



Brief Original Contribution

The Association Between Irregular Menstruations and Acne With Asthma and Atopy Phenotypes

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Earlier menarche and irregular periods, among other markers of sex-hormone levels, have been associated with a higher risk of asthma and allergic diseases. This has suggested an etiologic role of sex hormones in the development of these conditions. The authors investigated the association of age at menarche, irregular periods, duration of menstruation, and acne with reported medical history of asthma and/or atopy (hay fever and/or eczema/urticaria) in a historical cohort of students born before the rise in asthma prevalence in the United Kingdom and attending university in 1948–1968. Finding consistent associations in a cohort that has experienced different life-course exposures and has different confounding structure can help to identify causal associations. In the Glasgow Alumni Cohort, irregular periods were associated with atopic asthma (multinomial odds ratio (MOR) = 2.79, 95% confidence interval (CI): 1.33, 5.83) and atopy alone (MOR = 1.40, 95% CI: 1.06, 1.84) but not with nonatopic asthma (MOR = 1.02, 95% CI: 0.45, 2.30), compared with students reporting no asthma and no atopy. The authors found no association with acne, a marker of high testosterone levels, that they hypothesized could point to polycystic ovary syndrome underpinning these associations. In summary, the authors found evidence for a potentially etiologic role of irregular menstruations with some specific asthma phenotypes, namely, atopic asthma and atopy, but not with nonatopic asthma.

acne; age at menarche; asthma; atopy; irregular menstruation

Several markers of sex-hormone levels (age at menarche, irregular periods, pregnancy, menopause, oral contraceptives, hormone replacement therapy) have been associated with asthma, suggesting a potentially etiologic role of sex hormones on asthma (1–5). Although not always consistently, markers indicating increased (e.g., pregnancy) or earlier (e.g., earlier age at menarche) exposure to sex hormones tend to relate to higher asthma risk, whereas markers indicating lower levels of sex hormones (e.g., menopause) are associated with lower risk. An overlap between metabolic and endocrine disorders, such as obesity or insulin resistance, has been reported and could explain or mediate these links (6). In this context, polycystic ovary syndrome, associated with the metabolic syndrome and high testosterone levels, is the most common cause of irregular periods in young women and could underlie an association between asthma and sex-hormone levels (3).

The aim of this study is to investigate the association of sex-hormone markers, including acne as a marker of

testosterone levels (7), with asthma and atopy in female and male students attending university between 1948 and 1968. Participants in this cohort were born before the well-documented rise in asthma prevalence in the United Kingdom (8). Finding consistent associations in cohorts that have experienced different life-course exposures and have therefore different confounding structure compared with contemporary cohorts can help to identify whether these associations might be causal (9).

MATERIALS AND METHODS

The Glasgow Alumni Cohort Study is a cohort of students who attended a medical examination carried out by trained physicians with at least 3 years of clinical experience at the Student Health Service at Glasgow University between 1948 and 1968 (11,274 males and 3,502 females) (10). Information on sociodemographic characteristics, health behaviors, and “previous medical history” (list of

conditions) was obtained through a standardized questionnaire. Data collected during the physical examination included measurements of height and weight among other characteristics. About 50% of the student population attended this examination. Students could participate in subsequent annual examinations, although these did not include medical history. Data in this report are based on the initial examination at university entry.

Health behaviors and “previous medical history” included asthma, bronchitis, pneumonia, pleurisy, hay fever, eczema/urticaria, and acne, among other health-related conditions. These were classified into atopic asthma (asthma with eczema/urticaria or hay fever), nonatopic asthma (asthma without eczema/urticaria or hay fever), and atopy alone (eczema/urticaria or hay fever only). Eczema and urticaria were asked jointly in the questionnaire and could not be separated in the analysis. Chest infection was defined as medical history of bronchitis, pneumonia, or pleurisy and was used here as a control outcome to evaluate potential residual confounding due to smoking and/or socioeconomic circumstances. Data collected during the physical examination included measurements of height and weight, which were used to calculate body mass index. Father’s occupation was used to categorize early life social class by using the Registrar General’s Social Class Classification (11, 12). Student’s smoking was categorized as none versus moderate or heavy smokers. Menstrual history included age at menarche, duration, and regularity of menstruation from female students as part of the standardized questionnaire. We obtained ethical approval to collect these historical data.

With regard to statistical analysis, multinomial regression analyses were used to estimate the association between sex-hormone markers and a 4-group categorical outcome: atopic asthma, nonatopic asthma, atopy alone, and no asthma or atopy as the referent group. Results from these models are expressed as multinomial odds ratios and 95% confidence intervals (13), although they are also referred to in the literature as relative risk ratios (14). Logistic regression analysis was used to estimate the association between sex-hormone markers and chest infection. The role of potential confounders, including age, year of student examination, student’s smoking, and father’s social class, and the role of factors previously associated with asthma and/or atopy, such as body mass index and birth order, were evaluated through the likelihood ratio test. All statistical analyses were conducted with Stata, Release 11.1, statistical software (StataCorp LP, College Station, Texas).

RESULTS

More male students reported nonatopic asthma than females, but there were no differences with atopic asthma (Figure 1). Female students reported atopy alone more frequently than male students. Table 1 shows descriptive characteristics of this population of university students. More than 50% of both male and female students had fathers from a higher social class (class I or II) and were firstborns. The average age at menarche was 13.0 (standard deviation, 1.2) years with an average duration of 4.9 (standard deviation, 1.0) days; 16.4% of female students reported irregular

menstruations. These were more common among students reporting later age at menarche. Similar proportions of both female (17.3%) and male (18.0%) students reported previous history of acne. Later age at menarche was associated with atopic asthma; irregular menstruation was associated with atopic asthma and atopy alone but not with nonatopic asthma (Table 2). The odds of atopic asthma for these markers were attenuated when both were introduced simultaneously in the model (multinomial odds ratio (age at menarche) = 1.3, 95% confidence interval: 0.9, 1.7; multinomial odds ratio (irregular menstruation) = 2.5, 95% confidence interval: 1.2, 5.2). Female students with acne had lower odds of atopic asthma, and male students with acne had lower odds of atopy alone but, in both cases, chance could not be ruled out as wide confidence intervals included the null. Finally, there were no associations between markers of sex-hormone levels and chest infections in either male or female students.

DISCUSSION

Reporting irregular periods was associated with higher odds of atopic asthma and atopy alone but not with nonatopic asthma in this historical cohort. This suggests that sex-hormones’ role in asthma might take place through a higher risk of allergy-related outcomes. Most studies have not differentiated between different asthma phenotypes, but our finding is consistent with a previous report relating both asthma and hay fever with irregular menstruations (15). Students participating in the Glasgow Alumni Cohort were born and experienced life-course exposures prior to the reported rises in asthma prevalence (8). Observing an association in this very different context gives support to a potentially etiologic mechanism related to irregular menstruations.

On the other hand, we did not find support for a potential mechanism involving acne, a marker of high testosterone levels and therefore support for a role of polycystic ovary syndrome in the development of asthma and/or atopy in female students. Acne was not associated with asthma/atopy outcomes among male students either, thus not supporting a role of testosterone in these outcomes in our cohort (16). Acne is only an indirect marker of high testosterone levels, although we have previously reported a lower cardiovascular disease and higher prostate cancer mortality among students with acne, suggesting it does identify high levels of this hormone (17). High levels of testosterone appear to promote T helper type 2 (Th2) cell responses, which are associated with higher antibody production (18). Whether acne is associated with specific asthma phenotypes and the role of testosterone in asthma and/or atopy need to be replicated in other studies. Finally, an initial association with later age at menarche, also reported elsewhere (4), was partly explained by irregular periods.

In this historical cohort, outcome measures were obtained through a standardized questionnaire and administered by trained physicians, but they were based on self-report. Distinction between asthma and bronchitis is difficult, and there might be overlap between these conditions. However, in a previous report from this study, we found higher

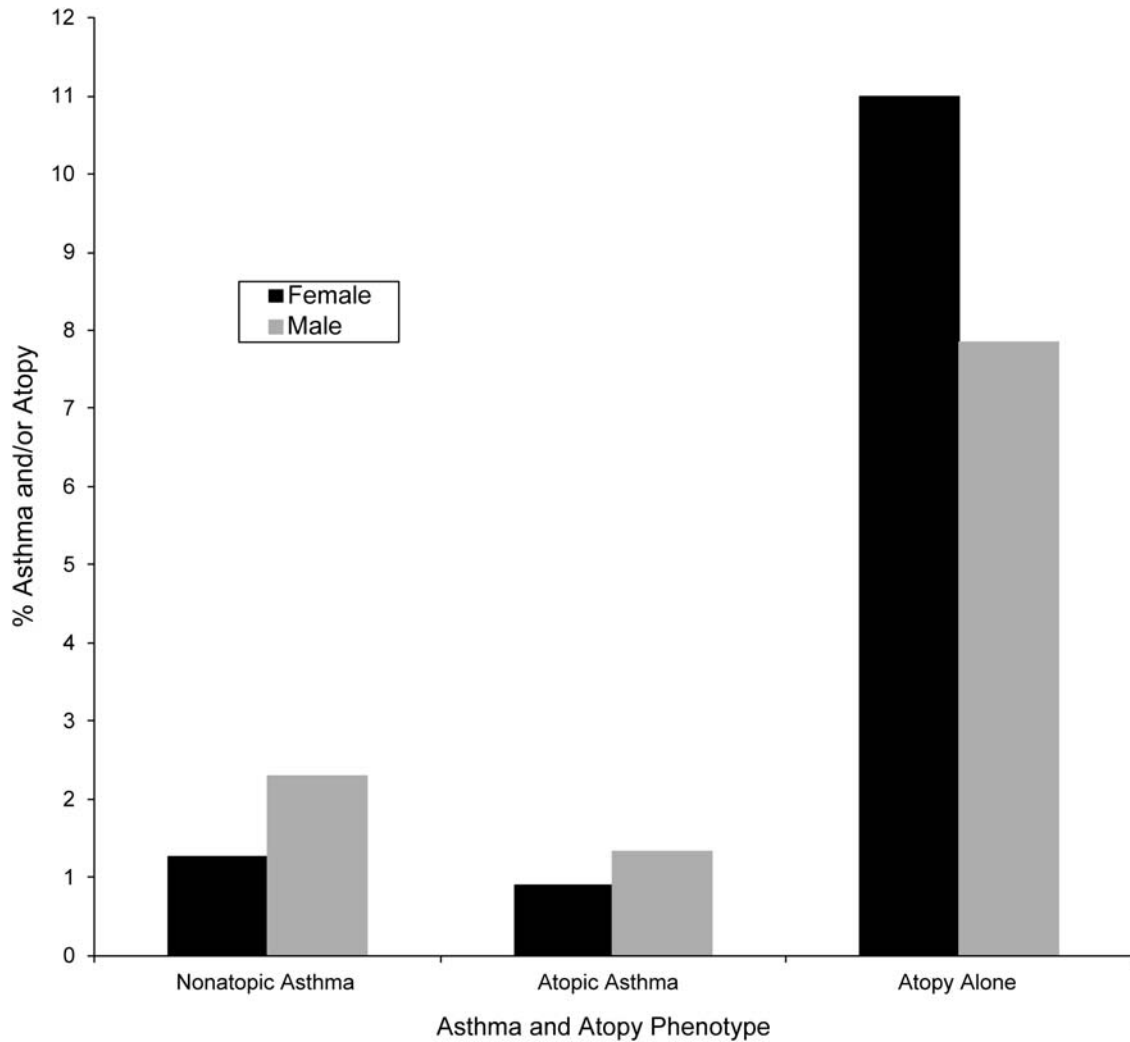


Figure 1. Proportion of male and female students reporting asthma or atopy (hay fever and/or eczema/urticaria), Glasgow Alumni Cohort Study, 1948–1968. $P < 0.001$ for gender differences in nonatopic asthma and atopy alone.

respiratory mortality in adulthood among students reporting asthma and bronchitis in early adulthood but higher cardiovascular mortality only among those with history of bronchitis (as reported in the literature), suggesting some degree of ability to differentiate between these 2 conditions (19). No objective tests (e.g., prick test or immunoglobulin E levels to identify atopy; bronchial reactivity test to identify asthma/reversible airway obstruction) were available. There is no “gold standard” to identify asthma and atopy. Current studies designed to investigate these conditions administer a battery of questionnaires and objective tests (which are likely to identify different asthma phenotypes) and often rely on questionnaire data to define asthma outcomes (20, 21). It is unlikely that students with late menarche or irregular menstruations would have reported more asthma or atopy symptoms as this potential link was unknown when the survey was carried out, and we did not find an

association with other respiratory outcomes, such as chest infections.

The results presented in this work are based on cross-sectional data collected at the initial health examination. Reverse causality, due for example to asthma treatment, could explain the association with irregular menstruation. It is, however, less likely that this is the case for atopic conditions, such as eczema, where most treatments are topical rather than systemic.

Finally, baseline health examinations were obtained from almost 50% of the student population attending university between 1948 and 1968. Gender distribution and faculty of study were similar to those of students who did not participate (10). Compared with that of the general population, father’s social class was high (shown in Table 1), reflecting the privileged nature of university education at that time. The number of women was low, as few women attended

Table 1. Descriptive Characteristics and Markers of Sex-Hormone Levels by Gender Among Students Participating in the Glasgow Alumni Cohort Study, 1948–1968

	Female				Male			
	No.	%	Mean (SD)	Median (IQR)	No.	%	Mean (SD)	Median (IQR)
Age, years	3,502			18.8 (18.2–20.1)	11,274			19.7 (18.6–22.0)
Height, cm	3,468		163.2 (5.8)		11,224		174.8 (6.3)	
Body mass index ^a	3,463		21.4 (2.4)		11,217		21.6 (2.2)	
Light or moderate smoking	3,403	19.8			10,727	34.0		
Father's social class								
I	795	23.2			2,190	20.1		
II	1,330	38.9			3,913	36.0		
III–V	1,297	37.9			4,763	43.8		
Birth order								
1	2,111	60.5			6,045	54.3		
2	899	25.8			2,986	26.8		
≥3	479	13.7			2,106	18.9		
Acne	3,502	17.3			11,274	18.0		
Age at menarche, years	3,391		13.0 (1.2)		NA		NA	
Duration, days	3,382		4.9 (1.0)		NA		NA	
Irregular menstruation	3,424	16.4			NA	NA		

Abbreviations: IQR, interquartile range; NA, not applicable; SD, standard deviation.

^a Body mass index: weight (kg)/height (m)².

university at that time. A further limitation, common to most historical cohorts, is the limited number of potential confounders or mediators available in the study. The strength of this report is finding an association in a

historical cohort before the well-documented rise in asthma prevalence in the United Kingdom. The life-course experience of this cohort in terms of exposures and confounders is very different from those of contemporary cohorts and

Table 2. Multinomial Odds Ratio and 95% Confidence Interval Between Asthma and/or Atopy With Sex-Hormone Markers, Glasgow Alumni Cohort Study, 1948–1968

	No Asthma and No Atopy ^a			Nonatopic Asthma			Atopic Asthma			Atopy Alone		
	No.	MOR	95% CI	No.	MOR	95% CI	No.	MOR	95% CI	No.	MOR	95% CI
Female students												
Age menarche, years	2,946	1.0	Referent	44	0.98	0.77, 1.25	33	1.37	1.03, 1.81	369	0.95	0.87, 1.04
+ Birth order, BMI		1.0	Referent		0.97	0.76, 1.24		1.39	1.04, 1.84		0.95	0.87, 1.04
Irregular menstruations (yes/no)	2,916	1.0	Referent	44	1.02	0.45, 2.30	32	2.82	1.35, 5.90	364	1.40	1.06, 1.84
+ Birth order, BMI		1.0	Referent		1.02	0.45, 2.30		2.79	1.33, 5.83		1.40	1.06, 1.84
Acne (yes/no)	2,998	1.0	Referent	44	0.74	0.31, 1.76	32	0.31	0.07, 1.31	376	0.91	0.68, 1.21
+ Birth order, BMI		1.0	Referent		0.74	0.31, 1.77		0.31	0.07, 1.30		0.90	0.68, 1.21
Duration, days	2,937	1.0	Referent	44	0.86	0.64, 1.15	32	0.99	0.71, 1.39	369	1.10	0.99, 1.22
+ Birth order, BMI		1.0	Referent		0.85	0.64, 1.15		0.98	0.69, 1.38		1.10	0.99, 1.23
Male students												
Acne (yes/no) ^b	9,809	1.0	Referent	255	0.92	0.66, 1.27	144	1.04	0.68, 1.58	873	0.88	0.73, 1.06
+ Birth order, BMI		1.0	Referent		0.91	0.66, 1.27		1.03	0.67, 1.57		0.88	0.73, 1.06

Abbreviations: BMI, body mass index; CI, confidence interval; MOR, multinomial odds ratio.

^a Referent group: students reporting no asthma and no atopy.

^b Adjusted for age.

helps to pinpoint a potentially causal association with irregular menstruations and asthma/atopy.

In summary, we found evidence for a potentially etiologic role relating irregular menstruations with atopic asthma and atopy alone. Importantly, this association was not present for nonatopic asthma. Our results suggest that considering specific asthma phenotypes is important if we are to understand the mechanisms that generate these associations. Furthermore, investigating the consistency of overall patterns of sex-hormone markers, which evaluate specific mechanisms (such as polycystic ovary syndrome), is likely to be more helpful at pinpointing potentially causal mechanisms than examining single markers independently.

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