Postmenopausal hormone therapy and asthma onset in the E3N cohort.

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Running Title: Hormone therapy and asthma

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Abstract

Background: Epidemiological studies have suggested that female hormones might play a role in asthma and that menopausal hormone therapy (MHT or HRT) might increase the risk of asthma in postmenopausal women. The only prospective study addressing this issue reports an increase in the risk of developing asthma which was similar for estrogen alone and estrogen/progestagen treatment.
Methods: The association between the use of different types of MHT and the risk of asthma onset in postmenopausal women was investigated prospectively from 1990 to 2002 by biennial questionnaire as part of the French E3N cohort study. Asthma onset was considered to be the time of medical diagnosis of asthma cases occurring during the follow up of women who were asthma free at baseline. Cox proportional hazards models were used, adjusting for potential confounding factors.
Results: Among 57,664 women free of asthma at menopause 569 incident cases of asthma were identified during 495,448 years of follow-up. MHT was related to an increased risk of asthma onset (HR= 1.20, 95% CI 0.98-1.46) among recent users. The increase in risk of asthma onset was only significant among women reporting the use of estrogen alone (HR= 1.54, 95% CI 1.13-2.09).particularly in never smokers (HR= 1.80 95% CI 1.15-2.80) and women reporting allergic disease prior to asthma onset (HR= 1.86 95% CI 1.18-2.93). A small increase in the risk of asthma onset associated with the use of estrogen/progestagen was also observed in these subgroups.
Conclusion: Postmenopausal use of estrogen alone was associated with an increased rate of newly diagnosed asthma in menopausal women.

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Introduction

The major increase in asthma prevalence observed in most developed countries in recent years[1] suggests that it may in part be due to environmental factors. Differences in asthma incidence during the life cycle suggest that reproductive hormones influence the development of asthma and asthma severity.[2] Asthma is more frequent in girls after menarche than before.[3] Adult asthma and hospital admissions for asthma are more prevalent in women than in men and asthma severity has been shown to vary during the menstrual cycle and pregnancy.[4] In addition, the incidence of asthma tends to decrease after menopause.[5] The increase of asthma onset in postmenopausal women with increasing weight points to an endocrine mechanism such as increased endogenous estrogen synthesis.[6] Menopausal hormone therapy (MHT) might therefore play a role in asthma onset. Different studies have investigated the role of MHT in asthma. Cross-sectional studies have reported an association between prevalent asthma and asthma-like symptoms and MHT use in perimenopausal[7] and postmenopausal women,[8, 9] with a larger effect in lean women. However, these studies were cross-sectional and therefore could not evaluate the effect of MHT on asthma onset. None of these studies evaluated the risk related to different types of MHT. To date only one cohort study, the Nurses' Health Study, has suggested that MHT use is associated with an increased risk of developing asthma. It observed a similar significant (two fold) increase in risk with the use of estrogen alone or estrogen plus progestin.[2]
The mechanisms underlying the link between hormonal factors and asthma risk are still not clearly understood.[10] Knowing whether MHT affects this risk and if so, whether different preparations have a similar effect, would provide a useful insight into the mechanisms by which the hormonal milieu acts on the airways.
We used data from the E3N study, a large cohort of French women followed for over 10 years, to evaluate the association between asthma onset and MHT use with special focus on the types of MHT and the duration of use.

Methods

Study population: the E3N cohort

E3N, a prospective cohort initiated in 1990, consists of 98,995 French women born between 1925 and 1950 and insured under a health insurance plan covering mostly teachers. The study was approved by the French National Commission for Data Protection and Privacy. E3N is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC). Participants, who gave written informed consent, completed biennial self-administered questionnaires addressing medical history, menopausal status, and a variety of lifestyle characteristics.

Definition of incident cases of asthma

Women were considered incident cases of asthma if they stated at baseline (menopause) that they had never had an asthma attack and met the ATS criteria for asthma definition at follow-up ("Have you ever had asthma attacks?" and if yes “Was this diagnosis confirmed by a doctor?”),[11] with a coherent reported age of asthma-onset (time of first attack between baseline and 2002).

Identification of MHT use

Information on lifetime use of hormonal treatments was first recorded in the 1992 questionnaire. For each episode of treatment (defined as the non-stop use of the same hormonal brand or combination), brand name, age at initiation of use and duration were recorded. The information was updated in each of the subsequent questionnaires. The complete history of MHT use was established using data from all the questionnaires. MHT use was categorized by i) type of estrogen: weak estrogens (orally or vaginally administered promestriene or estriol) or estradiol compounds (unopposed MHT consisted almost exclusively of estradiol compounds; only 1.3% of women ever used conjugated equine estrogens (CEEs) corresponding to 8% of the total person years of follow up and ii) type of oral progestagen used in association with the estrogen: none, micronized progesterone, pregnane or norpregnane derivatives, and testosterone derivatives.

Body mass index

Body mass index (BMI) was calculated from the height and weight self-reported in each questionnaire. BMI was used in the different analyses as a continuous or categorical time-dependent variable. Information on anthropometric measurements provided by our questionnaire have been shown to be highly reliable.[12]

Other information

Information on tobacco smoking was reported in each questionnaire and respondents were categorized as never, past, regular or occasional smokers. The last two categories were combined into a "current smokers" category. Atopy was defined as present if the woman reported diagnosis of allergic rhinitis, eczema or any other allergic disease on the questionnaire prior to asthma 2002.

Population for analysis and follow-up

Our analysis was based on 57,664 postmenopausal women, corresponding to 495,448 person-years of follow-up. These women were free of asthma at inclusion and all subsequent self-reports of asthma onset were validated according to the ATS criteria. Subjects contributed person-time until the date of the first asthma attack or July 2002 (date of dispatch of the seventh questionnaire), whichever occurred first.

Figure 1 presents a diagram of the initial population, the reasons for exclusion and the population included in the analysis.

Statistical analysis

Hazard ratios (HRs) for asthma were estimated using Cox proportional hazards models, with age as the time scale. We adjusted our model for tobacco smoking and BMI included in the model as time-dependent[or time-varying] covariables , and for other risk factors. MHT use was included in the model as a time-dependent variable. A woman contributes to person year of ever use from the date she starts her treatment to the end of the follow up, contributes to person year of recent use from the date she starts her treatment to 1.5 years after she stops and contributes to person year of past user thereafter. This cutoff (1.5 years) was chosen because 65% of the cases occurring after cessation of MHT use did so within a year and a half of cessation. The reference group in each model consisted of women who indicated

that they had not used yet any MHT. Further analyses were conducted after stratification of the data by hysterectomy, type of menopause (surgical non surgical), smoking status as well as the atopic status of the women. All tests of statistical significance were two sided, and significance was set at the 0.05 level. All analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, North Carolina) (for further details of methods used, see the online supplement).

Results

Among the 57,664 women who reported being postmenopausal and had information on MHT use, there were 569 incident cases of asthma between 1992 and 2002, corresponding to an incidence of 1.15/1000 per year.

Never user of MHT accounted for 35.7% of the person-years, past users for 4.5%, recent users for 55.8%, and 4% did not provide information on duration of treatment. The mean age of ever users and never users at the start of follow-up was 52.25 years (SD=4.00) and 54.58 years (SD=4.74) ($p<0.0001$) respectively. Women excluded from the analysis were less likely to have used MHT or oral contraceptives, and were slightly older and had a larger BMI (chi2 test p-value <.001) than those included.

Table 1 presents the characteristics of ever users and never users of MHT included in the analysis. After adjusting for age, ever users were more likely to have a lower BMI ($p<0.001$) and to have ever used oral contraceptive ($p<0.0001$) than never users.

Surgical menopause was reported by 10% of the women. The use of estrogen alone was reported by 9.4% of the women with natural menopause and by 28.1% of the women with surgical menopause. Hysterectomy was reported by 19% of the women. Among women who had an hysterectomy 58% reported a natural menopause and 27% a surgical menopause (n=2986), 36% of these reported using estrogen alone (see online supplement).

The HR of asthma onset among women who had ever used MHT was 1.21 (95% CI 1.00-1.46) compared to never users after adjusting for age, smoking, BMI, oral contraceptive use, parity and total caloric intake (Table 2).

The HR Among recent MHT users the HR was 1.20 (95% CI 0.98-1.46), and was 1.16 (95% CI 0.86-1.57) among past users. Women who reported using MHT for less than 2 years had a HR of 1.25 (95% CI 1.02-1.53) and those who reported using MHT for two years or more a HR of 1.09 (95% CI 0.85-1.38), compared to never users (Table 2).

Estrogen alone was reported as the last treatment used by 11.2% of the women. These women were at higher risk of asthma onset (HR=1.54, 95% CI 1.13-2.09) compared to never users. The risk was not significantly increased among women who reported estrogen/progesterone (18.3%), a combination of estrogen and another progestagen (54.7%) or another MHT (15.8%) as the last treatment used. In subsequent analyses, users of any type of estrogen-progestagen were therefore combined into an “estrogen/progestagen users” category. The risk of asthma onset associated with the use of estrogen alone was significantly different from that associated with the use of estrogen/progestagen (test for homogeneity p=0.04). The route of estrogen administration (oral or transdermal) did not significantly affect the risk (Table 2).

For recent users of estrogen alone the HR of asthma onset was 1.67 (95% CI 1.20-2.27), while for past users it was 1.04 (95% CI 0.51-2.12). Among women who reported using estrogen alone for less than 2 years the HR was 1.60 (95% CI 1.12-2.27) while among those who reported using estrogen alone for 2 years or more the HR was 1.39 (95% CI 0.84-2.31). These HRs were non significantly different (test for homogeneity p=0.63). The route of administration of estrogens without progestagen did not affect the risk. Among women reporting the use of estrogen/progestagen there was no indication of an increase in the risk of asthma onset whatever the duration or recency of use or route of estrogen administration (Table 3).

Among never smokers, MHT use was significantly related to the risk of asthma onset (HR=1.45, 95% CI 1.10-1.90) while among smokers the HR was 1.02 (95% CI 0.79-

1.31) (test for interaction p=0.09) (see online supplement Table E1). Among women who reported using estrogen alone, the HR was 1.80 (95% CI 1.15-2.80) for never smokers and 1.31 (95% CI 0.85-2.03) for ever smokers (test for interaction p=0.37). Never smokers using estrogen/progestagen had a HR of 1.38 (95% CI 1.02-1.86), while no effect (HR=0.92, 95% CI 0.69-1.21) was observed in ever smokers (test for interaction p= 0.16) (Table 3).

Higher BMI was associated with an increased risk of asthma onset (p for trend <0.001) but there was no indication of an interaction between MHT use and BMI on the risk of asthma (p=0.45). Among women with a BMI less than 22 the HR of estrogen alone users was 1.25 (95% 0.65-2.40); among women with a BMI from 22 to 25, the HR was 1.67 (95% CI 0.93-3.01) and among women with BMI>25 the HR was 1.54 (0.99-2.39).

After stratification by the presence of hysterectomy or the type of menopause we observed a small increased risk in non hysterectomized women using estrogen alone and among women declaring a natural menopause , although the small number of cases in some of the subgroups limited the interpretation of the results (see online supplement tables E2 and E3)

Women who reported a diagnosis of allergic disease prior to asthma onset appeared to have a larger risk of asthma related to MHT than their counterpart.. An increased risk of asthma was present for the use of estrogen alone (HR = 1.86 (95% CI 1.18-2.93) and a marginal significant increase was observed for the use of estrogen/progestagens (HR=1.39 95% CI 1.01-1.91) in women with allergic disease as compared to women without allergic disease (Table 4).

Discussion

In this large prospective study of French women including 569 incident cases of asthma over 495,448 person-years, use of estrogen alone as last treatment was significantly associated with an increased risk of asthma onset in postmenopausal women, after adjustment for potential confounding factors. The increase in risk was mostly observed among women reporting an allergic disease prior to asthma onset

and never smokers. In these subgroups, the risk of asthma onset was strongly related to the use of estrogen alone and a marginal association was observed with the use of estrogen/progestagens.

Our results agree in part with other recent reports. In the Nurses' Health Study (NHS), MHT use was significantly related to the risk of asthma onset in postmenopausal women. However, a similar increased risk was reported for both estrogen alone and estrogen/ synthetic progestin. The effect was stronger in current users, and the risk diminished with time after cessation. In addition, an interaction was observed between MHT and BMI, with a larger risk of newly diagnosed asthma in lean women.[2]

In the cross-sectional Copenhagen City Heart Study, the prevalence of self-reported asthma was significantly related to MHT in non-smokers.[9] Two further recent cross-sectional studies reported an association between prevalent asthma and asthma-like symptoms with MHT use in women aged 46-54[7] and postmenopausal women,[8] but only in lean women. None of these cross-sectional studies provided information on the type of HRT used.

In our study, the increased risk of asthma onset among women using MHT was present only in users of estrogen alone. The effect was observed only in recent users including current users and women for whom time since last use was less than 1.5 years. Overall no increased risk was observed in users of estrogen/progestagen while a marginally significant increase was observed among women reporting a diagnostic of allergic disease prior to asthma onset and among non smokers.

Our study and the NHS are comparable in design, number of cases and person years of follow up. Results of both studies agree on the adverse effect of estrogen alone MHT; however we observed conflicting results with regards to estrogen/progesterone MHT in the overall analysis. The marginal increased risk observed in some subgroups of our population is difficult to compare given that no stratified data on smoking or allergic disease are presented in the report from the NHS.[2]

Several mechanisms have been proposed to explain the role of female hormones in asthma risk. However, there is still some uncertainty. Estrogen appears to have both anti- and pro-inflammatory effects, depending on criteria such as cell types, conditions in the milieu, estrogen concentration and the target organ.[13] While estrogen may have a pro-inflammatory effect regulating the response to allergens, it may also down-regulate the traffic of eosinophils to the lung during the effect or phase of the response to antigens.[14] It has also been shown that estrogen acts to down-regulate airway hyperresponsiveness in a dose-dependent manner and relatively rapid, nongenomic manner by enhancing the activity of endothelial nitric oxide synthase.[15] Several animal studies have reported increased susceptibility to allergic airway disease in female mice compared to male mice. Estrogens appear to exert most of their effects through estrogen receptors alpha and beta, both of which are present in the lung.[10] Ovariectomized rats developed less airway inflammation than controls and estrogen replacement re-established airway inflammation to the level found in intact females. A recent study suggested that female rats have fewer Treg cells and therefore less protection against inflammatory stimuli such as allergens.[16] Estrogen (estradiol) has also been shown to alter beta-2-adrenergic responsiveness[17] and to activate endothelial nitrite oxide synthase,[18] involved in the pathogenesis of asthma. Estrogen is capable of inhibiting the activity of 11β hydroxysteroid dehydrogenase type I isoenzyme; thereby reducing its ability to regenerate active cortisol from cortisone, and cortisol is an extremely powerful anti-inflammatory agent that may be protective against the development of chronic inflammation.[19] Finally, estrogen levels have been related to lower levels of adiponectin, a protein that is secreted exclusively by adipocytes, acts as insulin sensitizer and has anti-inflammatory properties.[20] This citokyne is inversely associated with fat mass and insulin resistance and has been proposed as a link between obesity and inflammation in humans.[21] Most likely several of these mechanisms and pathways play a role and interact with individual susceptibility.

Unopposed estrogens are used in women who have had a hysterectomy, and hysterectomy may lead to hormonal changes and respiratory morbidity, or alternatively a common underlying pathology may lead both to gynecological morbidity resulting in hysterectomy and to asthma.[8]In our data, among MHT never users, the HR of asthma onset associated with hysterectomy was 1.31 (95% CI 0.85-

2.01) suggesting that hysterectomy could not fully explain the increased risk observed among the estrogen users. Only 38.8% of women with hysterectomy reported using estrogen alone and the reason for hysterectomy was unknown. In stratified analyses by hysterectomy or type of menopause, there was no indication of differential effects of MHT in these subgroups.

We did not observe a clear increase in the risk of asthma onset with estrogen/progestagen treatment in contrast to the results of the Nurses´ Health study. In our population, a marginal increased risk was restricted to never smokers and women who reported a diagnostic of allergic disease prior to asthma onset . While we do not have a clear explanation for this, combined HT regimen have been shown to positively affect the lung functions of postmenopausal women while estrogen alone has no effect.[22] Progesterone has receptors in the lungs and trachea and can therefore have local effects at these sites and cause ventilatory stimulation via chemoreceptor activity.[23] In a rat model of allergic lung inflammation, estradiol increased the number of neutrophils, eosinophils, and mononuclear cells in the bronchoalveolar lavage of ovariectomized allergic rats, whereas progesterone induced an additional reduction. Degranulation of bronchial mast cells from ovariectomized rats was reduced after in vitro challenge, an effect reverted by estradiol but not by progesterone.[24] These authors suggest that intensity of allergic lung inflammation might be related to the estradiol-to-progesterone ratio at the time of immune sensitization and antigen challenge. Exogenous progesterone might also down-regulate beta2-adrenoceptors, which would explain part of the difference between MHTs.[17] A possible explanation for the difference of effect observed between the NHS and our study could be the difference in the type of progestorene used by Us and French women and /or the ratio of estrogen-to progesterone. In the US combined MHT uses mostly medroxyprogesterone acetate (MPA) while in our study this type of treatment represented only 10.2% of person years of FU. Micronized progesterone corresponding to 19.7% and other pregnane and norpregnane derivatives to 38.3%.

The association of MHT use with increased risk of asthma onset was more apparent among never smokers, as reported in other studies.[7, 9] This might be due to the anti-estrogenic effect of smoking[25] or to the difficulty of isolating the additional

effect of MHT among smokers. In contrast to other studies, we did not observe an interaction between BMI and MHT use.[2, 7, 8] An earlier analysis of our data found a significant association between BMI and the risk of asthma onset in both MHT ever users and never users.[6] The lack of interaction in our data might be due to the BMI distribution of our population, which was leaner than that of the Nurse's Health Study.

Women reporting a diagnostic of allergic disease prior to asthma onset had a higher risk of MHT related asthma than their counterpart. A crossectional study among English women Jarvis et al[8] reported that current use of HRT was related to wheeze but not related to markers of allergy (IgE). No data on atopic asthma was presented. Our data suggest that women with allergic predisposition might be more susceptible to the effect of MHT in developing asthma. However, these results should be interpreted with caution given the small number of cases in some subgroups and the potential misclassification of allergic disease based only on women's reports at baseline and in the follow up questionnaires.

The strengths of our study include the large number of postmenopausal incident cases of asthma. While we imputed age at menopause for some women with missing information (n=9,585), results remained similar when these women were excluded from the analysis. Information on current and past MHT use was updated every two years, decreasing the potential risk of misclassification of MHT. In our analysis, we used the information relating to the hormone therapy at the time of asthma onset. Fifty eight percent of women reporting the use of estrogen alone at the time of asthma onset or as last treatment before asthma onset had previously used another MHT. This supports our finding that the increased risk of asthma onset is linked to estrogen use. We also conducted additional analyses in which exposure was defined as exposure to the MHT with the longest duration of use. Results remained similar. For 80.5% of the women, the last treatment used was also the longest. In addition, most participants in the E3N cohort were teachers, with a high level of education and health-consciousness,[26] while the prospective design and high rate of follow-up of our study (3.8% lost to follow-up) minimized the possibility of recall bias or bias due to loss of follow-up.

Our definition of asthma met the ATS criteria, and there was a consistent reported date of asthma onset (time of first attack between 1990 and 2002). In addition, we conducted an analysis including as asthma cases only women who reported having asthma in at least two questionnaires (persistent asthma). Results were similar to those observed when all cases of asthma onset were included. Some women may suffer not from asthma but from chronic obstructive pulmonary disease (COPD). We did not measure pulmonary function so the possibility of COPD in older women, particularly ex- and current smokers, cannot be excluded. However, 51% of the cases were non-smokers and were therefore unlikely to have COPD. Furthermore, asthma risk was related to MHT use in non-smokers suggesting that neither smoking nor the misclassification of asthma as COPD could explain the association observed between MHT and asthma incidence. In the Nurses' Health Study, MHT was not related to newly diagnosed COPD.[2]

Our results could be biased if MHT users systematically reported more asthma attacks or if asthma was diagnosed more often in MHT users because of more frequent doctor visits. During the follow up, 93% of the MHT users had a mammogram versus 78% of the non users. However, our population had access to free medical care and there is no reason to believe that MHT users make more frequent medical visits than non-users for non gynecological related health issues.

In conclusion, our study shows an association between the use of estrogen alone as MHT and asthma onset in a large cohort of postmenopausal women. This effect might be linked to an increase in airway inflammation mediated by different pathways, such as inflammatory cytokine release or stimulation of NO synthesis. The increase in asthma risk associated with MHT must be judged in the light of all other health effects of MHT use taking including its beneficial effect on the quality of life of menopausal women.

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Table 1. Characteristics of the study population (n= 57,664), E3N cohort study.

	Never user of MHT N=16138	Ever user of MHT N=41526	p*
BMI (kg/m2)			
			<.0001
<20	1713 (10.72%)	5114 (12.26%)	
20 - 22	3299 (20.65%)	10363 (24.85%)	
22 - 22	5327 (33.35%)	15425 (36.99%)	
>25	5632 (35.28%)	10791 (25.90%)	
Tobacco use†			
			0.19
Never smoker	9601 (60.20%)	23023 (55.28%)	
Ex-smoker	4918 (30.83%)	14484 (34.78%)	
Current smoker	1429 (8.97%)	4134 (9.94%)	
Caloric intake (kcal/d) †			
			0.84
<1760	3393 (26.06%)	8196 (23.20%)	
1760 - 2112	3293 (25.29%)	8918 (25.25%)	
2112 - 2513	3167 (24.32%)	9128 (25.84%)	
>2513	3166 (24.33%)	9071 (25.71%)	
Pregnancy			
			0.06
Nulliparous	2293 (14.35%)	4574 (10.97%)	
<=2 children	8766 (54.88%)	25257 (60.57%)	
>2 children	4912 (30.77%)	11862 (28.46%)	
Oral contraceptive use			

			<.0001
Never	8269 (51.77%)	14562 (34.92%)	
Ever	7702 (48.23%)	27131 (65.08%)	
Menopausal status[†]			
			<.001
Natural	13213 (86.78%)	36593 (90.45%)	
Surgical	2013 (13.22%)	3862 (9.55%)	
			<.0001
Natural estrogen alone		3459 (67.48%)	
Surgical estrogen alone		1086 (21.19%)	

* p-value from age adjusted logistic regression for assessing differences between users and never users

[†] Missing data not shown (tobacco use 0.1% caloric intake 16.2%; menopausal status: 3.4%)

Table 2. Hormone therapy and asthma onset among postmenopausal women, E3N cohort study

	Cases	Person-year	Multivariate-adjusted* hazard ratio (95% CI)
Never use	186	177029	1
Use†	383	318419	1.21 (1.00 - 1.46)
Recency‡			
Recent	283	276506	1.20 (0.98 - 1.46)
Past	73	22294	1.16 (0.86 - 1.57)
Duration‡			
< 2 yrs	236	104607	1.25 (1.02 - 1.53)
2 + yrs	120	194193	1.09 (0.85 - 1.38)
Type of treatment‡			
Estrogen alone	55	33426	1.54 (1.13 - 2.09)
Estrogen-progesterone	67	58978	1.13 (0.85 - 1.51)
Estrogen-norPregnane derivate	52	54616	1.01 (0.74 - 1.38)
Estrogen-pregnane derivative§	103	89663	1.13 (0.88 - 1.46)
Estrogen-testosterone derivative	20	14882	1.36 (0.86 - 2.15)
Other‖	59	47235	1.22 (0.90 - 1.66)
Estrogen route**,‡			
Oral	88	65476	1.26 (0.97 - 1.65)
Transdermal	209	187794	1.15 (0.93 - 1.41)

* Adjusted for tobacco use (never smoker / current smoker / past smoker / missing information), BMI (kg/m2), ever use of oral contraceptive (yes / no), parity (nulliparous / 2 or fewer full term pregnancies / more than 2 full term pregnancies / no information), total caloric intake (kcal/day), type of menopause (natural / surgical / unknown), further stratified by year of birth ([1925-1929]/[1930-1934]/[1935-1939]/[1940-1944]/[1945-1950].

† Women whose age of start of MHT is missing are excluded.

‡ Women without any information other than age of start of MHT are excluded.

§ As part of Pregnane derivatives, dydrogeterone users (HR: 1.06 95% CI: 0.75 - 1.48) accounted for 41795 PY and 43 cases of asthma.

‖Tibolone, weak estrogen (unopposed or not), estrogen/testosterone, progestin only and unknown MHT.

** Combined or not with a progestagen. P for heterogeneity 0.45. Nasal estrogen, weak estrogen, other HT and unknown HT not shown

Table 3. Hormone therapy and asthma onset among postmenopausal women by type of treatment, E3N cohort study

*	Cases	Person-year	Multivariate adjusted† Hazard Ratio (95% CI)	Cases	Person-year	Multivariate-adjust hazard ratio (95%
		Estrogen alone			*Estrogen-Progestagens‡*	
Recency						
Recent	41	29035	1.67 (1.20 - 2.32)	208	210608	1.14 (0.92 - 1.40
Past	14	4391	1.04 (0.51 - 2.12)	34	7531	0.97 (0.64 - 1.46
Duration						
< 2 yrs	38	13760	1.60 (1.12 - 2.27)	159	67671	1.20 (0.96 - 1.50
2 + yrs	17	19666	1.39 (0.84 - 2.31)	83	150468	0.99 (0.76 - 1.30
Estrogen route§‡						
Oral	10	5367	1.78 (0.93 - 3.38)	78	59791	1.21 (0.92 - 1.60
Transdermal	45	28006	1.50 (1.07 - 2.09)	163	158263	1.08 (0.86 - 1.34
Smoking Status						
Never Smoker	28	31724	1.80 (1.15 - 2.80)	128	122585	1.38 (1.02 - 1.86
Ever smoker	27	14273	1.31 (0.85 - 2.03)	114	95342	0.92 (0.69 - 1.21

* Women without any information other than age of start of MHT are excluded.

† Adjusted for tobacco use (never smoker / current smoker / past smoker / missing information), BMI (kg/m^2), ever use of oral contraceptive (yes / no), parity (nulliparous / 2 or fewer full term pregnancies / more than 2 full term pregnancies / no information), total caloric intake (kcal/day), type of menopause (natural / surgical / unknown), further stratified by year of birth ([1925-1929]/[1930-1934]/[1935-1939]/[1940-1944]/[1945-1950].

‡ Progestagens include: progesterone, pregnane derivatives, norpregnane derivatives and testosterone derivatives.

§ Combined or not with a progestagen. Nasal estrogen, weak estrogen, other HT and unknown HT not shown

Table 4. Hormone therapy and asthma onset among postmenopausal women by atopic status, E3N cohort study

		Multivariate -adjusted†		Multivariate-adjusted†	
	PY	non atopic (306 cases)		atopic (251 cases)	
*		cases	HR 95%CI	cases	HR 95%CI
Never use	177029	114	1	67	1
Use	318419	192	1,04 (0,81 - 1,33)	184	1,52 (1,13 - 2,05
Recency					
Recent	276506	137	1,02 (0,79 - 1,33)	139	1,52 (1,11 - 2,07
Past	22294	41	1,04 (0,69 - 1,56)	32	1,42 (0,90 - 2,25
Duration					
< 2 yrs	104607	123	1,11 (0,84 - 1,45)	110	1,55 (1,12 - 2,13
2 + yrs	194193	55	0,88 (0,63 - 1,22)	61	1,42 (0,98 - 2,05
Type of treatment‡					
Estrogen alone	33426	29	1,43 (0,96 - 2,11)	25	1,86 (1,18 - 2,93
Estrogen-progestagens	218139	122	0,98 (0,75 - 1,28)	114	1,39 (1,01 - 1,91
Other□	47235	27	0,97 (0,64 - 1,47)	32	1,76 (1,16 - 2,68
Estrogen route§‡,					
Oral	65476	44	1,19 (0,84 - 1,69)	42	1,56 (1,05 - 2,33
Transdermal	187794	107	1,01 (0,77 - 1,33)	97	1,43 (1,04 - 1,97

*Women without any information other than age of start of MHT are excluded.

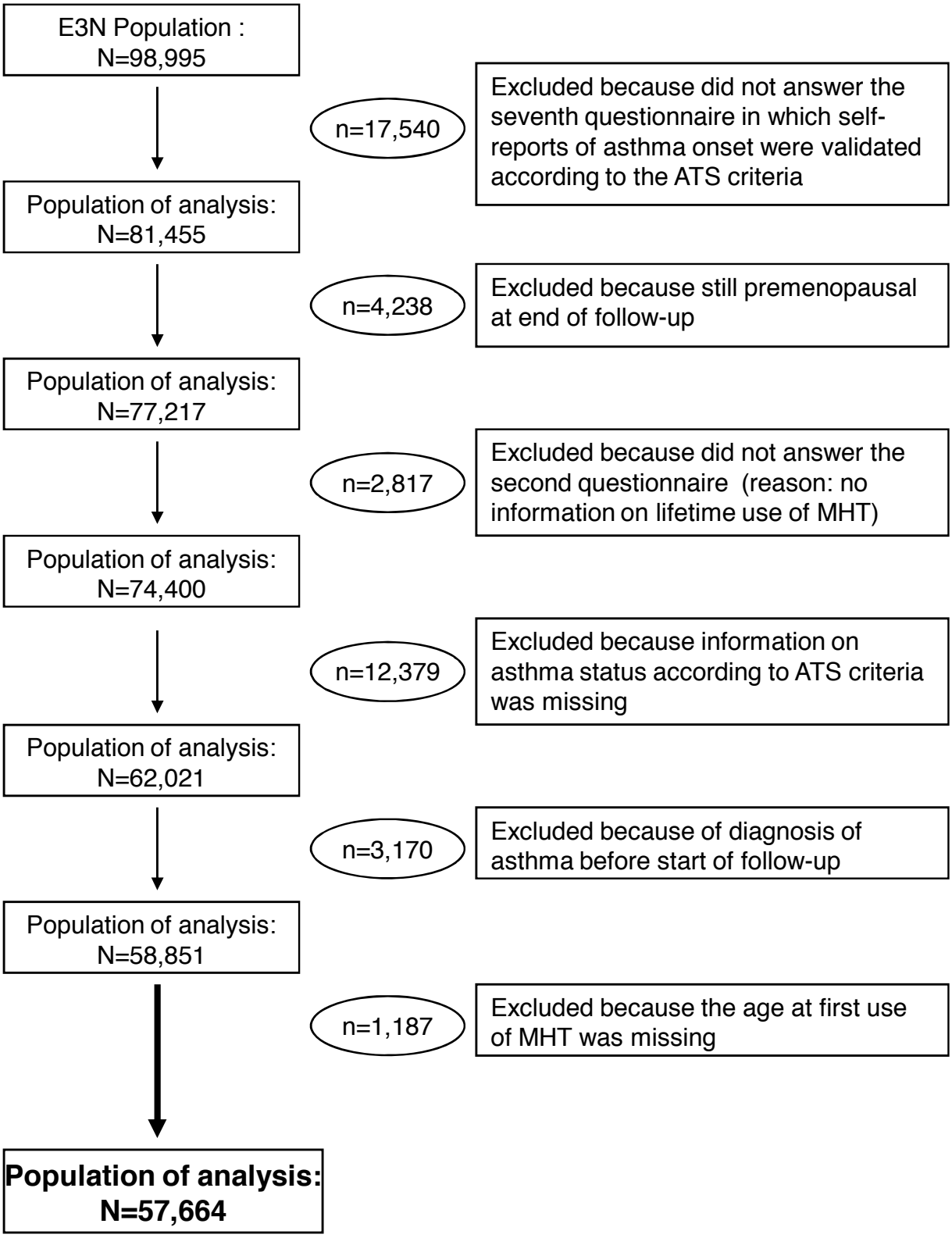
†Ajusted for tobacco use (never smoker / current smoker / past smoker / missing information), BMI (kg/m^2), ever use of oral contraceptive (yes / no), parity (nulliparous / 2 or fewer full term pregnancies / more than 2 full term pregnancies / no information), total caloric intake (kcal/day), type of menopause (natural / surgical / unknown), further stratified by year of birth ([1925-1929]/[1930-1934]/[1935-1939]/[1940-1944]/[1945-1950].

‡ Progestagens include: progesterone, pregnane derivatives, norpregnane derivatives and testosterone derivatives.

‖Tibolone, weak estrogen (unopposed or not), estrogen/testosterone, progestin only and unknown MHT.

§ Combined or not with a progestagen. Nasal estrogen, weak estrogen, other HT and unknown HT not shown

Figure 1. Diagram of the initial population, the reasons for exclusion and the population included in the analysis.


E3N Population : N=98,995
n=17,540
Excluded because did not answer the seventh questionnaire in which self-reports of asthma onset were validated according to the ATS criteria
Population of analysis: N=81,455
n=4,238
Excluded because still premenopausal at end of follow-up
Population of analysis: N=77,217
n=2,817
Excluded because did not answer the second questionnaire (reason: no information on lifetime use of MHT)
Population of analysis: N=74,400
n=12,379
Excluded because information on asthma status according to ATS criteria was missing
Population of analysis: N=62,021
n=3,170
Excluded because of diagnosis of asthma before start of follow-up
Population of analysis: N=58,851
n=1,187
Excluded because the age at first use of MHT was missing
Population of analysis: N=57,664