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Early View

Original research article

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

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Abstract

Research question: Does menopausal hormone therapy with exogenous estrogens 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 June 1, 1995 to June 30, 2018. We investigated whether hormone therapy with estrogen 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 hormone therapy. We calculated mean dose of medications and odds ratios of increases in the 12 months following hormone therapy initiation.

Results: We included 139483 women with asthma, of whom 116014 (83.2%) were unexposed subjects and 23469 (16.8%) exposed subjects. Mean age was 53.0 (SD 5.2) years. Initiation of HT was not consistently associated with increased mean doses of inhaled corticosteroids, or long- and short-acting beta$_2$-agonists. Women receiving systemic estrogens had increased odds ratios of large increases (>100 µg) in inhaled corticosteroids at six months (1.09; 95%CI 1.04-1.13; P<0.001) and nine months (1.07; 95%CI 1.03-1.12; P<0.001). Progestogens were protective against increases in inhaled corticosteroids at six and nine months (OR 0.87; 95%CI 0.82-0.93; P<0.001 and 0.86; 95%CI 0.81-0.91; P<0.001).

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

Take-home message

In women with asthma, use of exogenous female sex hormones in menopause did not significantly change the use of inhaled medications. However, data suggest that there could be beneficial effects of progestogens and detrimental effects of estrogens.

Key words

Asthma, Estrogen, Progesterone, Menopause, Hormone replacement therapy, Budesonide equivalent, Epidemiology, Cohort study

Abbreviations

HT – Hormone therapy

ICS – Inhaled corticosteroids

LABA – Long-acting beta$_2$-agonists

STROBE - Strengthening the Reporting of Observational studies in Epidemiology

SABA – Short-acting beta$_2$-agonists

COPD – Chronic obstructive pulmonary disease

ATC – Anatomical Therapeutic Chemical system

ICD – International Classification of Diseases

WHO – World Health Organization

SD – Standard deviation

SE – Standard error

CI – Confidence interval

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 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 beta$_2$-agonists (LABA) until the patient experiences asthma control[6]. Thus, if HT impacts asthma negatively, with increasing level of symptoms, we expect that physicians prescribe increased amounts of ICS and LABA[6]. Known adverse events to HT ranges 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 if 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 June 1, 1995 and June 30, 2018. The study was reported by the STROBE-guidelines[9]. Our aim was to determine if current use of menopausal hormone therapy was associated with change in use of inhaled anti-asthma medications such as ICS, LABA and short-acting beta$_2$-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 she had filled at least two prescriptions of ICS within two years. A woman was included in the cohort at her asthma diagnosis date, or at her 45th birthday, whichever came last.

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) or/and 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 System (ATC codes)[10]. The Danish National Patient Register contains information on all hospital admissions in Denmark since 1978 with indexing by ICD-10 as described by the World Health Organisation[11, 12]. Information about, household income, education level, age and sex were 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 hormone therapy. Therefore, 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 hormone therapy within one 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 hormone therapy

For systemic vasomotor symptoms of menopause, women are currently recommended combined systemic use of estrogens and progestogens or estrogen-only therapy if previously hysterectomized, since 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 (Estrogens, systemic and local), G03D (Progestogens), or G03F (Progestogens and estrogens in combination) within one year or prescription of G02BA03 (Progestogens, intrauterine device)[18]. We registered which type of HT was used as initial treatment. Monotherapy with estrogen was defined as filled prescriptions of G03C without concurrent prescriptions of G03D or G02BA03. Combination HT with estrogen 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 analyzed 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 ≥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 the supplementary material (e-Table 1-2).

As LABAs come in different substances and sizes and no apparent equivalents are available, doses of LABAs were calculated for each substance (Formoterol, Indacaterol, Salmeterol and Vilanterol). The same was done for SABAs (Terbutaline and Salbutamol).

Statistical considerations

Baseline characteristics were reported as frequencies or means with standard deviations and compared with Student's t-test for continuous variables and Chi-square test for frequency distributions.

Mean daily amounts of ICS were calculated as daily budesonide equivalent doses in micrograms and were returned in date intervals. For each month following hormone therapy 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 three, six, nine and 12 months and compared the groups. Changes in budesonide equivalent doses of ICS were defined as any increase (change in dose > 0 µg) or a large increase (change in dose > 100 µg). Odds ratios (OR) 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 the supplementary material (e-Table 3-5). If an exposed woman discontinued their hormone treatment, 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 (e-Figure 1-2).

All results are presented with 95% confidence intervals used to determine significant differences between exposed and non-exposed subjects. As analyses are based on public registries, all analyses represent complete-case analyses. All analyses were performed using RStudio with R version 3.6.1[19].

Results

In this matched cohort study, we included 139483 women with asthma, of whom 116014 (83.2%) were unexposed subjects (no HT) and 23469 (16.8%) exposed subjects (HT) (Table 1; Figure 1). In the cohort, participants were followed for a total of 1091261 person years (mean 7.8 years per participant). The mean age in both groups was 53.0 years (SD 5.2). Among the exposed subjects, 1782 (7.6%) had received monotherapy with systemic estrogen; 11736 (50.0%) had received monotherapy with local estrogen; 5164 (22.0%) had received combination hormone therapy with progestogens and estrogens, and 4787 (20.3%) had received monotherapy with progestogens. From the population included in the analyses, 22.6% and 28.4% had terminated HT treatment at six months and one year following the index date. The mean budesonide equivalent dose of ICS at baseline was lower in the unexposed group (406 µg vs. 422 µg; difference -15 µg; 95%CI -26 to -6; P=0.002).

Inhaled corticosteroids

In the first month following the index date, women exposed to HT showed a significant increase in use of ICS (Month 1: 22.5 vs. 7.0 µg; 95%CI 17.5-27.4 vs. 4.9-9.1; P<0.001). From month two and forward, the significant differences disappeared (Figure 2). Sensitivity analyses in different age groups showed similar results (e-Figure 1-2). Crude analyses showed that exposed women had higher odds of using more ICS at six months (OR 1.04; 95%CI 1.00-1.08; P=0.032) following the index date (Table 2). We observed no differences at three, nine and 12 months. Women exposed to HT were more likely to experience a large increase (>100 µg) at three, six and nine months (Odds ratios: 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 the supplementary material (e-Table 3).

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

Long-acting beta$_2$-agonists

In exposed women compared with unexposed women, mean daily doses at baseline were 8.94 µg vs. 8.76 µg (difference -0.18 µg; 95%CI -0.18-0.43; P=0.20) for formoterol; 185.6 µg vs. 175.6 µg (difference -10.06 µg; 95%CI -38.28-18.16; P=0.48) for indacaterol; 58.8 µg vs. 57.7 µg (difference -0.98 µg; 95%CI -2.73-0.77; P=0.98) for salmeterol and 17.47 µg vs. 18.51 µg (difference 1.04 µg; -1.43-3.52; 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). Exposed women had an increased crude OR of receiving increased doses of salmeterol at 12 months (1.12; 95%CI 1.02-1.22; P=0.013) and formoterol at 6 months (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 the supplementary material (e-Table 4-5).

Short-acting beta$_2$-agonists

Among exposed women compared with unexposed women, mean daily doses at baseline were 0.53 mg vs. 0.56 mg (difference 0.03 mg; 95%CI 0.01-0.05; P=0.005) for terbutaline and 0.22 mg vs. 0.25 mg (difference 0.03 mg; 95%CI 0.01-0.04; P=0.004) for salbutamol. Among users of terbutaline, there was a statistically significant increase in use in the second month of hormone therapy (0.025 mg vs. 0.005 mg; 95%CI 0.012-0.038 vs. -0.001-0.010; P<0.001). We observed no differences in mean values at the other timepoints. Women receiving HT and terbutaline had lower odds of being increased in dose at nine 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 the supplementary material (e-Table 6-7).

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 large effect on use of inhaled anti-asthma medications. However, in logistic regression analysis, we found that systemic formulations of HT with estrogen were associated with increased odds of filling prescriptions corresponding to significantly higher doses of ICS. In contrast, treatment with progestogens and local estrogens seemed to have protective effects against increased use of inhaled medications.

In this study, there were only small differences in mean doses of ICS, LABA and SABA (2-8%) and the clinical manifestations which lead 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 biologic effect which diminishes over time. It is notable that formulations containing systemic estrogen (combination therapy or monotherapy with estrogen) were associated with increased odds of experiencing a large increase in use of inhaled corticosteroids. This suggests that in some women, estrogen 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[20]. A recent cross-sectional study indicated that high testosterone levels are associated with lower odds of hospital admissions due to exacerbations of asthma[21]. Progestogens in high doses can bind to androgen receptors, thus it is possible that progestogens' potentially protective effects share common pathways with testosterone[22]. The protective effect of progestogens and the detrimental effects of estrogens 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 estrogen 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[23–25]. 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 already 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 have well-regulated asthma, and thus earlier have been prescribed a LABA, while women who do not seek menopausal could be more prone to use SABA instead. Further, users of HT could also be more adherent to their anti-asthma medication after initiating HT as it could act as a reminder to take their regular medication. We tried to minimize bias and confounding by matching women on age, household income, and level of education as these are previously described differences between users and non-users 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 of randomized studies investigating the effect of

female sex hormones on airway hyperresponsiveness, 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 simultaneously 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 if HT have any effect on asthma outcomes.

A strength with the current study is that we have access to all filled prescriptions of hormone therapy 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 in 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 (e-Figure 1-2) of different age groups did not indicate significant differences, a further limitation with this study is that we could not confirm if 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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Conflicts of interest and funding

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Author contributions

ESH and VB developed the initial protocol. CTP granted access to data. ESH, KA, AML, CTP performed the data analysis. ESH was responsible for the initial manuscript. ESH, KA, AML, EJG, AM, CTP and VB contributed to the interpretation of data and manuscript

writing. All authors approved the final manuscript before submitting for publication. ESH and VB take full responsibility for the results.

Transparency declaration

ESH and VB affirm that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1: Population characteristics

	No HT	HT	P-value
N	116014	23469	
Age			
Mean (SD)	53.0 (5.2)	53.0 (5.2)	1.00
Age groups, n (%)			1.00
45-49	31703 (27.3%)	6387 (27.2%)	
50-54	39673 (34.2%)	8054 (34.3%)	
55-59	24649 (21.2%)	4946 (21.1%)	
60-64	19989 (17.2%)	4082 (17.4%)	
Years of asthma			
Mean (SD)	7.7 (5.9)	7.4 (5.8)	<0.001
Household income levels, n (%)			1.00
Lowest	7 (0.0%)	20 (0.1%)	
Second lowest	4711 (4.1%)	1013 (4.3%)	
Second highest	37355 (32.2%)	7558 (32.2%)	
Highest	73941 (63.7%)	14878 (63.4%)	
Level of education, n (%)			1.00
Long-cycle higher education	6818 (5.9%)	1419 (6.0%)	
Medium-cycle higher education or bachelors' degree	30893 (26.6%)	6245 (26.6%)	
Upper or lower secondary school	36696 (31.6%)	7387 (31.5%)	
Vocational upper secondary school	41607 (35.9%)	8418 (35.9%)	
Inhaled anti-asthma medication, n (%)			
Inhaled corticosteroids	74681 (64.4%)	15800 (67.3%)	<0.001
Mean dose, µg (SEM)	406 (5)	421 (5)	0.002
Long-acting beta-agonists			
Formoterol	23014 (19.8%)	5142 (21.9%)	<0.001
Salmeterol	14622 (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 beta-agonists			
Terbutaline	45854 (39.5%)	9526 (40.6%)	<0.001
Salbutamol	22035 (19.0%)	4908 (20.9%)	<0.001

Table 1: Study population characteristics. SD, standard deviation; N, number; HT, hormone therapy; SEM, Standard error of the mean

Table 2: Crude odds ratios of increased use of ICS 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 estrogen				
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 estrogen				
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

Table 2: Crude odds ratios of experience 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 subtypes of hormone therapy is a factorized, five-level exposure. Odds for unexposed women is the reference odds for all categories. OR, odds ratio; ICS, inhaled corticosteroids; µg, micrograms; CI, confidence interval

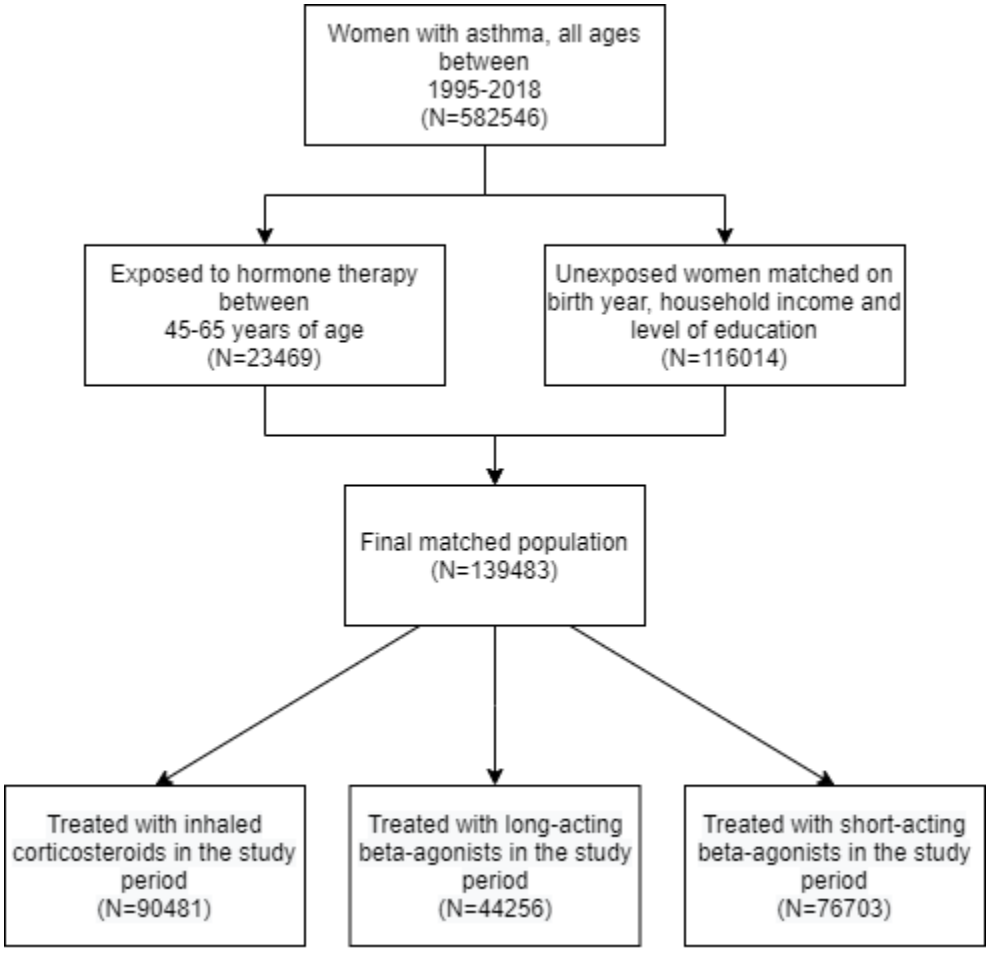
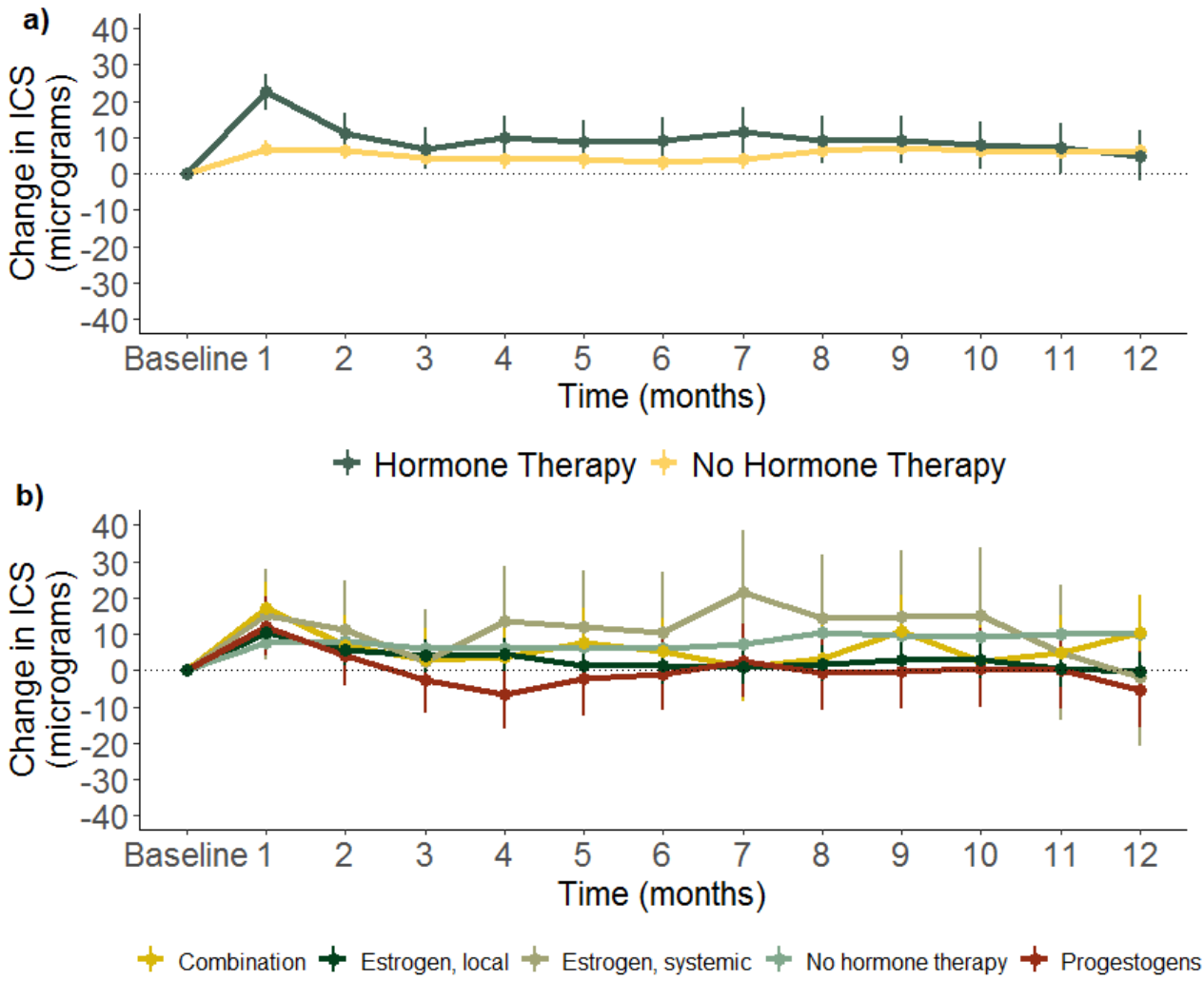


Figure 1: Flowchart of population

Figure 1: Flowchart of the study population. From the original 582546 women with asthma, 23469 women were identified as receiving hormone therapy (exposed) and subsequently matched with five unexposed women. N, number.


a)
Change in ICS (micrograms)
40
30
20
10
0
-10
-20
-30
-40
Baseline 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
Hormone Therapy
No Hormone Therapy
b)
Change in ICS (micrograms)
40
30
20
10
0
-10
-20
-30
-40
Baseline 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
Combination
Estrogen, local
Estrogen, systemic
No hormone therapy
Progestogens

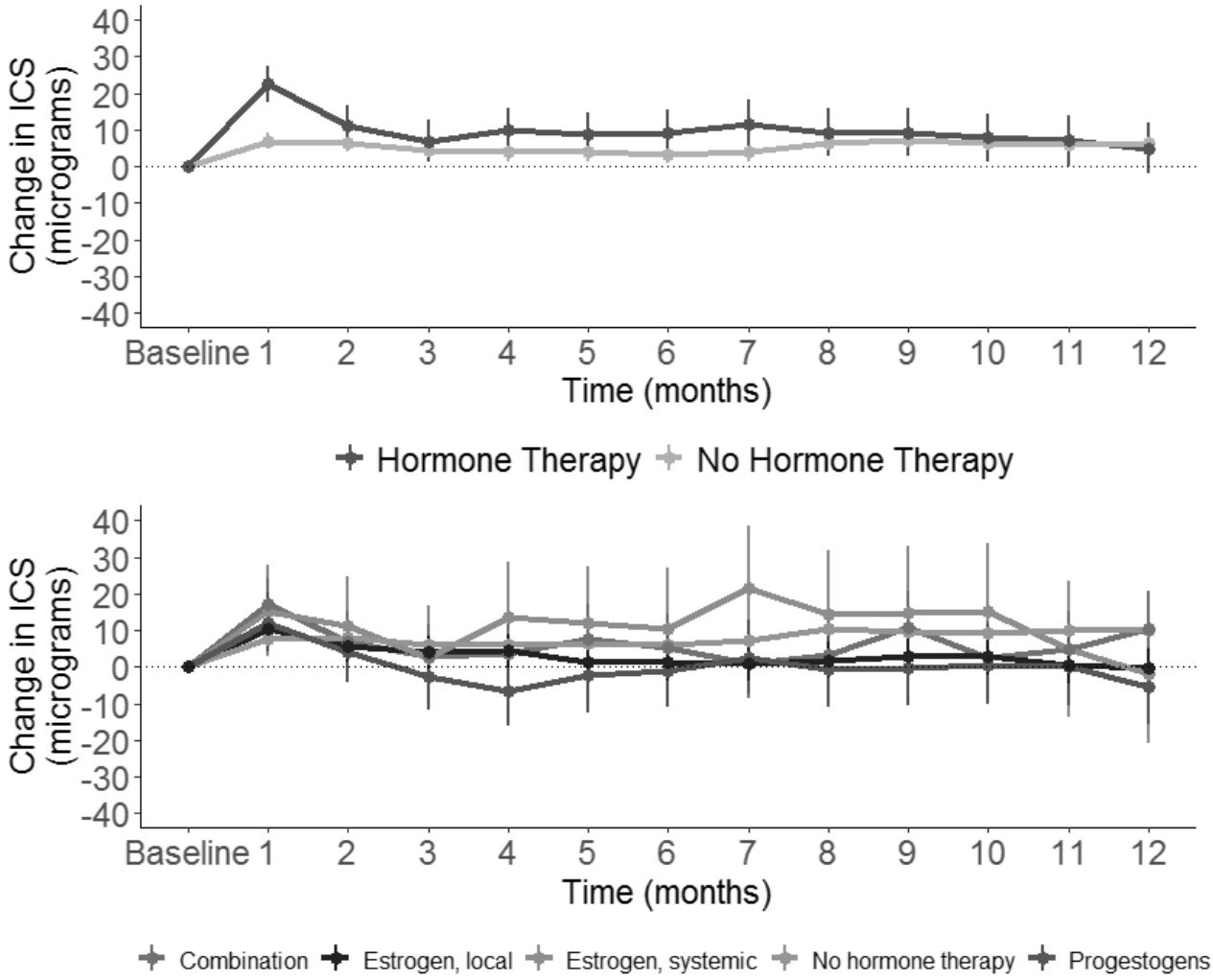
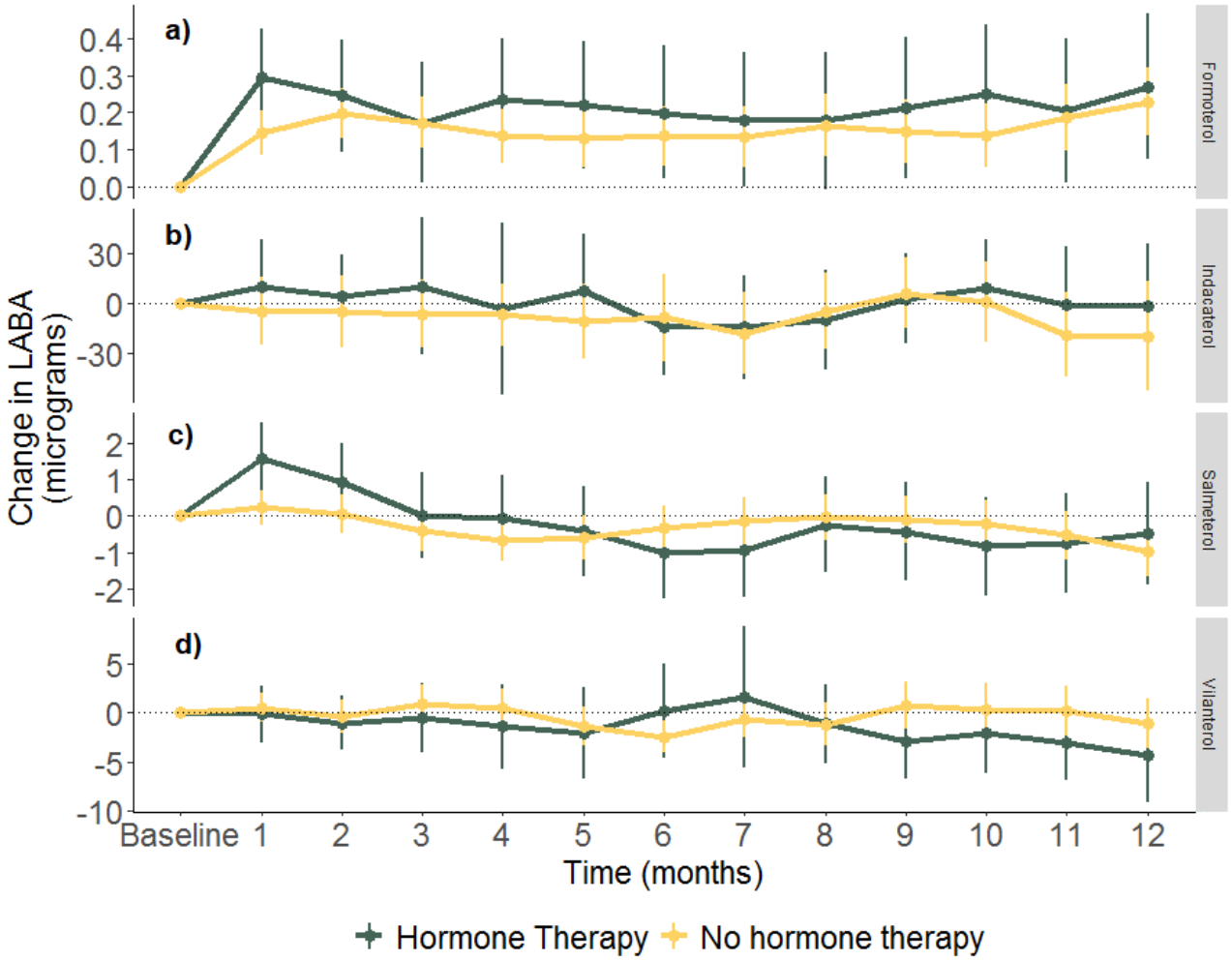


Figure 2: Change in mean doses of ICS

Figure 2: Change in use of ICS among exposed vs. unexposed women in the first 12 months following the index date. The panel a) shows HT as a compound exposure while in panel b) HT is divided into specific substances. ICS, inhaled corticosteroids.


a)
b)
c)
d)
Formoterol
Indacaterol
Salmeterol
Vilanterol
Change in LABA (micrograms)
0.4
0.3
0.2
0.1
0.0
30
0
-30
2
1
0
-1
-2
5
0
-5
-10
Baseline
1
2
3
4
5
6
7
8
9
10
11
12
Time (months)
Hormone Therapy
No hormone therapy

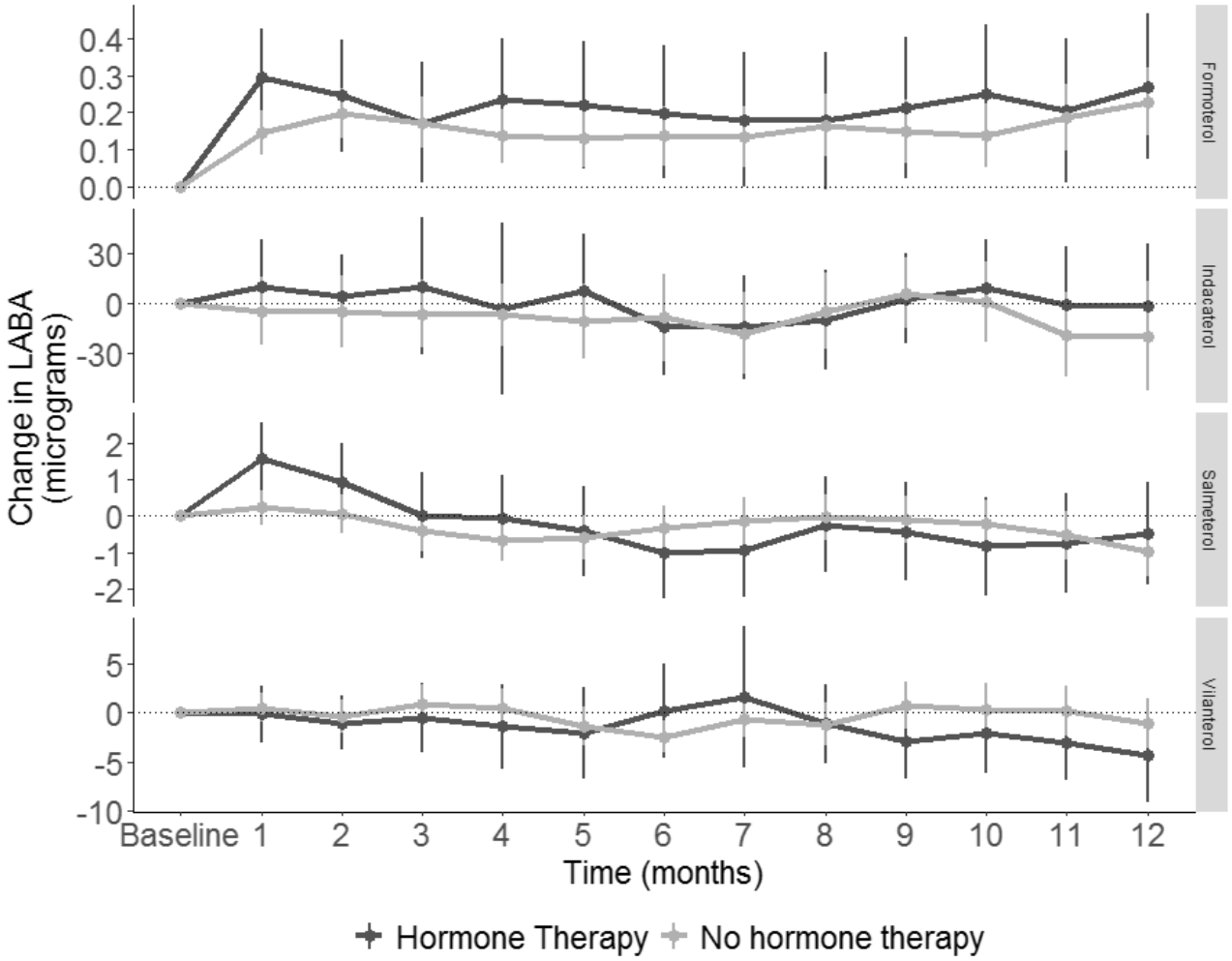
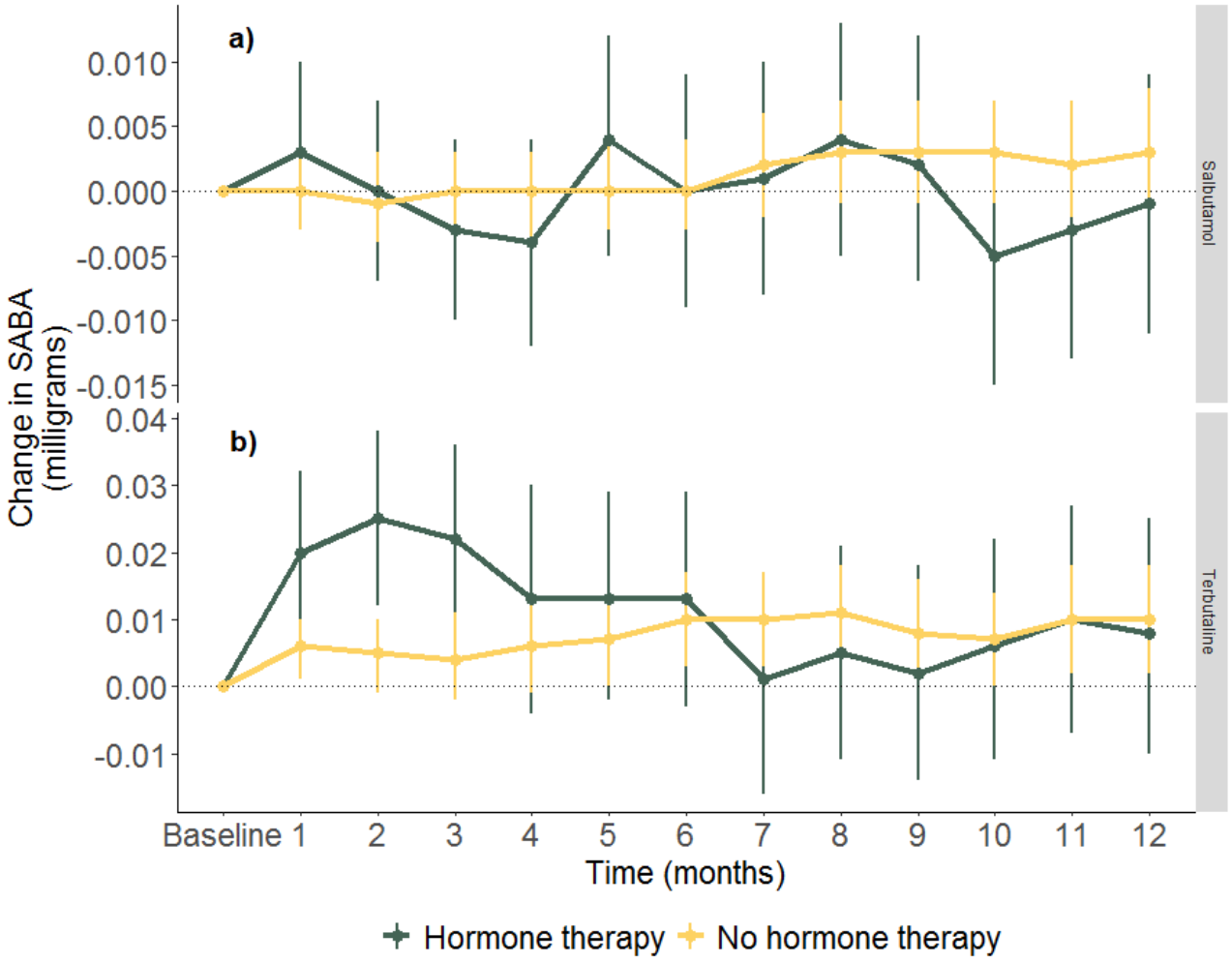


Figure 3: Change in mean doses of LABA

Figure 3: Change in use of LABA among exposed vs. unexposed women in the first 12 months following the index date. LABAs are divided into the four different subtypes of LABA (panel a-d). LABA, long-acting beta$_2$-agonists


a)
b)
Salbutamol
Terbutaline
Change in SABA (milligrams)
0.010
0.005
0.000
-0.005
-0.010
-0.015
0.04
0.03
0.02
0.01
0.00
-0.01
Baseline 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
Hormone therapy
No hormone therapy

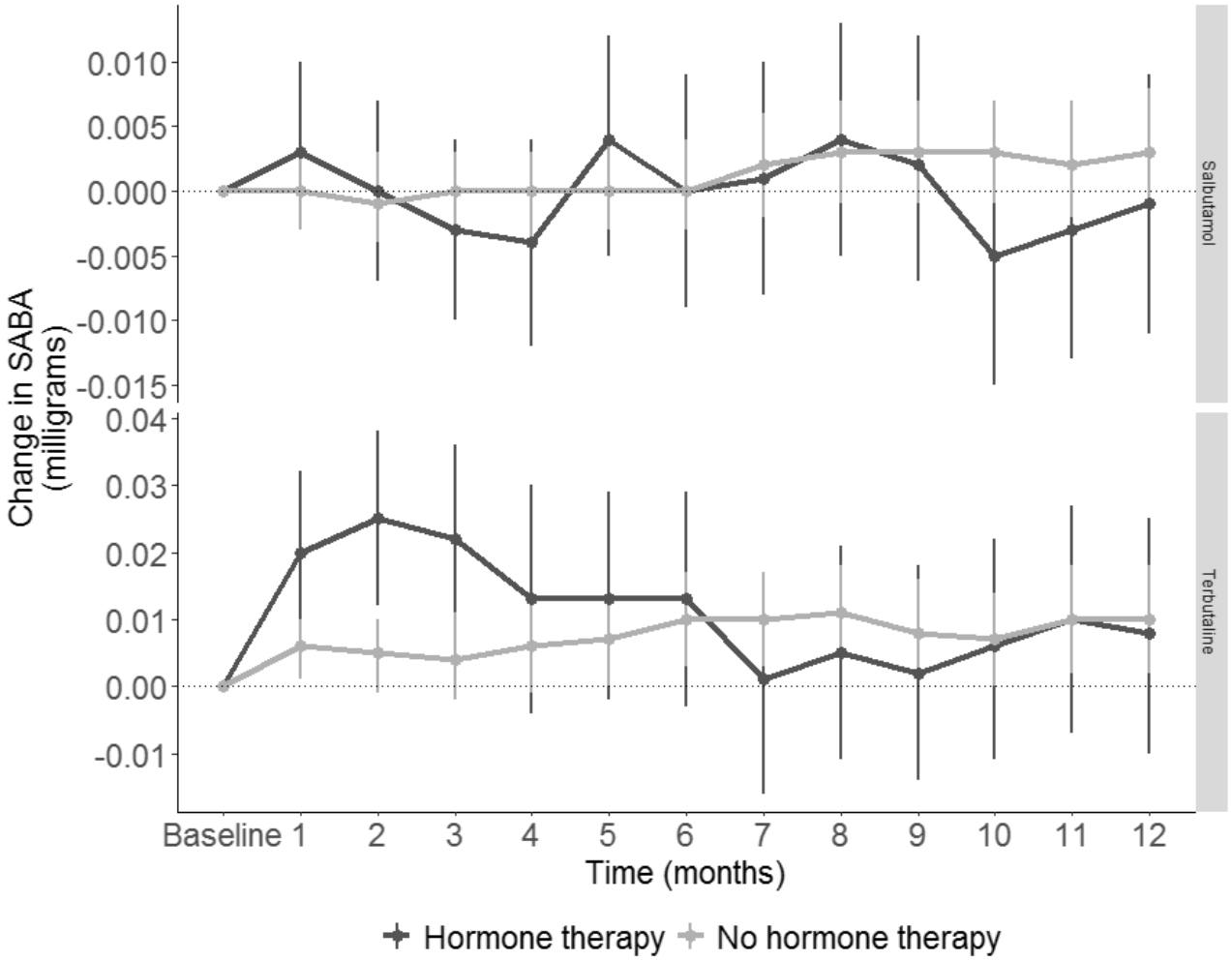


Figure 4: Change in mean dose of SABA

Figure 4: Change in use of SABA among exposed vs. unexposed women in the first 12 months following the index date. SABAs are divided into the two different subtypes of SABA (panel a and b). SABA, short-acting beta$_2$-agonists

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

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Online data supplement

Contents

Abbreviations

HT – Hormone therapy

ICS – Inhaled corticosteroids

LABA – Long-acting beta$_2$-agonists

STROBE - Strengthening the Reporting of Observational studies in Epidemiology

SABA – Short-acting beta$_2$-agonists

ATC – Anatomical Therapeutic Chemical system

ICD – International Classification of DiseasesOnline tables

e-Table 1: Budesonide equivalents

Substance	Multiplying factor
Budesonide	1.0
Beclometasone	2.0
Ciclesonide	2.5
Fluticasone propionate	2.0
Mometasone	1.4
Fluticasone furoate	4

e-Table 1: Multiplying factors to calculate budesonide equivalents. Example: 200 micrograms of ciclesonide =200 x 2.5 = 500 micrograms of budesonide.

e-Table 2: ATC-codes of inhaled anti-asthma medication

Substance	ATC
Inhaled corticosteroids Budesonide	R03BA02, R03AK07, R03AK12
Beclometasone	R03BA01, R03AK08
Ciclesonide	R03BA08
Fluticasone propionate	R03BA05, R03AK06, R03AK11
Mometasone	R03BA07, R03AK09, R03AK14
Fluticasone furoate	R03BA09, R03AK10
Long-acting beta$_2$-agonists Salmeterol	R03AC12, R03AK06, R03AK12
Vilanterol	R03AK10
Indacaterol	R03AC18, R03AK14
Formoterol	R03AC13, R03AK07, R03AK08, R03AK09, R03AK11
Short-acting beta$_2$-agonists Salbutamol	R03AC02
Terbutaline	R03AC03

e-Table 2: Overview of ATC-codes for inhaled anti-asthma medications. If a given drug was a combined drug (e.g. R03AK12 – Budesonide/Salmeterol) the components were separated into long-acting beta$_2$-agonists and inhaled corticosteroids. ATC, Anatomical Therapeutic Classification system.

e-Table 3: Adjusted odds ratios of increased use of ICS in hormone therapy users

Time points (months)	Any increase (>0 µg) OR (95%CI)	P value	Increase (>100 µg) OR (95%CI)	P value
Hormone therapy				
3	0.99 (0.95-1.03)	0.6	1.05 (1.00-1.09)	0.031
6	1.04 (1.00-1.08)	0.060	1.08 (1.04-1.13)	<0.001
9	1.00 (0.96-1.04)	1.00	1.07 (1.03-1.11)	0.001
12	0.98 (0.94-1.01)	0.20	1.02 (0.98-1.06)	0.39
Hormone therapy by type				
Systemic estrogen				
3	0.91 (0.83-0.99)	0.023	1.08 (1.98-1.19)	0.092
6	1.00 (0.92-1.08)	0.9	1.12 (1.02-1.23)	0.014
9	0.92 (0.84-1.00)	0.055	1.08 (0.98-1.19)	0.099
12	0.85 (0.78-0.93)	<0.001	1.01 (0.92-1.11)	0.8
Combination				
3	0.94 (0.90-0.99)	0.027	1.06 (1.00-1.12)	0.053
6	0.95 (0.90-1.00)	0.058	1.06 (1.00-1.13)	0.036
9	0.99 (0.94-1.04)	0.6	1.09 (1.03-1.16)	0.003
12	0.92 (0.87-0.97)	0.002	1.02 (0.96-1.08)	0.6
Progestogens				
3	0.82 (0.77-0.87)	<0.001	0.97 (0.91-1.04)	0.42

6	0.87 (0.82-0.93)	<0.001	1.00 (0.94-1.08)	0.9
9	0.86 (0.81-0.91)	<0.001	0.96 (0.90-1.03)	0.32
12	0.83 (0.78-0.88)	<0.001	0.91 (0.85-0.98)	0.014
Local estrogen				
3	0.94 (0.91-0.97)	<0.001	1.03 (0.99-1.07)	0.092
6	0.94 (0.91-0.97)	<0.001	1.00 (0.97-1.04)	0.8
9	0.94 (0.91-0.97)	<0.001	0.99 (0.96-1.03)	0.7
12	0.90 (0.87-0.94)	<0.001	0.96 (0.93-1.00)	0.050

e-Table 3: Odds ratios of being increased in ICS at the four timepoints. Reference for all odds ratios is “No hormone therapy”. ICS, inhaled corticosteroids; CI, confidence interval

e-Table 4: Crude odds ratios of increased use of LABA among users of hormone therapy

Timepoint	OR	Lower CI (95%)	Upper CI (95%)	P value	Type of LABA
Month 3	1.02	0.95	1.09	0.54	Formoterol
Month 3	1.04	0.95	1.12	0.42	Salmeterol
Month 3	1.04	0.45	2.42	0.91	Vilanterol
Month 3	0.51	0.24	1.02	0.06	Indacaterol
Month 6	1.09	1.01	1.17	0.022	Formoterol
Month 6	1.04	0.96	1.14	0.35	Salmeterol
Month 6	2.09	0.81	5.46	0.13	Vilanterol
Month 6	0.52	0.24	1.07	0.085	Indacaterol
Month 9	1.05	0.98	1.13	0.15	Formoterol
Month 9	1.05	0.96	1.15	0.25	Salmeterol
Month 9	0.73	0.25	2.00	0.54	Vilanterol
Month 9	0.68	0.31	1.43	0.31	Indacaterol
Month 12	1.06	0.98	1.14	0.12	Formoterol
Month 12	1.12	1.02	1.22	0.013	Salmeterol
Month 12	0.77	0.22	2.49	0.67	Vilanterol
Month 12	0.73	0.32	1.60	0.44	Indacaterol

e-Table 4: Crude odds ratios of having an increased use of LABA at the four different timepoints following the index date (HT initiation date). OR, Odds ratio; CI, confidence interval; LABA, long-acting $beta_2$-agonist.

e-Table 5: Adjusted odds odds ratios of increased use of LABA among users of hormone therapy

Timepoint	OR	Lower CI (95%)	Upper CI (95%)	P value	Type of LABA
Month 3	1.02	0.95	1.10	0.56	Formoterol
Month 3	1.04	0.95	1.13	0.41	Salmeterol
Month 3	1.12	0.47	2.64	0.80	Vilanterol
Month 3	0.44	0.20	0.90	0.029	Indacaterol
Month 6	1.09	1.01	1.16	0.024	Formoterol
Month 6	1.04	0.96	1.14	0.35	Salmeterol
Month 6	1.99	0.75	5.33	0.17	Vilanterol
Month 6	0.45	0.20	0.96	0.044	Indacaterol
Month 9	1.05	0.98	1.13	0.17	Formoterol
Month 9	1.05	0.97	1.15	0.24	Salmeterol
Month 9	0.71	0.24	2.03	0.53	Vilanterol
Month 9	0.55	0.24	1.20	0.14	Indacaterol
Month 12	1.06	0.98	1.14	0.12	Formoterol
Month 12	1.12	1.03	1.22	0.012	Salmeterol
Month 12	0.67	0.18	2.28	0.53	Vilanterol
Month 12	0.74	0.31	1.68	0.47	Indacaterol

e-Table 5: Adjusted odds ratios of having an increased use of LABA at the four different timepoints following the index date (HT initiation date). Analyses were adjusted for household income, level of education and birth year. OR, Odds ratio; CI, confidence interval; LABA, long-acting $beta_2$-agonist.

e-Table 6: Crude odds ratios of increased use of SABA among users of hormone therapy

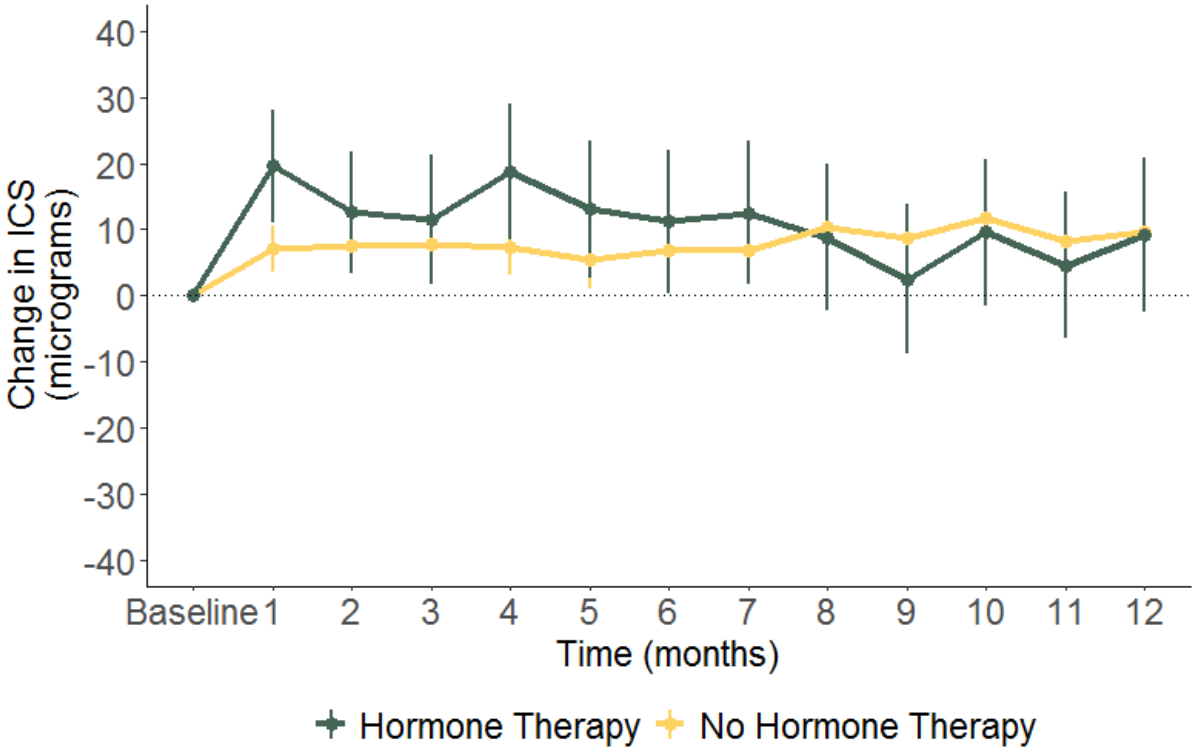
Timepoint	OR	Lower CI (95%)	Upper CI (95%)	P value	Type of SABA
Month 3	1.01	0.96	1.07	0.64	Terbutaline
Month 3	1.00	0.93	1.08	0.99	Salbutamol
Month 6	0.98	0.93	1.03	0.42	Terbutaline
Month 6	1.00	0.93	1.08	0.97	Salbutamol
Month 9	0.95	0.90	1.00	0.035	Terbutaline
Month 9	0.98	0.91	1.06	0.66	Salbutamol
Month 12	0.94	0.89	0.99	0.020	Terbutaline
Month 12	0.95	0.88	1.03	0.21	Salbutamol

e-Table 6: Crude odds ratios of experiencing an increase in use of SABA in the 12 months following hormone therapy initiation. OR, Odds ratio; CI, confidence interval; SABA, short-acting beta$_2$-agonists

e-Table 7: Adjusted odds ratios of increased use of SABA among users of hormone therapy

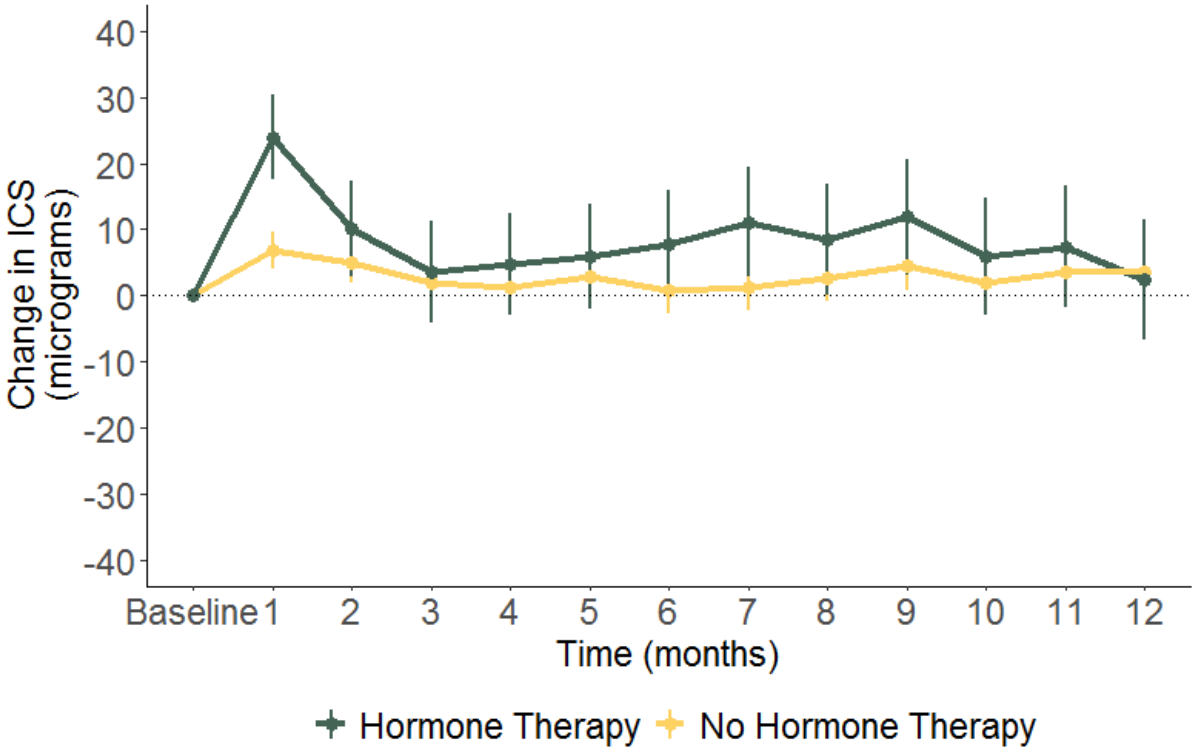
Timepoint	OR	Lower CI (95%)	Upper CI (95%)	P value	Type of LABA
Month 3	1.01	0.96	1.06	0.71	Terbutaline
Month 3	1.00	0.93	1.08	0.96	Salbutamol
Month 6	0.98	0.93	1.03	0.36	Terbutaline
Month 6	1.00	0.93	1.08	0.98	Salbutamol
Month 9	0.94	0.89	0.99	0.028	Terbutaline
Month 9	0.99	0.91	1.06	0.71	Salbutamol
Month 12	0.94	0.89	0.99	0.017	Terbutaline
Month 12	0.95	0.88	1.03	0.23	Salbutamol

e-Table 7: Adjusted odds ratios of experiencing an increase in use of SABA in the 12 months following hormone therapy initiation. Models are adjusted for baseline value, income level, household income and birth year. OR, Odds ratio; CI, confidence interval; SABA, short-acting beta$_2$-agonists



e-Figure 1: Analysis of changes in use of inhaled corticosteroids in women aged 54 years or older

e-Figure 1: Plot displaying the differences in use of inhaled corticosteroids in the 12 months following initiation of hormone therapy among women >= 54 years of age. The results were similar to the main analyses.



e-Figure 2: Analysis of changes in use of inhaled corticosteroids in women below 54 years of age

e-Figure 1: Plot displaying the differences in use of inhaled corticosteroids in the 12 months following initiation of hormone therapy among women < 54 years of age. The results were similar to the main analyses.