Original Article

Hormonal Contraceptives Are Associated With an Increase in Incidence of Asthma in Women

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What is already known about this topic? Exogenous female sex hormones including hormonal contraception and hormone replacement therapy are suggested to alter the incidence of asthma. However, the direction of the association remains uncertain.

What does this article add to our knowledge? Hormonal contraception in women is associated with a higher incidence of asthma in this nationwide study. This study adds to the evidence that exogenous female sex hormones may increase the incidence of asthma in women.

How does this study impact current management guidelines? In this study, first-time users of hormonal contraception had an increased incidence of asthma compared with nonusers. Clinicians and patients should, therefore, be aware that airway symptoms may develop following the initiation of hormonal contraception.

BACKGROUND: Use of exogenous female sex hormones is associated with the development of asthma, but the question of whether the effect is protective or harmful remains unresolved.
OBJECTIVE: To investigate whether initiation of hormonal contraceptive (HC) treatment was associated with development of asthma.
METHODS: We performed a register-based, exposure-matched cohort study including women who initiated HC treatment of any kind between 10 and 40 years of age and compared the incidence of asthma with women who did not initiate HCs. Asthma was defined as 2 redeemed prescriptions of inhaled corticosteroids within 2 years. Data were analyzed using Cox regression models adjusted for income and urbanization.
RESULTS: We included 184,046 women with a mean age of 15.5 years (SD 1.5 y), in which 30,669 initiated HC treatment and 153,377 did not. We found that initiation of HCs was associated with an increased hazard ratio (HR) of developing new asthma by 1.78 (95% CI 1.58−2.00; $P < .001$). The cumulative risk of new asthma was 2.7% after 3 years among users of HCs compared with 1.5% in nonusers. In the different subtypes of HCs, second- and third-generation contraceptives carried significant associations (second-generation HR 1.76; 95% CI 1.52−2.03; $P < .001$; third-generation HR 1.62 95% CI 1.23−2.12; $P < .001$). The association with increased incidence was seen only in women younger than 18 years.

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Abbreviations used
HC- Hormonal contraceptive
HR- Hazard ratio
ICD-10- International Classification of Diseases, Tenth Revision
ICS- Inhaled corticosteroids
IL- Interleukin

CONCLUSIONS: In this study, first-time users of HCs had an increased incidence of asthma compared with nonusers. Clinicians prescribing HCs should be aware that airway symptoms may develop. **(J Allergy Clin Immunol Pract 2023;11:2484-90)**

Key Words: *Asthma; Estrogen; Gestagen; Hormonal contraceptives; Side effects; Cohort study*

INTRODUCTION

Hormonal contraceptives (HCs) are annually prescribed to millions of young, healthy women worldwide—mainly as birth control or to relieve dysmenorrhea and menorrhagia.[1,2] Before puberty, asthma is more common among boys, but around puberty, there is a shift toward asthma being more common in girls.[3] Interestingly, this correlates well with the typical timing of initiation of HCs, which are used by up to 85% of the female population before the age of 20 years.[4] Hormonal contraceptives are increasingly linked to development and modulation of the pathology in asthma, but the current body of evidence has failed to determine whether HCs should be considered protective or harmful in respiratory disease.[5] To complicate the matter further, hormonal treatment in women includes several different substances and formulations that have potentially different effects on the risk of developing asthma.[4,6-8] Recent observational studies have suggested that HCs protect against asthma exacerbations and lower the incidence of asthma.[7-9] In contrast, other researchers have shown that HCs are associated with increased prevalence of asthma.[10-12] The mechanistic pathways for female sex hormones to affect the airways are yet to be fully understood, but mechanistic mice studies have suggested that estrogen can reduce airway hyperresponsiveness.[13] Contradictory to lowering of airway hyperresponsiveness, female sex hormones have also been shown to upregulate interleukin-17 which is suspected to be a significant inflammatory pathway of severe asthma.[14,15] Because medication for asthma and HCs are so commonly prescribed, the impact of potential effects—harmful or protective—are of great public interest.[4] Therefore, we sought to investigate the association between first-time use of HCs (and the subtypes of HCs) and the incidence of asthma in a large cohort of young Danish women.

Material and methods

We performed an exposure-density matched cohort study of first-time users of HCs based on the Danish registers. The aim was to determine whether HCs and its subtypes, were associated with an increased incidence of asthma in young women. The study was reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.[16]

Data sources and ethics. We used the data from the Danish registers, which have been described in detail previously.[17] The Danish National Patient Register contains data on all admissions in Denmark since 1978 in accordance with the International Classification of Diseases, Tenth Revision (ICD-10), described by the World Health Organization.[17] Further, the Danish National Prescription Registry holds information on all prescriptions filled from Danish pharmacies since 1995 by use of the Anatomical Therapeutic Chemical System codes.[18] The Danish birth registry holds information on all births from 1973 from which date of pregnancy was estimated.[19] Information about income statistics was retrieved from the Danish Income Register, which is based on the Danish tax registration. In Denmark, research into the registries does not require approval from the ethics committee. The first author (E.S.H.H.) vouches for the integrity of the data and the accuracy of the analysis.

Study population. We included all women without asthma who were first-time users of HCs between the ages of 10 and 40 years. Women were sampled from January 1, 2008 until December 31, 2017. Women exposed to HCs were subsequently matched with 5 women without asthma who had not yet initiated HC treatment. The event of interest was the development of new asthma. Women were censored from the cohort at pregnancy, emigration, death, end of treatment with HCs, or at the end of the study (December 12, 2017), whichever came first. The date of initiation of HC treatment for the exposed woman was the index date for her and the 5 matched controls in her risk set. In the event of an unexposed woman filling a prescription for HCs, she, and her complete risk set, was censored from the study at the date of initiation of HCs.

Asthma diagnosis. We defined new asthma as 2 redeemed prescriptions of inhaled corticosteroids (ICS) within 2 years without previous filled prescriptions, or by registration of an ICD-10 code of J45 from an admission or a visit to an outpatient clinic without previous filled prescriptions.[20] For women diagnosed by filled prescriptions, the date for asthma onset was the date of filling the second prescription. Women with prescriptions of ICS before the index date or an ICD-10 code indicating asthma were excluded from the study.

Hormonal contraceptives. Hormonal contraceptives (Anatomical Therapeutic Chemical System codes G03A) included both combined HC methods with estrogen and progestin (second- to fourth-generation oral pills, transdermal patches, vaginal rings, or older orally administered HCs) and progestin-only methods (intrauterine devices, oral pills, injections, and subdermal implants). We did not include emergency contraceptives (G03AD). The use of HCs was estimated through filled prescriptions, and duration of use was determined by the amount of daily dose purchased. In Denmark, it is only possible to receive HC by filling a prescription and thus being registered in the register. The only exceptions are intrauterine devices that, under certain conditions, can be administered in the hospital or by a gynecologist without a previous prescription. When a filled prescription was estimated to be finished, a study participant was considered to initiate a pause in treatment. Treatment pauses of 90 days or a change in treatment was considered as termination of treatment.

Covariates. Based on the index year, we included information on household income, urbanization, and region of living. Household income was divided into quartiles (lowest, second lowest, second highest, and highest). Urbanization was divided

into densely populated, intermediate populated, and thinly populated. Regions in Denmark were divided into the 5 regions (Capital Region, Southern Denmark, Northern Jutland, Zealand, and Middle Jutland). Covariates were included in models based on previous research that have shown associations between both exposure and outcome. Urbanization and region were considered correlated and, thus, only urbanization was included in the model whereas region served as a descriptive variable.

Statistical considerations and matching. We used exposure-density matching to match women exposed to HCs to women who were not exposed. The matching algorithm was based on risk-set sampling techniques as described by Langholz and Goldstein in 1996.[21] We matched every exposed woman with 5 unexposed women born the same year.

We analyzed whether initiation of HCs increased the hazard for new asthma development by fitting Cox regression models for overall HC use. Further, we divided the women into subgroups based on what type of HCs they initiated and estimated hazard ratios (HRs) for these as well. All models were adjusted for age, household income, and urbanization/region. Covariates used for adjustment of the models were defined using a directed acyclic graph[22] (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org), and weight gain was considered a mediating variable because HCs are suspected to affect weight and obesity can influence asthma.[23,24]

In addition, we estimated the cumulative risk of new asthma development during the first 3 years after treatment initiation (index date) using the Aalen-Johansen estimator. This was to account for multiple competing risks and informative censoring. To assess whether the cumulative risk of new asthma onset varied according to age, cumulative risk of developing asthma was also estimated for subgroups according to age (age groups 10−13, 14−17, and ≥18). The significance level was set at 5% for all analyses.

To account for cases in which a woman might have initiated HCs and experienced airway symptoms and subsequently terminated treatment with HCs before a second prescription of asthma medication was filled, we performed sensitivity analyses in which 1 prescription of ICS was sufficient for diagnosis.

All analyses were performed using RStudio with R version 3.6.1 (www.r-project.org).

RESULTS

We included a total of 184,046 women of whom 30,669 were treated with HCs and 153,377 were not (Table I and Figure E2; available in this article's Online Repository at www.jaci-inpractice.org). The mean age of HC initiation was 15.6 years (SD 1.42 y). Women initiating HCs were more likely to come from families with higher incomes and to live in densely populated areas than women not on HCs. The included women were on average followed for 763 days. Total follow-up time in the population was 384,949 person years.

The most common types of HCs prescribed to first users of contraception (for any indication) were the second- and third-generation oral pills, both of which are combined HC methods (second-generation 83% and third-generation 12%) (Table E1; available in this article's Online Repository at www.jaci-inpractice.org). The mean length of HC treatment was 1,050 days (SD 836 d). Only a few women (<5%) were treated with other types of HCs as first-time contraception.

TABLE I. Characteristics of study population*

Characteristics	No HCs (n = 153,377)	HCs (n = 30,669)
Age (y), mean (SD)	15.5 (1.51)	15.6 (1.42)
Age groups (y)		
10−13	15,439 (10.1)	2,640 (8.6)
14−17	134,238 (87.5)	27,279 (88.9)
≥18	3,700 (2.4)	750 (2.4)
Household income		
Lowest quartile	40,120 (26.2)	5,897 (19.2)
Second quartile	37,986 (24.8)	8,020 (26.2)
Third quartile	41,631 (27.1)	9,696 (31.6)
Highest quartile	33,640 (21.9)	7,056 (23.0)
Type of populated area		
Densely populated	45,958 (30.0)	6,945 (22.6)
Intermediate populated	53,512 (34.9)	11,058 (36.1)
Thinly populated	53,907 (35.1)	12,666 (41.3)
Region		
Capital	45,910 (29.9)	6,986 (22.8)
Middle Jutland	36,699 (23.9)	7,164 (23.4)
Northern Jutland	15,128 (9.9)	3,494 (11.4)
Zealand	22,474 (14.7)	5,683 (18.5)
Southern Denmark	33,166 (21.6)	7,342 (23.9)
HCs		
No HCs	153,377 (100)	0 (0)
Combined HCs		
Second-generation oral pill	0 (0)	22,566 (73.6)
Third-generation oral pill	0 (0)	3,923 (12.8)
Fourth-generation oral pill	0 (0)	767 (2.5)
Other†	0 (0)	952 (3.1)
Progestin-only methods		
Levonorgestrel IUD	0 (0)	266 (0.9)
Oral pills	0 (0)	1,485 (4.8)
Other progestin-only methods‡	0 (0)	710 (2.3)

IUD, Intrauterine device.
*Values are number (%) unless otherwise stated.
†Includes transdermal patches and vaginal rings.
‡Includes subdermal implants and injectables.

After adjusting for urbanization and household income, we found that women who initiated HC treatment of any kind were more likely to initiate treatment for asthma following initiation of HCs (HR 1.78; 95% CI 1.58−2.00; $P < .001$). Unadjusted estimates were similar (HR 1.76; 95% CI 1.56−1.98; $P < .001$). The cumulative risk of initiating treatment for asthma after 3 years was 2.7% among users of HCs compared with 1.5% in nonusers (Figure 1). Sensitivity analysis with a more sensitive cut-off for asthma diagnosis (1 filled prescription) showed a higher cumulative risk of asthma in both groups (4.0% vs 2.4%; Figure E3; available in this article's Online Repository at www.jaci-inpractice.org).

We examined the incidence of initiating treatment for asthma following initiation of the different subtypes of HCs. We found that, among the combined HC methods (estrogen + progestin), second- and third-generation oral pills were significantly associated with an increased HR of initiating daily treatment for asthma (second-generation HR 1.73; 95% CI 1.47−2.04; $P < .001$ and third-generation HR 1.50; 95% CI 1.04−2.17; $P < .001$; Figure 2), whereas fourth-generation did not reach

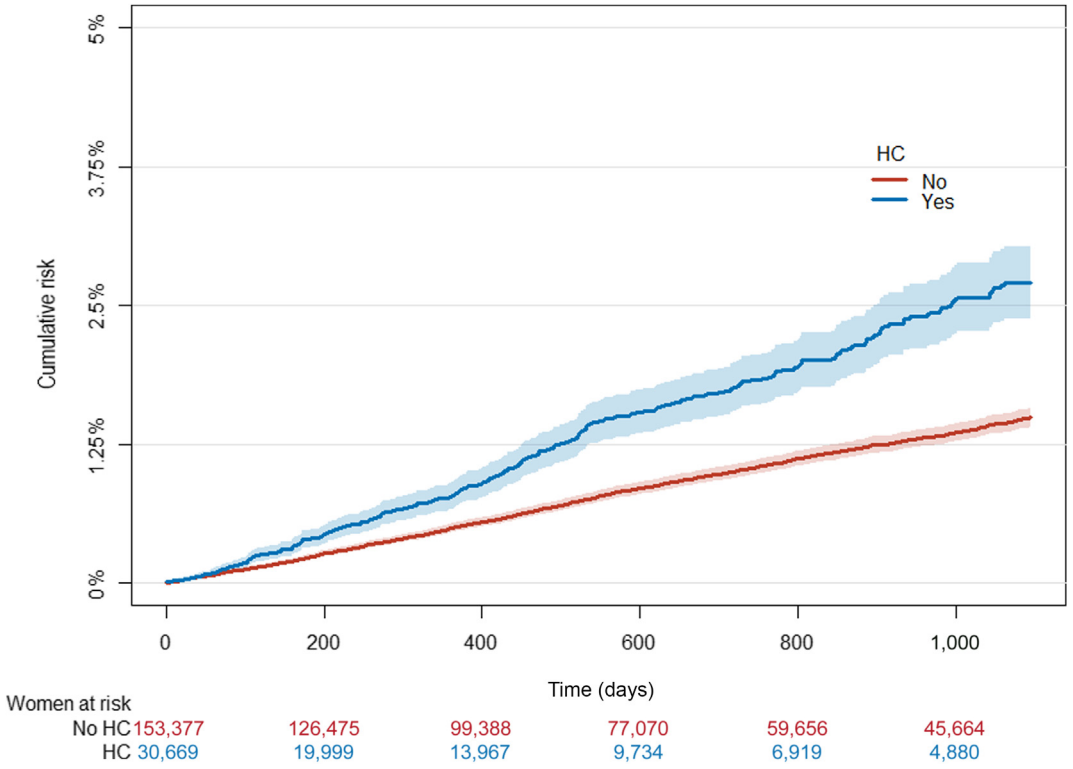

FIGURE 1. Incidence of asthma following initiation of HC treatment. Cumulative risk of developing new asthma among young women in the first 3 years following initiation of HCs.

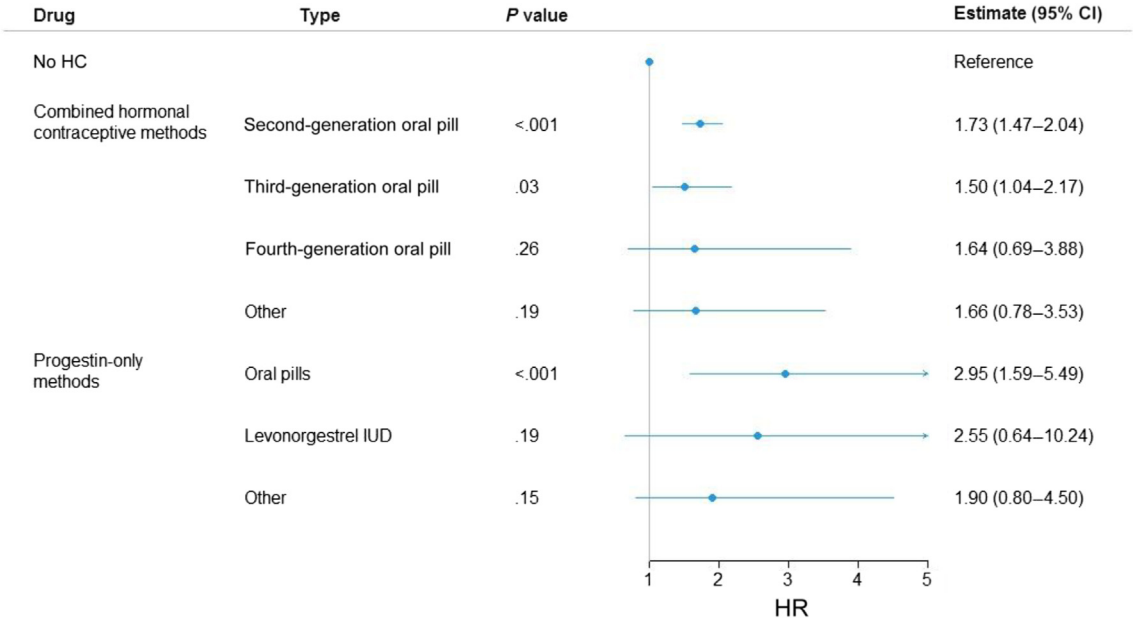

FIGURE 2. HRs of asthma by type of HC treatment. HRs of initiating treatment for asthma according to type of HC. First, all types of combined HCs are described. Second, all progestin-only methods are described. The most common HCs were the second-generation oral pills (HR 1.73; $P < .001$), a combined HC method. *IUD,* Intrauterine device.

significance. Among progestin-only methods, only oral pills were associated with a significantly increased HR (2.95; 95% CI 1.59−5.49; $P < .001$).

Mean age of initiation of HCs was 15.5 years and 88% initiated HCs between 14 and 17 years of age (Table I). We found that women who initiated HCs between younger than 18

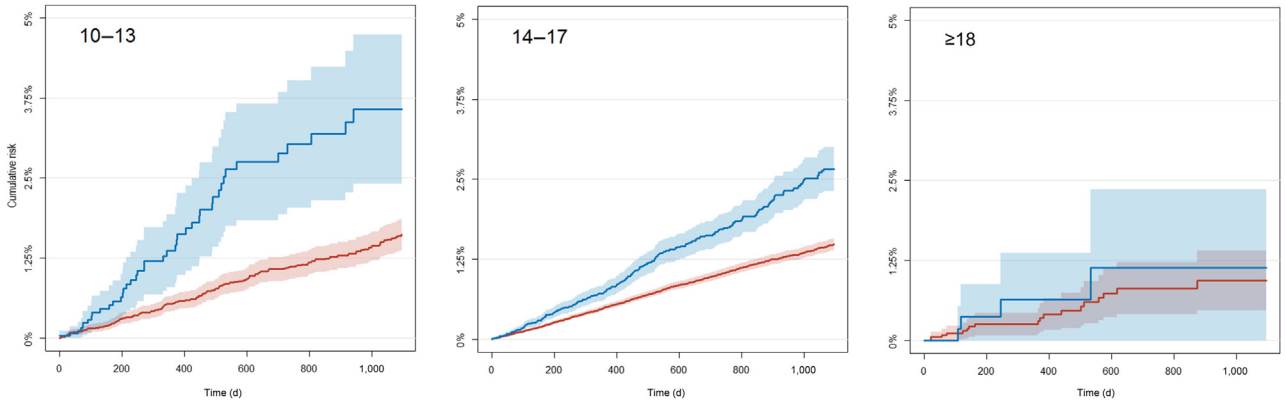

FIGURE 3. Incidence of asthma following initiation of HC treatment in different age groups. The cumulative risk of initiating treatment for asthma in different age groups (10–13 y [n_{HC} = 2,640; $n_{non\text{-}HC}$ = 15,439]; 14–17 y [n_{HC} = 27,279; $n_{non\text{-}HC}$ = 134,238]; and ≥ 18 y [n_{HC} = 750; $n_{non\text{-}HC}$ = 3,700]) in the first 3 years following initiation of HCs. Analyses showed significant differences between the groups among 10–13 year olds, and 14–17 year olds, but not among women aged 18 years or older. n_{HC}, number of women taking hormonal contraceptives; $n_{non\text{-}HC}$, number of women not exposed to hormonal contraceptives.

TABLE II. HRs for initiating treatment for asthma in the different age groups*

Age groups (y)	n_{HC}	$n_{non\text{-}HC}$	HR	95% CI	*P* value
10–13	2,640	15,439	2.16	1.47–3.20	<.001
14–17	27,279	134,238	1.71	1.50–1.95	<.001
≥18	750	3,700	1.34	0.37–4.80	.66

n_{HC}, number of women taking hormonal contraceptives; $n_{non\text{-}HC}$, number of women not exposed to hormonal contraceptives.
*Results from independent, multivariable Cox proportional hazards model adjusted for household income and urbanization.

years had a significantly increased HR of developing new asthma (Figure 3 and Table II). The cumulative risk of developing asthma among users of HCs compared with nonusers was 3.6% (95% CI 2.4–4.7) versus 1.6% (95% CI 1.4–1.9) in 10 to 13 year olds; 2.7% (95% CI 2.3–3.0) versus 1.5% (95% CI 1.4–1.6) in 14 to 18 year olds and 1.1% (95% CI 0.0–2.4) versus 0.9% (95% CI 0.0–1.4) in women 18 years or older.

DISCUSSION

In this large, population-based study, we found that initiation of exogenous female sex hormones was associated with an increased hazard of initiating asthma among women younger than 18 years. Further, the cumulative risk of initiating treatment for asthma was significantly increased within the first 3 years. Second- and third-generation HC pills carried the most statistically significant association with new-onset asthma, which were also the most used types of HC. Lastly, we also found that progestin-only oral pills were significantly associated with the development of new asthma.

We found that HCs increased the cumulative risk of treatment for asthma (2.7% vs 1.5%). Even though the absolute difference in percent is small, on a population level, this can amount to numerous new cases. That is why it is critical that this association is investigated further. It is interesting that this study points to an increased risk of asthma after initiating HCs. Especially because a recent cohort study by Nwaru and colleagues[7,8] has found that HCs might decrease the risk of new asthma and asthma exacerbations. The difference in results could be explained by different cohorts and questions addressed. Nwaru and colleagues[7,8] used the Optimum Care Database in the United Kingdom, which is a large database comprising patients from general practitioners. Our cohort is sampled from the complete Danish population that, at least in theory, should protect from this particular selection bias. Further, we investigated first-time use and not overall use, which makes the studies different. We speculate that, in the study from the United Kingdom, HCs might be an indicator of good health and that their sample population is compared with a generally more ill population, whereas our sample population is compared with all women in Denmark, regardless of visits to general physicians, hospitals, or other types of medical care. These conflicting results clearly indicate the necessity of clinical investigation into the effect of HC and other hormonal substances on the airways.

We found that second- and third-generation oral pills (estrogen + progestin) were associated with increased incidence of asthma. This is interesting because combined hormonal treatments earlier have been found potentially harmful among menopausal women receiving hormone replacement therapy[6] and might indicate that the effect is unidirectional regardless of age. However, in this study, we only found an association in women younger than 18 years, which makes the data more ambiguous. Explanations could be that only few women initiate HCs after the age of 18 years or that initiation of HC treatment is an indicator of early menarche, which previously has been shown to be a risk factor for development of asthma.[3] It could also be that the study is limited owing to confounding by indication, and despite our efforts to account for possible confounders, there are other factors like lifestyle or health conditions that could affect the outcome. Nevertheless, this provides us with potential confounders for our model and this should be addressed in future prospective studies.

We found that progestin-only pills were associated with development of asthma. This was surprising because recent evidence have shown that both menopausal, progestin-only hormonal therapy and progestin-only HCs are associated with a

decreased risk of asthma.[6,7] This correlation should be investigated further both among young and adult women.

Our study is limited by its observational nature and estimates should be interpreted with caution. There might be residual confounding that was not accounted for. Two potentials confounders are obesity and weight gain. A previous study has suggested that HCs have a protective effect on asthma incidence in nonobese women while having a harmful effect in obese women.[11] Further, a commonly discussed side effect of HCs and other estrogens is weight gain.[23] Thus, weight and weight gain might be mediating variables in this possible causal relationship between HCs and asthma. Weight status before and after initiation of HCs of included participants would have been helpful to clarify this. We propose that clinical studies in women should investigate airway hyperresponsiveness and other asthma-related outcomes before and after HCs, or other exogenous female sex hormones to determine whether there is a relationship and its possible dependency of weight status. A further limitation in this study is the definition of asthma. Whereas our definition of 2 prescriptions of ICS is specific, it does not capture those patients only prescribed a short-acting beta-agonist. Thus, our study's findings are only applicable to an asthma population that has filled at least 2 prescriptions of ICS within a 2-year period, making the extrapolation of these results challenging. Further, there could be women in both groups who are subject to misclassification bias owing to wrongful diagnosis of asthma or not being investigated for asthma. However, we believe that this bias is nondifferential and affects both groups equally. Lastly, it would have been useful to have accurate data on whether the women in the study were treated for allergy. Unfortunately, most medications used for the treatment of allergy in Denmark, including antihistamines and nasal steroids, are sold over the counter. Therefore, to avoid misinterpretation of inaccurate data, we have not included assumed allergy status in our analyses. Future clinical studies investigating this relationship should include objective measurements of allergy such as a skin prick test or specific immunoglobulin E.

if exogenous female sex hormones are partly responsible for the development of new asthma, it is logical to assume that it also affects current asthma. Estrogen is shown to upregulate interleukin-17A (IL-17A), a component in the inflammatory pathway in severe non−type 2 asthma, for which there are very limited treatment options.[14,25,26] Furthermore, others have shown that estrogen can upregulate IL-13 and IL-4, which are related to type 2 airway inflammation.[27] It is, therefore, imperative that this relationship is investigated further—especially because most patients with severe asthma are women.[28,29]

CONCLUSIONS

In conclusion, HC treatment is clearly associated with an increase in asthma incidence in women younger than 18 years. Reports of any airway symptoms following initiation of HCs should lead to a clinical evaluation of whether the perceived symptoms could be the onset of asthma or a manifestation of asthma symptoms. Further studies are needed, and they should clinically and prospectively evaluate whether HCs trigger harmful reactions in the airways.

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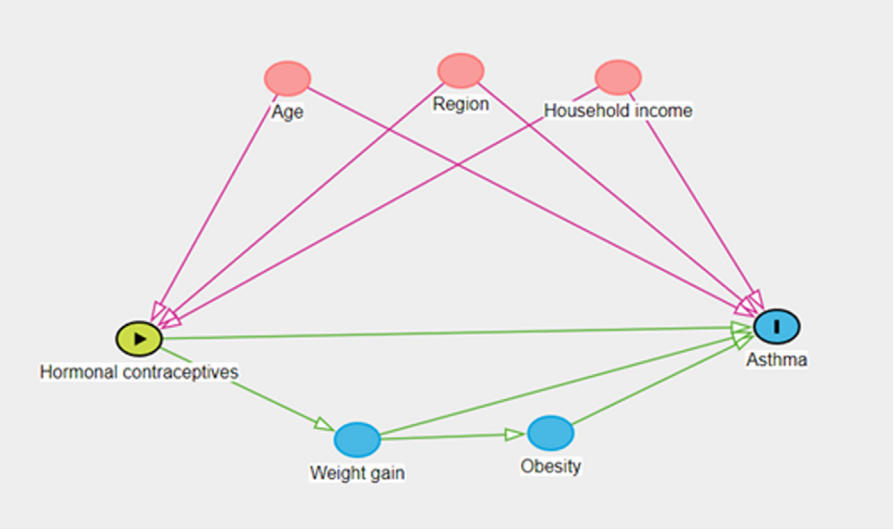

FIGURE E1. Directed acyclic graph produced using www.dagitty.net. The outcome of interest is asthma and the exposure of interest is hormonal contraceptives. Red indicates potential confounders, and blue represents mediating variables. Using this approach, we found that to minimize sufficient adjustment should include household income, region, and age.

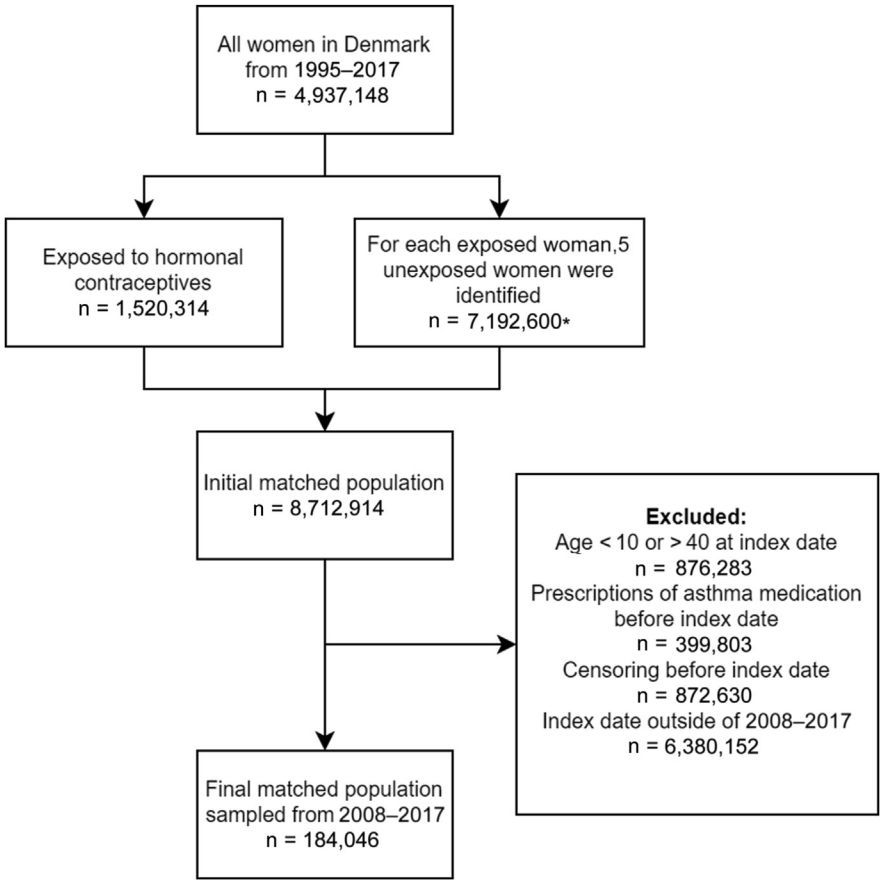

FIGURE E2. Overview of inclusion and matching process. Visualization of the steps to arrive at the final matched population. First, all women in Denmark between 1995 and 2017 were identified. They were given dates for first initiation of hormonal contraceptives, treatment of asthma, and birth year. Second, women exposed to hormonal contraceptives were matched with women, at the time, unexposed to hormonal contraceptives. Third, from the initial matched population, we excluded complete risk-sets (1 exposed woman and her 5 unexposed matched controls) if they were younger than 10 years or older than 40 years at the index date; if their index date was before 2008; or if they had been prescribed medication for asthma or hormonal contraceptives in the period before. The reason to exclude women with index date before 2008 was that the regional system in Denmark was changed to a new system. Finally, we ended up with a matched population with complete information on birth year, household income, region/urbanization, and age. *A woman could be used as control more than once.

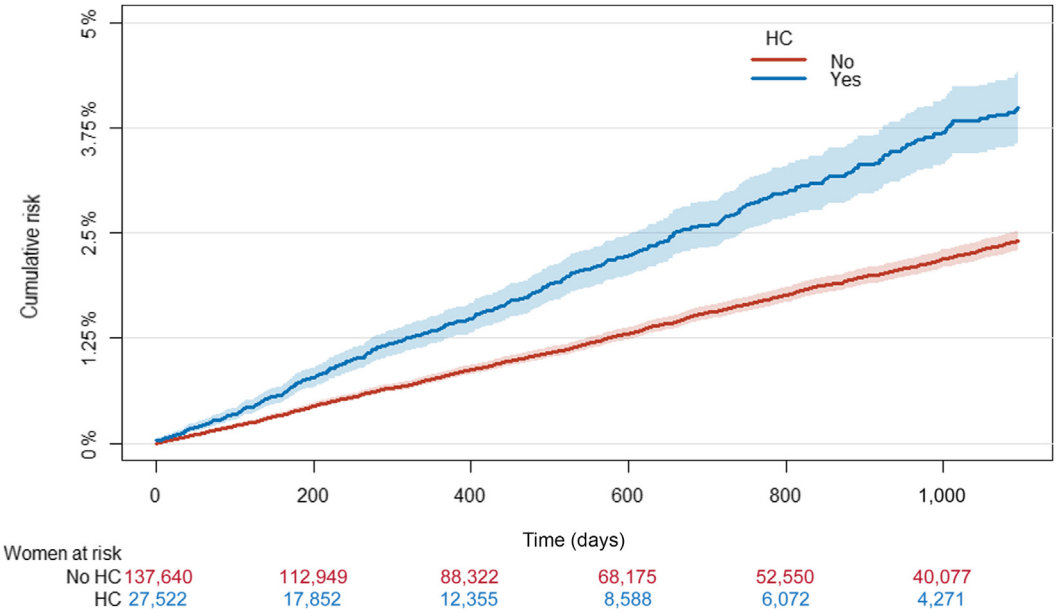

FIGURE E3. One filled prescription as definition of asthma. Sensitivity analysis using 1 prescription instead of 2 prescriptions of inhaled corticosteroids (ICS) as the definition for asthma. This shows a larger difference between the groups and a higher incidence of asthma in both groups and confirms our suspicion of an association between hormonal therapies and asthma. Further, it strengthens our hypothesis because the difference is larger than the original analyses. Cumulative risk in users of hormonal contraceptives (HCs) 4.0% vs 2.4% in nonusers.

TABLE E1. HC treatment by age group

	Age groups (y)		
Type of HC	10–13 (n = 2,640)	14–17 (n = 27,279)	≥18 (n = 750)
Second-generation oral pill	64%	74%	79%
Third-generation oral pill	17%	12%	7%
Fourth-generation oral pill	4%	2%	1%
Other combinations	4%	3%	4%
Levonorgestrel IUD	<1%	<1%	3%
Progestin-only oral pills	6%	5%	6%
Other progestin-only methods	4%	2%	1%

HC, Hormonal contraceptive; *IUD,* intrauterine device.