and compared the groups. Changes in budesonide equivalent doses of ICS were defined as any increase

TABLE 1 Study population characteristics			
	No hormone therapy	**Hormone therapy**	**p-value**
Patients	116 014	23 469	
Age, years	53.0±5.2	53.0±5.2	1.00
Age groups, years			1.00
45–49	31 703 (27.3)	6387 (27.2)	
50–54	39 673 (34.2)	8054 (34.3)	
55–59	24 649 (21.2)	4946 (21.1)	
60–64	19 989 (17.2)	4082 (17.4)	
Years of asthma	7.7±5.9	7.4±5.8	<0.001
Household income levels			1.00
Lowest	7 (0.0)	20 (0.1)	
Second lowest	4711 (4.1)	1013 (4.3)	
Second highest	37 355 (32.2)	7558 (32.2)	
Highest	73 941 (63.7)	14 878 (63.4)	
Level of education			1.00
Long-cycle higher education	6818 (5.9)	1419 (6.0)	
Medium-cycle higher education or bachelor's degree	30 893 (26.6)	6245 (26.6)	
Upper or lower secondary school	36 696 (31.6)	7387 (31.5)	
Vocational upper secondary school	41 607 (35.9)	8418 (35.9)	
Inhaled anti-asthma medication			
Inhaled corticosteroids	74 681 (64.4)	15 800 (67.3)	<0.001
Mean±SEM dose, µg	406±5	421±5	0.002
Long-acting β_2-agonists			
Formoterol	23 014 (19.8)	5142 (21.9)	<0.001
Salmeterol	14 622 (12.6)	3580 (15.3)	<0.001
Indacaterol	326 (0.3)	106 (0.5)	<0.001
Vilanterol	232 (0.2)	68 (0.3)	<0.001
Short-acting β_2-agonists			
Terbutaline	45 854 (39.5)	9526 (40.6)	<0.001
Salbutamol	22 035 (19.0)	4908 (20.9)	<0.001

Data are presented as n, mean±SD or n (%), unless otherwise stated.
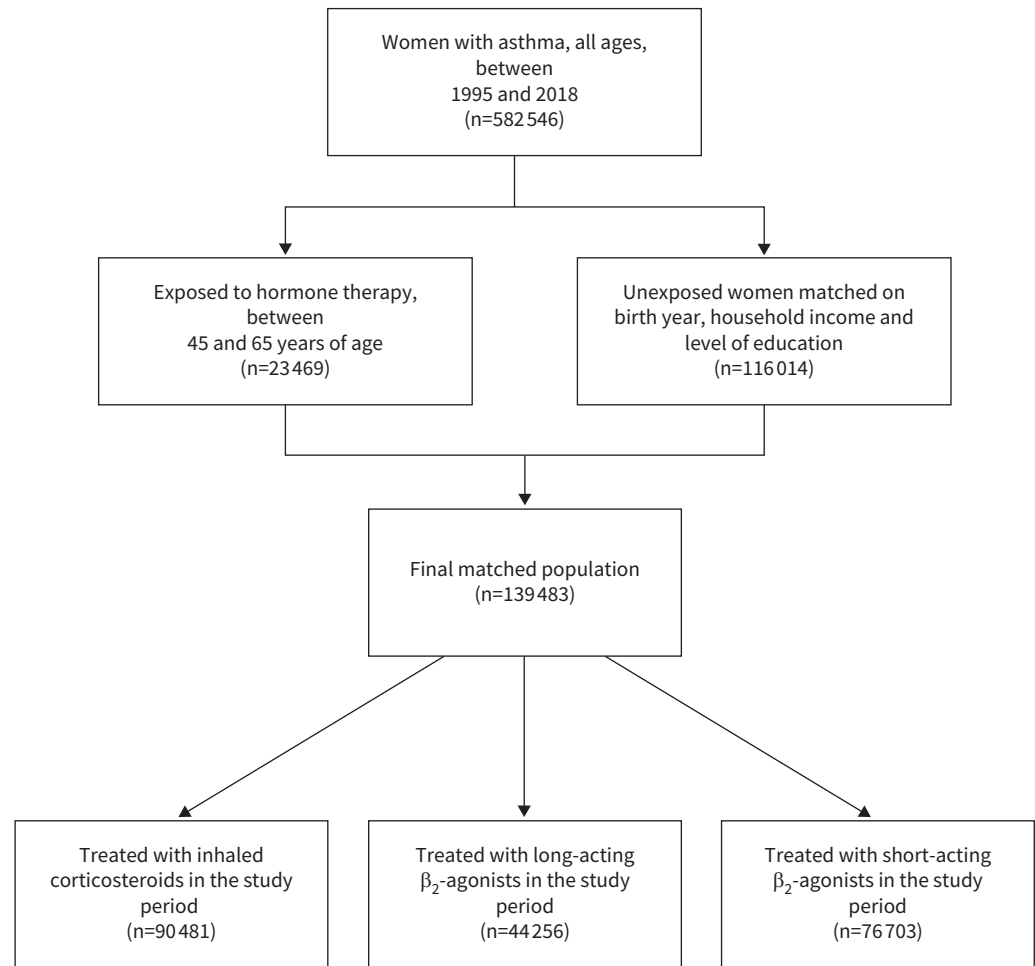
FIGURE 1 Flow chart of the study population. From the original 582 546 women with asthma, 23 469 women were identified as receiving hormone therapy (exposed) and, subsequently, each exposed woman was matched with five unexposed women.

(change in dose >0 µg) or a large increase (change in dose >100 µg). Odds ratios were calculated using logistic regression. We made crude analyses and analyses adjusted for birth year, education level, household income and baseline treatment level. Adjusted analyses are presented in supplementary tables S3–S5. If an exposed woman discontinued their HT, they (and their five corresponding unexposed women) were excluded from the analyses in the timepoints following termination of treatment. Further, sensitivity analyses were performed in different age groups (⩽54 and >54 years of age) to illuminate any differences in response to HT (supplementary figures S1 and S2).

All results are presented with 95% confidence intervals used to determine significant differences between exposed and nonexposed subjects. As analyses are based on public registries, they all represent complete-case analyses. All analyses were performed using RStudio with R version 3.6.1 (www.r-project.org).

Results

In this matched cohort study, we included 139 483 women with asthma, of whom 116 014 (83.2%) were unexposed subjects (no HT) and 23 469 (16.8%) were exposed subjects (HT) (table 1; figure 1). In the cohort, participants were followed for a total of 1 091 261 person-years (mean 7.8 years per participant). The mean±SD age in both groups was 53.0±5.2 years. Among the exposed subjects, 1782 (7.6%) had received monotherapy with systemic oestrogen; 11 736 (50.0%) had received monotherapy with local oestrogen; 5164 (22.0%) had received combination HT with progestogens and oestrogens, and 4787 (20.4%) had received monotherapy with progestogens. From the population included in the analyses, 22.6% and 28.4% had terminated HT treatment at 6 and 12 months following the index date. The mean
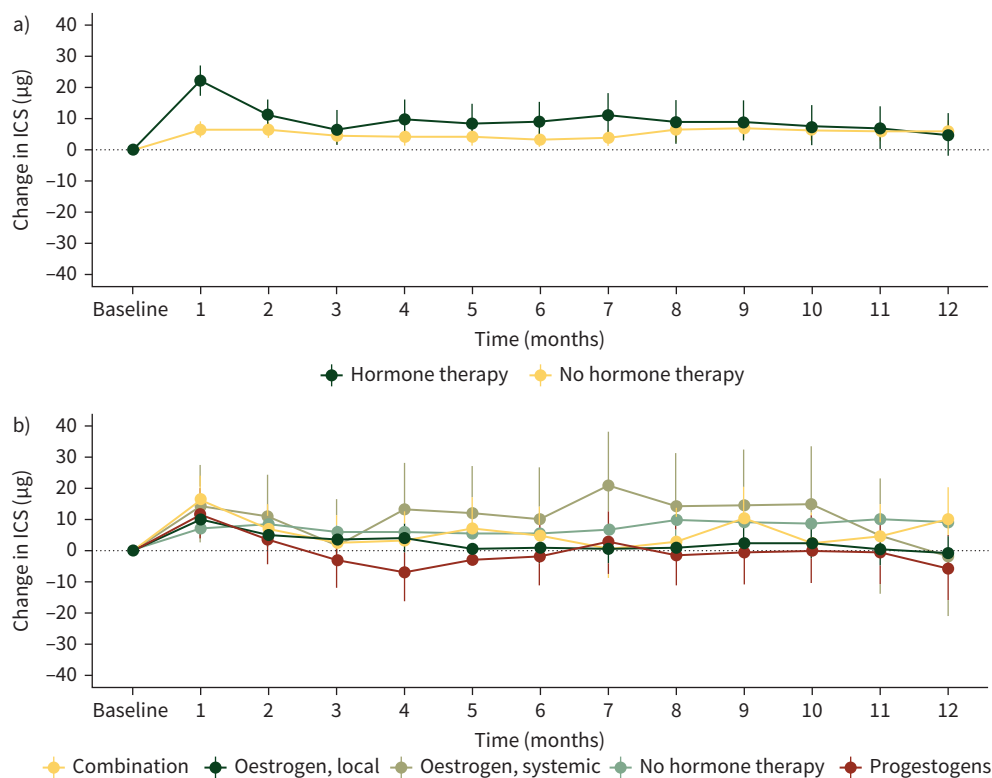
FIGURE 2 Change in use of inhaled corticosteroids (ICS) among exposed *versus* unexposed women in the first 12 months following the index date. a) Hormone therapy as a compound exposure; b) hormone therapy divided into specific substances.

budesonide equivalent dose of ICS at baseline was lower in the unexposed group (406 µg *versus* 422 µg; difference −15 µg; 95% CI −26 to −6 µg; p=0.002).

ICS

In the first month following the index date, women exposed to HT showed a significant increase in use of ICS (month 1: 22.5 *versus* 7.0 µg; 95% CI 17.5–27.4 *versus* 4.9–9.1 µg; p<0.001). From month 2 onwards, the significant differences disappeared (figure 2). Sensitivity analyses in different age groups showed similar results (supplementary figures S1 and S2). Crude analyses showed that exposed women had higher odds of using more ICS at 6 months (OR 1.04; 95% CI 1.00–1.08; p=0.032) following the index date (table 2). We observed no differences at 3, 9 and 12 months. Women exposed to HT were more likely to experience a large increase (>100 µg) at 3, 6 and 9 months (OR 1.05–1.09). Adjusted and crude analyses showed similar results. Adjusted odds ratios for any increase and large increases (>100 µg) are presented in supplementary table S3.

When HT was split into the different subtypes of HT, we saw no significant differences in doses of ICS (figure 2b). Users of combination HT had higher odds ratio of increasing >100 µg in mean daily dose in the first 9 months following the index date while users of progestogens and local oestrogen had consistently lower odds ratios of increasing their use of ICS when compared with unexposed women (table 2).

LABA

In exposed women compared with unexposed women, mean daily doses at baseline were 8.94 µg *versus* 8.76 µg (difference −0.18 µg; 95% CI −0.18 to −0.43 µg; p=0.20) for formoterol; 185.6 µg *versus* 175.6 µg (difference −10.06 µg; 95% CI −38.28 to −18.16 µg; p=0.48) for indacaterol; 58.8 µg *versus* 57.7 µg (difference −0.98 µg; 95% CI −2.73 to −0.77 µg; p=0.98) for salmeterol and 17.47 µg *versus* 18.51 µg (difference 1.04 µg; 95% CI −1.43 to −3.52 µg; p=0.41) for vilanterol.

We calculated changes in mean daily doses of LABA among the included women and compared with their baseline values. There were no differences in mean changes of LABA following HT initiation (figure 3).

TABLE 2 Crude odds ratios of increased use of inhaled corticosteroids in hormone therapy users				
Timepoints (months)	Increase >0 µg OR (95% CI)	p-value	Increase >100 µg OR (95% CI)	p-value
Hormone therapy				
3	1.00 (0.96–1.03)	0.9	1.05 (1.01–1.10)	0.012
6	1.04 (1.00–1.08)	0.032	1.09 (1.04–1.13)	<0.001
9	1.00 (0.97–1.04)	0.9	1.07 (1.03–1.12)	0.001
12	0.98 (0.94–1.01)	0.23	1.02 (0.98–1.06)	0.35
Hormone therapy by type				
Systemic oestrogen				
3	0.91 (0.83–0.99)	0.023	1.09 (1.00–1.20)	0.062
6	1.00 (0.92–1.08)	0.9	1.13 (1.03–1.24)	0.009
9	0.92 (0.84–1.00)	0.055	1.09 (0.99–1.19)	0.077
12	0.85 (0.78–0.93)	<0.001	1.02 (0.93–1.12)	0.7
Combination				
3	0.94 (0.90–0.99)	0.027	1.05 (0.99–1.12)	0.08
6	0.95 (0.90–1.00)	0.058	1.06 (1.00–1.12)	0.050
9	0.99 (0.94–1.04)	0.6	1.09 (1.03–1.15)	0.004
12	0.92 (0.87–0.97)	0.002	1.01 (0.96–1.08)	0.6
Progestogens				
3	0.82 (0.77–0.87)	<0.001	0.93 (0.87–1.00)	0.046
6	0.87 (0.82–0.93)	<0.001	0.97 (0.90–1.04)	0.37
9	0.86 (0.81–0.91)	<0.001	0.93 (0.87–1.00)	0.052
12	0.83 (0.78–0.88)	<0.001	0.89 (0.82–0.95)	0.001
Local oestrogen				
3	0.94 (0.91–0.97)	<0.001	1.03 (0.99–1.07)	0.16
6	0.94 (0.91–0.97)	<0.001	1.00 (0.96–1.04)	0.99
9	0.94 (0.91–0.97)	<0.001	0.99 (0.95–1.03)	0.5
12	0.90 (0.87–0.94)	<0.001	0.96 (0.92–0.99)	0.025

Crude odds ratios of experiencing any increase or a large increase in mean daily dose of inhaled corticosteroids among the exposed women with asthma. Odds ratios are results from univariate logistic regression for each month. Hormone therapy is a binary exposure while subtype of hormone therapy is a factorised, five-level exposure. Odds for unexposed women is the reference odds for all categories.

Exposed women had an increased crude odds ratio of receiving increased doses of salmeterol at 12 months (OR 1.12; 95% CI 1.02–1.22; p=0.013) and formoterol at 6 months (OR 1.09; 95% CI 1.01–1.17; p=0.022). Analyses adjusted for birth year, level of education and household income showed similar results. Crude and adjusted odds ratios for increased use of LABA are included in supplementary tables S4 and S5.

SABA

Among exposed women compared with unexposed women, mean daily doses at baseline were 0.53 mg *versus* 0.56 mg (difference 0.03 mg; 95% CI 0.01–0.05 mg; p=0.005) for terbutaline and 0.22 mg *versus* 0.25 mg (difference 0.03 mg; 95% CI 0.01–0.04 mg; p=0.004) for salbutamol. Among users of terbutaline, there was a statistically significant increase in use in the second month of HT (0.025 mg *versus* 0.005 mg; 95% CI 0.012–0.038 *versus* −0.001–0.010 mg; p<0.001). We observed no differences in mean values at the other timepoints (figure 4). Women receiving HT and terbutaline had lower odds of being increased in dose at 9 months (OR 0.95; 95% CI 0.90–1.00; p=0.035) and at 12 months (OR 0.94; 95% CI 0.89–0.99; p=0.020). Adjusted and unadjusted estimates are presented in supplementary tables S6 and S7.

Discussion

We performed a matched cohort study investigating the use of inhaled anti-asthma medications in women with asthma 12 months following initiation of HT and compared with women with asthma who did not initiate HT. Overall, HT did not have any major effect on the use of inhaled anti-asthma medications. However, in logistic regression analysis, we found that systemic formulations of HT with oestrogen were associated with increased odds of filling prescriptions corresponding to significantly higher doses of ICS. In contrast, treatment with progestogens and local oestrogens seemed to have protective effects against increased use of inhaled medications.
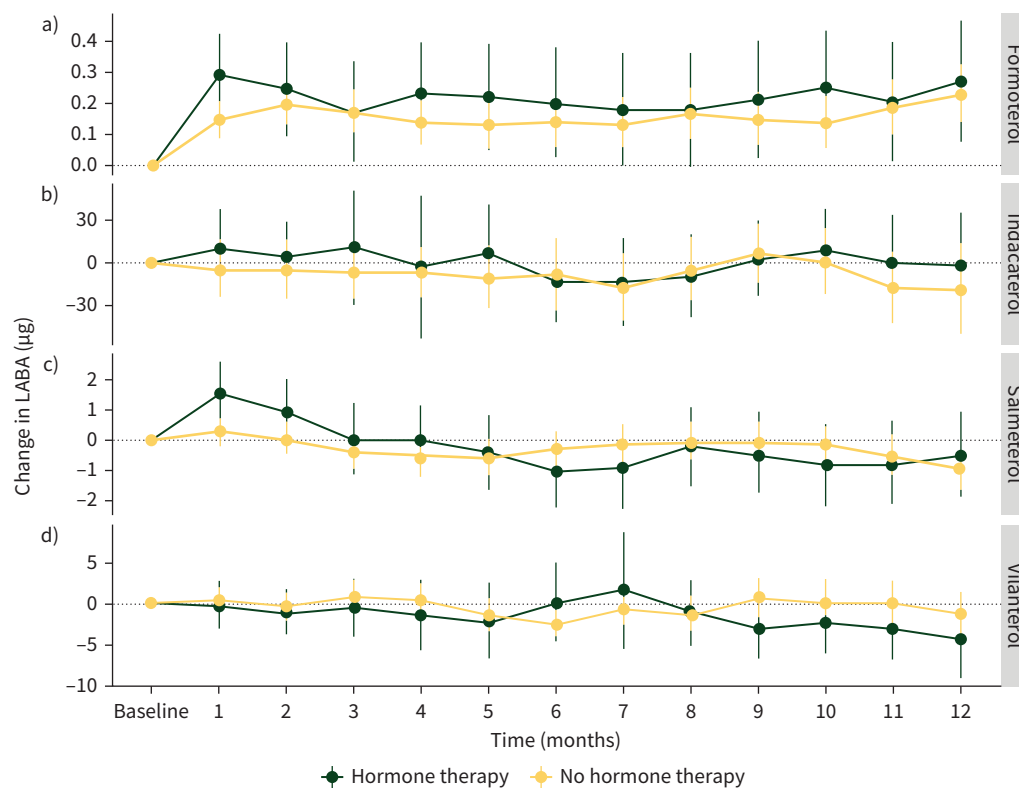
FIGURE 3 Change in use of long-acting β₂-agonists (LABA) among exposed *versus* unexposed women in the first 12 months following the index date. LABA are divided into the four different subtypes of LABA: a) formoterol; b) indacaterol; c) salmeterol; d) vilanterol.

In this study, there were only small differences in mean doses of ICS, LABA and SABA (2–8%) and the clinical manifestations which led to these differences are uncertain. Increases observed were largest in the first 2 months following initiation of HT and it is possible that HT induces an acute biological effect that diminishes over time. It is notable that formulations containing systemic oestrogen (combination therapy or monotherapy with oestrogen) were associated with increased odds of experiencing a large increase in use of ICS. This suggests that in some women, oestrogen could be detrimentally affecting the lungs. On the contrary, progestogens showed a potentially protective effect on increases in inhaled medication. This relationship has been described previously in relation to development of new asthma [19]. A recent cross-sectional study indicated that high testosterone levels are associated with lower odds of hospital admissions due to exacerbations of asthma [20]. Progestogens in high doses can bind to androgen receptors, thus it is possible that the potentially protective effects of progestogens share common pathways with testosterone [21]. The protective effect of progestogens and the detrimental effects of oestrogens should be further explored.

Previous studies have indicated that HT can increase the hazard ratio of new incidence of asthma and thus, we expected to see the same clear pattern of exogenous oestrogen inducing more severe disease in women already having asthma [1–3]. However, our results were more ambiguous, with inconsistent patterns over time. An explanation could be that women who already have asthma at the time of HT initiation have more classic type 2-dominated pheno- and endotypes of asthma compared with women without asthma at the time of HT initiation [22–24]. Thus, their airway reaction to female sex hormones might be different or less pronounced.

In the analyses of mean doses of SABA and ICS, we found that women who did not receive HT had a higher use of SABA at the index date while HT users received higher doses of ICS even before initiation of HT. These differences indicate that the matched groups could be different. Women who seek care for menopausal symptoms could be more prone to having well-regulated asthma, and thus having previously been prescribed a LABA, while women who do not seek menopausal treatment could be more prone to using SABA instead. Further, users of HT could also be more adherent to their anti-asthma medication
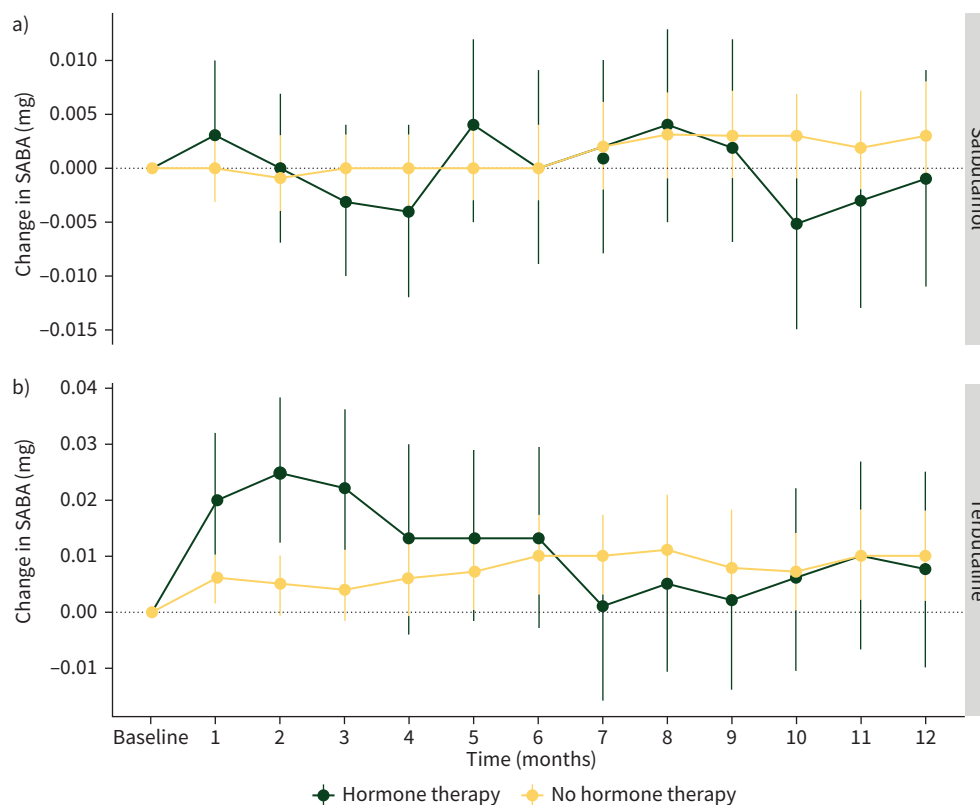
FIGURE 4 Change in use of short-acting β₂-agonists (SABA) among exposed *versus* unexposed women in the first 12 months following the index date. SABA are divided into the two different subtypes of SABA: a) salbutamol and b) terbutaline.

after initiating HT as it could act as a reminder to take their regular medication. We tried to minimise bias and confounding by matching women on age, household income and level of education, as these are previously described differences between users and nonusers of HT [16]. However, a limitation with our study is that there might be residual confounding that is unaccounted for, which was highlighted by the highly significant difference between the groups in years from asthma diagnosis to the index date. The significance level of the difference (p<0.001) is, however, most likely attributed to the sizes of the groups. Consequently, this highlights the need for randomised studies investigating the effect of female sex hormones on airway hyper-responsiveness, airway inflammation, systemic inflammation and patient-reported asthma outcomes.

A limitation with our study is that our diagnosis of asthma mainly was based on filled prescriptions of ICS. Although we made efforts to exclude patients with COPD, it is possible that some of our included patients received ICS for other reasons than asthma. A further limitation is that some women only received SABA instead of maintenance treatment with ICS at the same time as initiating HT. This could indicate that their asthma either was mild or that they were undertreated. Therefore, use of asthma medication before and after HT must be interpreted with caution as potential differences might arise from other causes not clearly associated with HT. In further studies, it would be interesting to follow peri- and postmenopausal women with well-treated asthma before and after they receive HT to observe whether HT has any effect on asthma outcomes.

A strength with the current study is that we had access to all filled prescriptions of HT bought in Denmark since June 1995. This makes our data complete as our doses of anti-asthma medications are based on filled prescriptions. In women who received HT, we observed a visible spike in daily ICS dose immediately after HT initiation. One reason could be that women with asthma who received HT had their prescriptions of anti-asthma medication refilled at the same doctor's appointment as initiation of HT. This hypothesis is strengthened by the diminishing differences in means after 2 months. If prescriptions are filled, but medication not taken, their mean dose would spike at the start of the period but flatten out afterwards, as it

would not be necessary to fill prescriptions from the pharmacy in the near future. Even though our sensitivity analyses (supplementary figures S1 and S2) of different age groups did not indicate significant differences, a further limitation with this study is that we could not confirm whether the women with asthma were truly postmenopausal as the inclusion into the study was based on filled prescriptions of HT and not menopausal status. Thus, it is possible that some of the women in our study were still under the influence of endogenous sex hormones, which could have affected our results. To address this issue, future prospective studies made in this type of study population should include a thorough evaluation of menopausal status.

In conclusion, in women with current asthma, treatment with exogenous female sex hormones around menopause did not have large effects on use of inhaled anti-asthma medications in the 12 months following HT. However, there was an observable increase in use of ICS in the first month following, which could indicate an acute effect of HT on symptoms of asthma. To eliminate confounding, randomised investigations into the effects of these hormones on outcomes of asthma are warranted. This would be helpful in discovering the mechanistic effects, as well as the clinical effects, of these commonly prescribed substances on asthma pathology.

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