



Hormonal contraception increases risk of asthma among obese but decreases it among nonobese subjects: a prospective, population-based cohort study

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ABSTRACT Epidemiological data on asthma suggest a sex difference that varies with age. Hormonal effects have been suggested as a possible explanation for these differences but there is a scarcity of evidence on these relationships. Our objective was to examine the relationship between reproductive factors and asthma risk among females and to examine whether body mass index (BMI) modifies this relationship.

Female participants in the 2004 fifth decade follow-up postal survey of the Tasmanian Longitudinal Health Study formed the study population. Reproductive history and data on hormonal contraceptive (HC) use were collected on 2764 females. Multiple logistic regression was used to assess the association between the reproductive factors and current asthma.

The mean age of participants was 43 years and the prevalence of middle-aged current asthma was 12.8%. Females with very early menarche (≤ 10 years) had higher odds of middle-aged current asthma (OR 1.91, 95% CI 1.14–3.2). Pregnancy history (number of births and age at first pregnancy) were not associated with current asthma risk at 44 years. Ever having used HCs, years of use and age started using HCs were not individually associated with current asthma risk. However, body mass index significantly modified the relationship between HC use and asthma. We found increasing years of pill use was associated with a significantly increased risk of current asthma in overweight/obese women but a reduced risk in normal weight women (interaction $p=0.015$).

Hormonal effects from use of HCs and early menarche may contribute to the sex differential in asthma risk. Our findings suggest that in obese women with a history of long-term HC use may be at an increased risk of chronic respiratory disease, and regular monitoring for asthma and asthma symptoms may be recommended.



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This article has supplementary material available from openres.ersjournals.com

Received: May 14 2015 | Accepted after revision: Sept 14 2015

Support statement: This study was funded by The National Health and Medical Research Council (NHMRC) of Australia, LEW Carty Charitable Fund, Clifford Craig Medical Research Trust of Tasmania, The Asthma Foundation of Victoria and Asthma Foundation of Tasmania. M.C. Matheson, S.C. Dharmage, A.J. Lowe, J.A. Burgess and E.H. Walters were supported by the NHMRC. M.Y.Z. Lau was supported by a Marjory Edwards OAM PhD Scholarship from Asthma Australia.

Conflict of interest: Disclosures can be found alongside this article at openres.ersjournals.com

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Introduction

Asthma prevalence and incidence vary by sex over the life span. Childhood asthma is more common in boys but around puberty, the prevalence/incidence switches to be higher in girls [1, 2]. This continues into adult life, with women having higher asthma prevalence than men [3]. Women also report worse symptoms and a greater effect on quality of life [4]. The reasons for these sex reversals are not well understood. Animal and human studies suggest that female sex hormones may play an important role. It is thought that these hormones can affect lung inflammation, airway smooth muscle and the function of the immune system [5, 6]. In addition, an interaction between these hormones and obesity has been reported [7–9].

Marked changes in female sex hormones result from menarche, pregnancy, use of hormonal contraceptives (HCs), use of hormone replacement therapy and the menopause. Many of these factors have been linked to asthma risk [8, 10–12], but have tended to be investigated in isolation without taking into account the possible confounding effects of each other. Furthermore, while there is evidence that the association between obesity and asthma is seen mainly among females, most studies have not taken into account the possibility of interaction between hormonal effects and obesity. Obesity has been identified as part of an asthma phenotype characterised by later disease onset and a higher proportion of females [13]. Both cross-sectional and longitudinal studies have reported a higher incidence of asthma or wheeze in overweight and obese females compared to normal weight females [9, 14, 15].

Very few studies have examined the joint effects of reproductive factors and obesity on asthma outcomes, despite the observed links between them. Hence, the aim of this study was to investigate several reproductive factors (specifically age at menarche, HC use and number of pregnancies), and identify any interaction between these factors and body mass index (BMI) on asthma risk. We used data on women from the Tasmanian Longitudinal Health Study (TAHS) who were perimenopausal at the time of survey.

Methods

Tasmanian Longitudinal Health Study

The methods of the baseline study and subsequent follow-up have been published elsewhere [16, 17]. In brief, TAHS began in 1968 when 8583 Tasmanian children (probands) born in 1961 and attending school in Tasmania were enrolled. Parents completed a respiratory health questionnaire for their child, who then underwent a clinical examination and lung function measurements. Follow-up surveys were completed in 1974, 1979 and 1992 at the ages of 13, 18 and 31 years, respectively. The most recent follow-up study started in 2002 when probands were in their fifth decade of life. Overall response rates for tracing and the postal survey have been reported previously [18]. This analysis was restricted to the female respondents, for whom we traced 3510 (83.8%) of the original 1968 cohort to an address and achieved a response to a postal survey from 2776 (80.7%). The 2004 follow-up study was approved by the Human Research Ethics Committee of the University of Melbourne, Melbourne, Australia (HREC number 010626X). All participants provided written informed consent.

Outcome definitions

“Current asthma” was defined in the fifth decade follow-up by an affirmative response to the question “Have you, at any time in your life, suffered from attacks of asthma or wheezy breathing?” and having the last attack of asthma within the previous year. “Ever asthma after menarche” was defined as reporting having asthma in the fifth decade follow-up survey and reporting for the question “At what age did these attacks begin?” an age later than that reported for the onset of menarche.

Exposure definitions

Information on reproductive characteristics was collected in the fifth decade follow-up postal survey. Age at menarche was defined by the question “What was your age when you had your first period?”. This was then divided into the categories: ≤ 10 years, 11 years, 12–13 years, 14–15 years and > 15 years.

HC use was defined by the questions “Have you ever used birth control pills or other hormonal contraceptives (implants or injections)?” and “Are you currently taking birth control pills or other hormonal contraceptives?”. HC use was then categorised into never, past or current use. Age starting HC was obtained from the question “At what age did you first use birth control pills or other hormonal contraceptives?”. Age when starting HC was then divided into categories: never, ≤ 16 years, 17–18 years and ≥ 19 years. Years of HC use was obtained from the question “Over your whole lifetime, in total how many months or years have you taken birth control pills or other hormonal contraceptives?”. Years of HC use was then divided into seven categories: nil use, 0.1–5 years, 5.1–10 years, 10.1–15 years, 15.1–20 years, 20.1–25 years and ≥ 25 years.

The women were also asked about current and past pregnancies. If they reported pregnancy, they were asked more details including their age when they became pregnant. Total number of live births was

categorised as no, one, two, three and four or more live births. Age at birth of first child was grouped into the following categories: no children, ≤ 20 years, 21–24 years, 25–28 years and ≥ 29 years.

Adult BMI was calculated from self-reported height and weight at the fifth decade follow-up postal survey, and categorised as normal weight ($\leq 25 \text{ kg}\cdot\text{m}^{-2}$) or overweight/obese ($>25 \text{ kg}\cdot\text{m}^{-2}$) according to the definitions suggested by the World Health Organisation [19]. Childhood BMI was calculated from measured height and weight at the baseline survey when participants were aged 7 years. Childhood BMI was also categorised into normal weight or overweight/obese according to the definitions suggested by COLE *et al.* [20].

Confounders

“Current asthma at age 7” was defined by an affirmative response by the parents to the question “Has he/she at any time of his/her life suffered from attacks of asthma or of wheezy breathing?” and having had the last attack <12 months ago in 1968. Maternal and paternal history of allergy was defined as a parent who reported a history of either asthma or allergic rhinitis in the 1968 survey. Smoking status of the participants was classified as current, past and never-smokers. Adult socioeconomic status (SES) was defined by the participant’s occupation as reported in the fifth decade follow-up and grouped into five categories based on skill level: 1) manager/administrators, 2) associate professionals, 3) tradespersons, 4) production/sales/clerical workers and 5) labourers/house persons.

Statistical analysis

The association between reproductive factors and middle-aged current asthma was examined while adjusting for confounding using multivariable logistic regression. Age at menarche was additionally examined in relation to any asthma after the onset of menarche. The interaction between reproductive factors and BMI in childhood and adulthood was examined for the middle-aged current asthma and stratified results are presented when the p-value for the interaction term was at least modest ($p \leq 0.1$).

All models were adjusted for maternal atopy, current smoking status and SES. Other potential confounders mentioned above were assessed and retained in the model if inclusion changed the point estimate by $\geq 10\%$. All analyses were performed using Stata Release 11.1 (Stata statistical software, release 11.1; StataCorp, College Station, TX, USA). A two-sided p-value of <0.05 was considered to be statistically significant.

Results

The mean \pm SD age of participants was 43 ± 0.83 years and the mean \pm SD adult BMI was $25.7 \pm 5.53 \text{ kg}\cdot\text{m}^{-2}$. Nearly 60% were past or current smokers with a median history of smoking of 12.8 pack-years (interquartile range 3.82–24.2 pack-years) (table 1). The prevalence of middle-aged current asthma was 12.8% (95% CI 11.6–14.1%) and the prevalence of ever asthma after menarche was 21.5% (95% CI 19.8–23.3%).

The mean \pm SD age at menarche was 13.0 ± 1.52 years. The prevalence of very early menarche (≤ 10 years) was 3.9% (95% CI 3.2–4.7%) while 5.4% (95% CI 4.6–6.3%) had late menarche (>15 years old). There was a significantly increased risk of middle-aged current asthma in females who had very early menarche (OR 1.91, 95% CI 1.14–3.20) (table 2). Childhood obesity did not confound the association between very early menarche and middle-aged current asthma (OR 2.05, 95% CI 1.20–3.48). There was also a trend for an association between ever asthma after menarche and very early age at menarche (≤ 10 years) (OR 1.54, 95% CI 0.93–2.55; $p=0.10$) but this was further attenuated after additional adjustment for childhood BMI (OR 1.40, 95% CI 0.82–2.40; $p=0.22$). The number of live births and the age at birth of the first child were not associated with middle-aged current asthma (table 2). None of these associations, including age at menarche, were modified by childhood obesity or adult obesity.

The associations between HC use and current asthma in middle-age are presented in table 3. There was no association between ever using HCs or the age at which a woman started using HC and current asthma (table 3). For years of using HCs, there was no association with asthma when grouped into categories or if assessed as a continuous measure (OR 0.99, 95% CI 0.97–1.01; $p=0.23$).

Next we examined if the relationships between reproductive factors and current middle-aged asthma were modified by BMI. For HC use, we found a statistically significant effect modification by BMI on the relationship between duration of HC use as a continuous variable and current asthma (interaction $p=0.015$). Figure 1 displays the predicted probabilities of current asthma that were computed using the estimates from the multivariate regression model. In this model, in overweight/obese women with increasing years of pill use, there was a significantly increased risk of current asthma in middle-age (table 4). However, for normal-weight women, the effect was reversed, with increasing years of HC use being protective against current asthma in middle age (online supplementary table S1). We did not observe any effect modification by BMI at 7 years ($p=0.76$) on the relationship between duration of HC use and current asthma.

TABLE 1 General and reproductive characteristics of the Tasmanian Longitudinal Health Study female participants

Age[#] years	43.0±0.83
Adult BMI[¶] kg·m⁻²	25.7±5.53
Duration of pill use⁺ years	12.0±7.69
Age at first menstruation[§] years	12.9±1.52
Age at first pregnancy^f years	25.1±5.3
Adult BMI categories	
Normal	1445 (53.9)
Overweight/obese	1235 (46.1)
Education	
Grade 1–6	172 (6.2)
Grade 10 or 11	1356 (49.1)
Trade/apprenticeship	693 (25.1)
University degree	537 (19.4)
Missing	6 (0.2)
SES	
Manager/administrator	733 (26.5)
Associate professional	199 (7.2)
Tradespersons	372 (13.5)
Production/sales/clerical	583 (21.1)
Labourer/house person	849 (30.7)
Missing	28 (1.0)
Smoking	
Never	1110 (40.2)
Past	829 (30.0)
Current	815 (29.5)
Missing	10 (0.4)

Data are presented as mean±SD or n (%). BMI: body mass index; SES: socioeconomic status. #: n=2763; ¶: n=2679; +: n=2753; §: n=2718; f: n=2375.

Discussion

In this perimenopausal group of women from a large population-based study, we found a statistically significant increased risk of current asthma at age 44 years and a trend towards statistical significance for

TABLE 2 Associations between age at menarche and pregnancy history, and current asthma at age 43 years

Variable	Middle-aged current asthma [#]		p-value
	% (n/N)	OR (95% CI)	
Age at menarche			
≤10 years	20.6 (22/107)	1.91 (1.14–3.20)	0.01
11 years	13.0 (41/316)	1.10 (0.75–1.61)	0.63
12–13 years	12.1 (164/1361)	1.0	
14–15 years	12.1 (95/785)	1.01 (0.76–1.34)	0.96
>15 years	15.7 (23/147)	1.36 (0.83–2.22)	0.22
Live births n			
0	12.6 (48/382)	0.82 (0.56–1.20)	0.31
1	12.4 (41/332)	0.86 (0.58–1.26)	0.44
2	12.8 (144/1128)	1.0	
3	13.1 (82/626)	0.91 (0.67–1.24)	0.54
≥4	13.3 (39/293)	0.99 (0.67–1.47)	0.98
Age at birth of first child years			
No children	12.6 (48/382)	0.96 (0.63–1.47)	0.86
13–20 years	14.5 (95/655)	1.25 (0.89–1.76)	0.20
21–24 years	11.1 (72/649)	1.0	
25–28 years	13.8 (83/601)	1.19 (0.84–1.69)	0.33
29–45 years	11.8 (55/468)	1.05 (0.71–1.54)	0.81

[#]: adjusted for maternal atopy, current smoking status and social class.

TABLE 3 Associations between hormonal contraceptive (HC) use and middle-aged current asthma

Variable	Middle-aged current asthma [#]		p-value
	% (n/N)	OR (95% CI)	
HC use			
Never	9.2 (10/109)	1.0	
Past	12.3 (256/2089)	1.36 (0.68–2.74)	0.39
Current	15.1 (83/551)	1.58 (0.76–3.29)	0.22
Duration of HC use			
Nil	9.2 (10/109)	1.0	
0.1–5 years	16.6 (97/583)	1.98 (0.96–4.09)	0.06
5.1–10 years	10.0 (66/660)	1.11 (0.53–2.31)	0.78
10.1–15 years	12.1 (62/513)	1.35 (0.64–2.83)	0.43
15.1–20 years	13.4 (61/455)	1.45 (0.69–3.05)	0.33
20.1–25 years	12.5 (40/320)	1.24 (0.57–2.71)	0.58
25.1–30 years	12.7 (14/110)	1.19 (0.47–3.03)	0.71
Per year of use of HCs		0.99 (0.97–1.01)	0.23
Age at start of HC use			
Never	9.2 (10/109)	1.0	
12–16 years	14.73 (105/713)	1.58 (0.77–3.25)	0.22
17–18 years	12.20 (131/1074)	1.37 (0.67–2.79)	0.39
19–42 years	12.13 (102/841)	1.35 (0.65–2.78)	0.42

[#]: adjusted for maternal atopy, current smoking status and social class.

asthma after menarche associated with an early age at menarche. Prolonged hormonal contraceptive use was also a risk factor for middle-aged current asthma in women who were overweight or obese. Furthermore, our study showed that asthma risk was significantly associated with HC use for ≥11 years. While our results on the interaction between HC use and obesity confirm previous findings from one other population-based study [8], we are the first to investigate and demonstrate the role of duration of HC use in this association.

Our finding of an association between early age at menarche and middle-aged current asthma and any asthma after menarche is consistent with reports from previous studies. SALAM *et al.* [2] found that women who had menarche before the age of 12 years had a 2.08-fold higher risk of asthma after puberty. MACSALI *et al.* [11] examined European Community Respiratory Health Survey data and found forced expiratory volume in 1 s and forced vital capacity were lower and asthma was more common in women with early menarche (≤10 years). We did not observe any modification of the association between early age at menarche and asthma risk by BMI in childhood or adulthood. One study had demonstrated an association between current adult BMI and asthma severity, which was stronger in the subgroup of women with early menarche (≥11 years) [21].

The current evidence on biological mechanisms supports the interaction between HC use, specifically oral contraceptive pill (OCP) use, and obesity in increasing the risk of asthma. The OCP provides moderate,

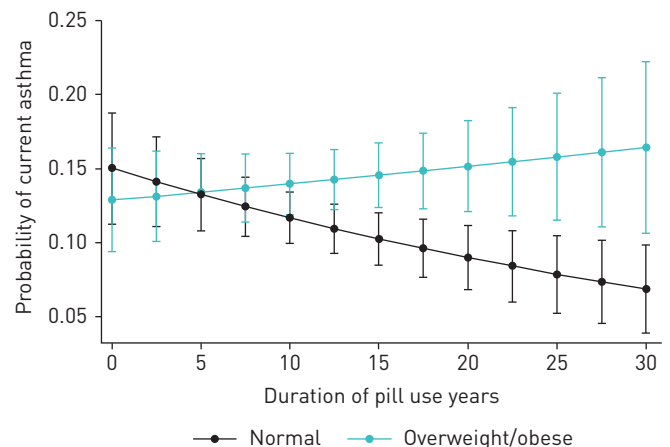


FIGURE 1 The association between years of hormonal contraceptive use and probability of current asthma in middle age, stratified by body mass index. Circles represent the probability of current asthma and the bars represent the 95% confidence interval of that probability.

TABLE 4 Risk of current asthma in overweight and obese women by years of hormonal contraceptive (HC) use

Duration of HC use	OR [#] (95% CI)	p-value
Nil	0.83 (0.54–1.29)	0.413
5 years	1.01 (0.74–1.39)	0.932
10 years	1.23 (0.97–1.57)	0.093
15 years	1.50 (1.15–1.95)	0.003
20 years	1.82 (1.27–2.61)	0.001
25 years	2.21 (1.35–3.61)	0.001
30 years	2.69 (1.43–5.05)	0.002

[#]: adjusted for maternal atopy, current smoking status and social class.

consistent levels of both oestrogen and progesterone, in the case of a combined OCP, or progesterone, in the case of a progesterone-only OCP. These hormones suppress the release of luteinising hormone and follicle-stimulating hormone that trigger the surge of progesterone immediately after ovulation [22]. These persistently elevated levels of oestrogen and/or progesterone beyond the body's normal rhythm may increase generalised systemic inflammation. Evidence from animal studies has shown that β -oestradiol, administered at doses comparable to those used for contraceptive purposes, decreased T-helper (Th)1 responses including suppressing interleukin (IL)-2 and interferon (IFN)- α production, while increasing Th2 responses by increasing gene expression of the Th2 cytokines IL-4 and IL-10 [23]. Furthermore, progesterone administered exogenously to ovalbumin-sensitised BALB/c mice led to enhanced bronchial hyperresponsiveness, elevated airway eosinophilia and elevated systemic IL-5 levels [24]. In studies of human peripheral blood mononuclear cells, the administration of oestrogen or progesterone to levels equivalent to those seen in pregnancy induced production of the Th2 cytokines IL-4 and IL-13 [25]. In humans, the strongest evidence of female sex hormones influencing the Th1/Th2 balance comes from the co-existence of persistently elevated progesterone levels and Th2 skewness during pregnancy. Furthermore, progesterone appears to influence IL-4 production by T-cells during pregnancy [26]. To date, no published study has examined the effects of non-pregnancy-like concentrations of oestrogen or progesterone on systemic or airway inflammation.

Similarly, it is hypothesised that the well-established relationship between BMI and asthma may at least be partly related to systemic inflammatory effects, with an alternative explanation being the mechanical effect of obesity. Obesity is associated with a state of chronic, low grade inflammation [27]. In obese individuals, there is an increase in the number of macrophages in adipose tissue, which can then secrete a number of inflammatory molecules including leptin, tumour necrosis factor α , IL-6, tumour growth factor-b1 and eotaxin [28]. This proinflammatory state has been suggested as contributing to a wide range of metabolic disturbances that include insulin resistance, dyslipidaemia and the metabolic syndrome [29]. However, how this systemic inflammation may lead to airway inflammation and asthma is not well understood. Evidence from animal models has shown that obese mice sensitised to ovalbumin have altered T-cell responses, IFN- γ production and mast cell numbers when compared to lean control animals [30]. Furthermore, obese mice have been shown to have increased airway responsiveness to exogenous stimuli [31] and administration of leptin has been shown to increase airway responsiveness in sensitised mice [32]. So, while the continuous elevation of oestrogen and progesterone at a moderate level leading to continuous systemic inflammation and Th1/Th2 imbalance individually may not be sufficient for asthma, when combined with obesity, the compounding effects may surpass a threshold level of airway inflammation critical for development of symptoms.

Our findings for HC are similar to those from a study by MACSALI *et al.* [8], who found that OCP use was associated with an increased risk of asthma, asthma with hay fever, wheeze with shortness of breath, hay fever and more than three asthma symptoms. These associations were present only in normal and overweight women, not lean women. Another study of younger women by SALAM *et al.* [2] found that in nonasthmatics, OCP use was associated with a higher risk of current wheeze but, conversely, in asthmatics, such use reduced the prevalence of current wheeze. We have previously shown, with an earlier follow-up of the TAHS, an increased risk of new-onset asthma developed after the age of 7 years was associated with increased parity and decreased oral contraceptive pill use [33]. This is consistent with our current findings for normal-weight women, where increasing years of pill use reduced the risk of asthma at the age of 43 years. However, we did not observe any interaction between increasing parity and HC use. The small difference in the findings may be due to the fact that the studies were conducted at different points in the women's reproductive lives, *i.e.* the present analysis was conducted when the women were entering the perimenopausal period. Another reason for the small difference in the findings between the current and

previous analyses may be related to the risk of metabolic syndrome, which increases with ageing, which can then modify the effect of exogenous hormones.

This study has some limitations, which include retrospective recall of HC use and other reproductive factors. Most of the reproductive factors examined in this analysis are major life events and most women are likely to recall them accurately [34]. The retrospective recall of HC use may be less reliable and subject to some recall error. Our definition of HC use was not specific for the combined OCP, and women who were using other hormonal contraceptives including implants or injections would have provided an affirmative response. However, a recent Australian study of young women reported that 95.5% of women using HCs were using the OCP [35], and it is likely that a similar proportion would have been using the combined OCP in our study. We do not have objective measures of hormone levels in our study and this limits our ability to explore the biological mechanisms for the observed associations. The use of participants' reporting of asthma is a limitation as it is likely to be less reliable than physician reporting or objective measures of lung function and bronchial hyperresponsiveness. However, the question used in TAHS to define asthma has been validated against physician diagnosis [36], and has been shown to be valid and reliable. Adult BMI may be subjected to random error, as it was calculated from self-reported height and weight. However, other studies have found self-reported height and weight to be fairly reliable [37].

In conclusion, we provide further evidence for the postulated association between very early menarche and asthma. We have also found that longer term HC use was associated with an increased risk of asthma among overweight or obese women. These findings add to the existing literature that suggests exogenous sex hormones may interact with metabolic status to affect respiratory health. This has important implications for physicians prescribing HC for women who are overweight or obese and may indicate that long-term use of HCs in this subgroup of women is not advisable. Further long-term studies in perimenopause and menopause on the interaction between HCs and obesity are needed.

Acknowledgements

We acknowledge the continued support and participation of the Tasmanian Longitudinal Health Study (TAHS) participants and acknowledge all previous investigators of the TAHS.

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