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Early menarche is associated with increased risk of asthma: Prospective population-based study of twins

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Summary

Aim: To examine the association between early menarche and risk of post-menarcheal asthma. **Methods:** Using data from two multidisciplinary questionnaire surveys, conducted eight years apart, we prospectively studied 10,648 female twins, 12–41 years of age, from the nationwide Danish Twin Registry. Early menarche was defined as menarche before 12 years of age. We performed a cohort analysis and a co-twin control analysis including twin pairs discordant for incident asthma.

Results: Early menarche was observed in 9.3% of the individuals. The eight-year cumulative incidence of asthma was higher in girls with early menarche compared to girls without early menarche (7.4 vs. 4.5%), OR = 1.71 (1.31–2.22), $p < 0.001$; also after adjustment for BMI, current age, physical activity, education, and smoking, OR = 1.53 (1.15–2.04), $p = 0.003$. The unadjusted risk of asthma was increased by 8% (1–15%), $p = 0.041$ per year earlier menarche occurred. Among 167 twin pairs discordant for incident asthma, there was a non-significant tendency towards early menarche being more common in the asthmatic than the non-asthmatic co-twin (12.0 vs. 9.6%), OR = 1.57 (0.61–4.05), $p = 0.350$. The risk of asthma was not uniform in discordant monozygotic and dizygotic twins.

Conclusion: Early menarche is associated with increased risk of asthma among Danish female twins independently of BMI, age, physical activity, educational level and smoking. Results indicate a complex relationship possibly mediated through innate and non-genetic effects.

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Introduction

During the last decades the incidence of asthma has increased [1] while the average age at menarche (a girl's first menstrual bleeding) has decreased [2]. Furthermore, as asthma is more prevalent among boys before puberty but becomes more prevalent among girls after puberty an association between early age at menarche and asthma has been suggested [3]. This hypothesis has been supported by a number of studies, and recently, in a systematic review and meta-analysis of population studies, we estimated an increased risk of post-menarcheal asthma in girls with early menarche of 37% [4].

Several mechanisms might explain the association between early menarche and asthma. First, the association between early age at menarche and debut of asthma could reflect effects of genes and early rearing environment, as both timing of menarche and risk of asthma are determined by these factors [5,6]. Particularly, early programming and genetic liability to obesity and metabolic syndrome and poor intrauterine development has been associated with early menarche [7,8] as well as asthma [9]. Second, early menarche itself might induce immunological and hormonal changes as well as changes in airway function and thereby directly cause asthma. Notably female sex hormones have been shown to modulate pulmonary inflammatory processes and smooth muscle function in ways that may lead to asthma [10].

In spite of several plausible theories, the causes for the association between early menarche and asthma remain poorly understood. An informative approach to investigate the impact of genetic and environmental factors on an association between two traits in humans is offered by twin studies. Therefore, in this study, we aimed to examine the association between early menarche and the risk of post-menarcheal asthma in a Danish nationwide twin population using a cohort design and a co-twin control design.

Methods

This prospective population-based study of twins built on data from the nationwide Danish Twin Registry [11]. The study used two multidisciplinary postal questionnaires answered in 1994 and 2002, respectively, by twins aged 12–41 years at baseline. The response rates in the two surveys were 86% and 75%, respectively. At baseline (in 1994) 19,349 subjects with no history of asthma were identified; 8701 (45.0%) males and 10,648 (55.0%) females. A total of 10,059 females had complete data on age at menarche.

Subjects having new-onset asthma were defined as those answering "no" to the question "Do you have, or have you ever had asthma?" in 1994, but "yes" to the same question in 2002. Information on age at menarche was obtained by asking subjects: "How old were you, when you first got your menstrual period?" Early menarche was defined as menarche before the age of 12 years. Additional information on possible confounding factors, i.e. current age, height, weight, smoking, leisure time physical activity, and years of education were also collected at baseline. Zygosity of the twins was determined by four questions about

similarity and mistaken identity, which have a frequency of misclassification of <5% compared with genetic marker information [12].

To assess whether asthma among girls with early menarche was predominantly atopic or non-atopic we estimated the prevalence of atopy using a self-reported lifetime history of atopic dermatitis and/or allergy to pollen, pets or dust.

Statistical analysis

First, the association between age at menarche and cumulative eight-year incidence of asthma was analysed in the whole population of female twins ($n = 10,648$), ignoring their familial relationships. In this analysis chi-square-tests were used for categorical data (early menarche, i.e. <12 years of age vs. late menarche ≥ 12 years of age), whereas unpaired t-tests were used for continuous data (age at menarche). Logistic regression was used to examine the association between early menarche and new-onset asthma with adjustment for possible confounders (current age, smoking, BMI, physical activity and years of education). Risk estimates were given as odds ratios (ORs) with 95% confidence intervals (CI). Data were analysed with the statistical package SPSS 19.0 (SPSS Inc., Chicago, IL). As some of the participants denied a history of asthma at baseline (in 1994) but in 2002 reported an asthma debut age before 1994, we performed secondary sensitivity analyses excluding these cases. We also performed analyses stratified by self-reported atopic status, and analyses restricted to women above 20 years of age at baseline.

Second, the association between age at menarche and asthma was analysed with a co-twin control method. In this analysis a 1:1 matched conditional logistic regression, including smoking, BMI, physical activity and years of education as covariates, was used in order to compare the age at menarche within monozygotic (MZ) and dizygotic (DZ) twin pairs in which only one of the twins developed asthma between 1994 and 2002. The matching of the twins in the co-twin control design allows an inherent adjustment for other factors that would otherwise confound the association between age at menarche and asthma such as genetic factors, asthmatic predisposition and effects of the rearing environment. Therefore the estimated risk of asthma can be assumed to reflect the influence of age at menarche more precisely. The following predictions can be made for the co-twin control design: if the association between age at menarche and asthma is mediated via genetics, then we do not expect to find any significant risk of asthma among discordant MZ twin pairs, regardless of differences in the age at menarche between these MZ twins, because MZ twins are concordant for genetic factors. In contrast, an increased risk of asthma in discordant DZ twin pairs would suggest that genetic factors might underlie the association, because DZ twins share only half their genetic variants, and therefore DZ twins would be more discordant for asthma if they are also discordant for age at menarche. Alternatively, if the association between age at menarche and asthma is mediated via environmental effects, then we would expect to find a significantly increased risk of asthma among discordant MZ twin pairs who are also discordant for age at

menarche. In contrast, the risk of asthma among discordant DZ twin pairs according to age at menarche would not be increased. Finally, if there is a direct (causal) effect of early menarche on the risk of asthma, or if the effect is due both to genetic and environmental factors, we would expect to find that asthma-discordant MZ as well as DZ twin pairs are also discordant on age at menarche [13].

Results

Analysis of the population as a whole

Early menarche (<12 years of age) was observed among 9.3% of the population. Girls with early menarche were, on average, younger when answering the questionnaire, more likely to have a lower educational level, to have a higher BMI, to be more physically active, and to be less frequently smokers (Table 1).

The overall eight-year cumulative incidence of asthma was 4.8%. The incidence of asthma was higher in girls with early menarche compared to girls without early menarche (7.4 vs. 4.5%), OR = 1.71 (1.31–2.22), $p < 0.001$. This effect remained significant after adjustment for BMI, current age, physical activity, education, and smoking, OR = 1.53 (1.15–2.04), $p = 0.003$ (Table 2).

Analysing age at menarche as a continuous trait (assuming a linear relationship between age at menarche and incident asthma) showed that the risk of asthma increased by 8% (1–15%), $p = 0.041$ per year earlier one's menarche occurred. This corresponded to a mean difference in age at menarche of 46 days (2–91 days) between those who developed asthma compared to those who did

not. After adjustment for confounders the risk of incident asthma was non-significant and increased only 5% (0–13%), $p = 0.197$ per year of earlier menarche. The risk of asthma according to age at menarche is depicted in Fig. 1.

The mean age at onset of asthma was slightly lower in girls reporting an early age at menarche compared to girls reporting later menarche (22.0 vs. 24.0 years), $p = 0.061$. However, this effect disappeared completely when adjusting for current age.

Analysis of discordant twin pairs

A total of 167 twin pairs (74 MZ and 93 DZ) were discordant for incident asthma. Among these, early menarche was more common in the asthmatic twin compared to her non-asthmatic co-twin (12.0 vs. 9.6%), OR = 1.57 (0.61–4.05), although statistically non-significantly ($p = 0.350$). This difference in risk between siblings was however, not uniform in MZ and DZ twins: among MZ twin pairs 9.5% of the asthmatic twins and 10.8% of the non-asthmatic co-twins had experienced early menarche, OR = 0.67 (0.11–3.99), $p = 0.657$, whereas, conversely, among DZ twin pairs 14.0% of the asthmatic twins and only 8.6% of the non-asthmatic co-twins had early menarche, OR = 2.25 (0.69–7.31), $p = 0.177$. The risk in MZ twins was, however, not statistically significantly different from the risk in DZ twins. Among MZ twin pairs, the mean difference in age at menarche was 89 days (later for the asthmatic twin), OR = 1.05 (1.001–1.10), $p = 0.045$, whereas among DZ twin pairs the mean difference in age at menarche was three days (earlier for the asthmatic twin), OR = 1.00 (0.98–1.02), $p = 0.960$.

Table 1 Characteristics of female twins, 12–41 years of age, according to age at menarche.

	Menarche <12 years (n = 933)	Menarche ≥12 years (n = 9126)	P-value
Asthma	69 (7.4)	407 (4.5)	<0.001
Current age	26.2 (8.5)	27.6 (7.6)	<0.001
Ever smoking	367 (39.5)	3915 (43.0)	0.042
Education	10.6 (2.5)	11.0 (2.4)	<0.001
BMI	22.9 (4.4)	21.7 (3.5)	<0.001
Frequent physical activity	169 (20.0)	1367 (16.4)	0.007

Asthma and ever smoking are numbers (%); Education is length of schooling/education, mean years (SD); BMI is kg/m², mean (SD); Frequent physical activity is more than 4 h per week of strenuous leisure time physical activity, number (%). Numbers are calculated from available data.

Table 2 Risk factors for incident asthma among female twins, 12–41 years of age.

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Early menarche	1.71 (1.31–2.22)	<0.001	1.53 (1.15–2.04)	0.003
Current age	0.84 (0.75–0.93)	0.001	0.88 (0.78–1.01)	0.067
Ever smoking	0.92 (0.77–1.10)	0.344	–	–
Education	0.92 (0.90–0.95)	<0.001	0.94 (0.91–0.98)	0.001
BMI	1.03 (1.00–1.05)	0.030	1.04 (1.01–1.06)	0.002
Frequent physical activity	1.29 (1.03–1.61)	0.029	1.22 (0.95–1.56)	0.116

OR (95% CI) is odds ratio (confidence interval). Early menarche is <12 years of age; Current age is per ten years; Education is length of schooling/education; Frequent physical activity is more than 4 h per week of strenuous leisure time physical activity.

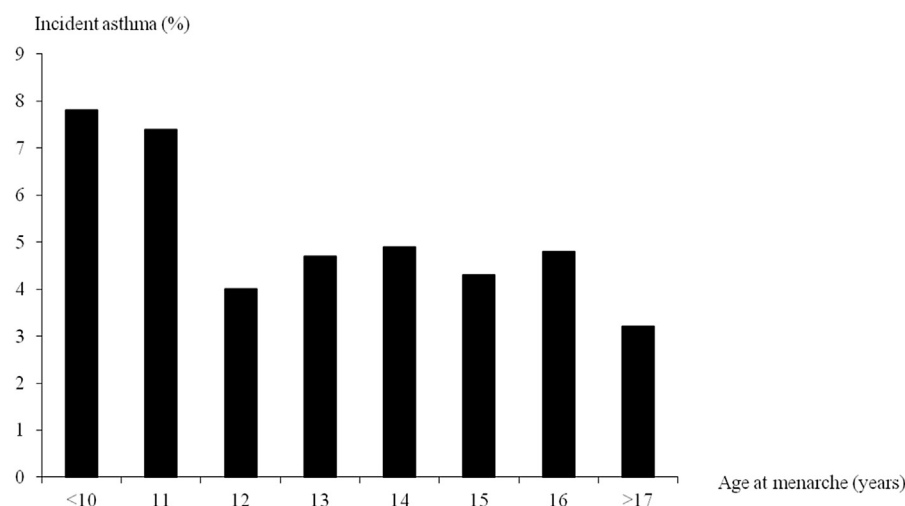


Figure 1 Eight-year incidence of asthma according to age at menarche among Danish twins 12–41 years of age.

Sensitivity analysis

Analysis restricted to the population of women 20 years of age or older at baseline (who had passed their expected age at menarche and who would therefore not contribute to survival bias in the analyses) confirmed that the incidence of asthma was higher in girls with early menarche compared to girls without early menarche (6.6 vs. 4.3%), OR = 1.55 (1.13–2.15), $p = 0.007$, also after adjustment for BMI, current age, physical activity, education, and smoking, OR = 1.46 (1.03–2.07), $p = 0.034$.

Excluding subjects who denied a history of asthma when asked in 1994, but who reported 'new onset' asthma in 2002, with an onset before 1994, showed an eight-year incidence of asthma of 3.0%. With this definition, asthma incidence was still higher in girls with early menarche compared to girls without early menarche (4.9 vs. 2.8%), OR = 1.77 (1.28–2.46), $p < 0.001$. This effect remained significant after adjustment for BMI, current age, physical activity, education, and smoking, OR = 1.64 (1.16–2.34), $p = 0.006$. In total 140 twin pairs were discordant for this definition of incident asthma. Among these, early menarche was also more common, however not statistically significantly so, in the asthmatic twin compared with her non-asthmatic co-twin (15.0 vs. 12.6%). The number of twins was too small to perform analyses stratified by zygosity.

The prevalence of atopy in incident asthmatic girls with early menarche was 65.2% compared with 60.9% in incident asthmatic girls with later menarche, $p = 0.499$.

Discussion

Main findings

This nationwide prospective twin study found a significantly increased risk of asthma in girls with early menarche, i.e. menarche before age 12 years, even when adjusting for possible confounding factors including BMI, current age, physical activity, education, and smoking. The adjusted risk of

asthma was increased by approximately 50% in girls with early menarche relative to girls with later menarche. Our data further suggest that the unadjusted risk of asthma increases by around 8% per year earlier one's menarche occurs.

The present study corroborates and expands upon earlier prospective and retrospective population-based studies in singletons, which, with one exception [14], have found a higher risk of asthma in girls with early menarche [15–20]. Particularly, in congruence with our study, a retrospective study by Macsali et al. [17] found that the risk of asthma increased with decreasing age at menarche with evidence of a threshold effect of menarche around 12 years of age.

We found no significant difference in the prevalence of atopy in asthmatic girls with early menarche compared to girls with later menarche. The few existing studies on the subject contradict this finding. For example, Macsali et al. found that non-atopic asthma was more strongly related to early menarche than atopic asthma [17], whereas Salam and colleagues [16] found an inverse relationship between age at menarche and risk of atopy.

Although most results were statistically non-significant, the analysis of discordant twin pairs showed that the twin sister with incident asthma also tended to have experienced an earlier age at menarche compared with her co-twin sister, thereby confirming our findings in the whole population with an approximately 50% increased risk of asthma according to early menarche. However, our findings among twin pairs discordant for incident asthma must be interpreted with caution due to the low number of twin pairs ($n = 167$ pairs) with this characteristic. In spite of this, the finding of differential effects of early menarche in discordant MZ and DZ twins could indicate that the association between early menarche and asthma is likely to be non-causal and possibly mediated through a complex interplay between genetic and non-genetic factors.

Interpretation

Several factors might collectively mediate the association between early menarche and asthma; female sex

hormones, metabolic profile, obesity, and exposures and growth during fetal and early post-natal life possibly interact with innate and genetic factors. Particularly, higher levels of female sex hormones estrogen and progesterone play a role in menarche timing and can act as inflammatory agents as well, thereby causing airway inflammation and obstruction [10]. Furthermore, female asthma incidence increases after puberty, is higher in the reproductive years, and declines after menopause [21]. In line with this, women taking oral contraceptives, which suppress progesterone, have a lower risk of asthma and less asthma symptoms [22].

High BMI is associated with both early menarche and asthma. Some have argued that the association between asthma and overweight could be attributable to less physical activity in women with high BMI, but studies have shown that the association between asthma and obesity is independent of physical activity [23,24] and that obese women with early menarche may have a more severe asthma phenotype [25]. Higher BMI is also associated with higher levels of female sex hormones [26] and systemic inflammation [27]. Leptin, a pro-inflammatory cytokine secreted by adipocytes, is associated with both early menarche [28] and asthma [29]. Leptin is a permissive factor for the initiation of pubertal events in both boys and girls [30] and leptin receptors are present in airway and lung cells, which proliferate when exposed to leptin [31]. Furthermore, circulating levels of leptin correlate with the amount of body fat and BMI [32]. Therefore, leptin may be a mediating factor for the association between early menarche and asthma, but at present, it is difficult to separate the associations of leptin with early menarche, obesity and asthma.

Factors related to the pre- and perinatal environment have also been associated with both early menarche and asthma. Particularly, preterm birth and low birth weight is associated with deficits in the structure and function of the lung at birth, which may increase the risk of subsequent asthma development. Moreover, low birth weight reflects a less fortunate nutritional environment in utero, which is associated with later development of metabolic syndrome including a higher incidence of type 2 diabetes and a higher BMI, as well as early menarche and asthma [33–35].

Finally, both menarche timing and asthma are genetically determined. Yet, no shared genes or genetic pathways have been established. It is well-known that the mother's age at menarche is highly determining for the offspring's menarche timing. However, a population study by Xu et al. [14] did not find any association between maternal age at menarche and asthma risk in the offspring. Still we cannot preclude an underlying genetic trait for age at menarche and asthma, particular since we observed an attenuation of the risk of asthma in discordant MZ twins relative to DZ twins for early menarche.

Evaluation of the study quality

This study is the first to examine the association between age at menarche and risk of asthma in a twin cohort. The study is prospective and nationwide, and based on

multidisciplinary questionnaires, which increases the robustness against selection and ascertainment bias.

Nonetheless, the study suffered from several shortcomings. Importantly, we were only able to identify 93 DZ and 74 MZ twin pairs discordant for incident asthma, which affected the statistical power of the co-twin control analysis. Due to the low power our results can only be used as indicators of what larger studies may find. Furthermore, we were limited to control for BMI, current age, physical activity, education, and smoking, and not for several other important confounding factors such as for example birth weight, use of oral contraceptives, and pregnancies during the study period, irregular menstruations, and comorbidities. The questions used to assess physical activity were adopted from The Copenhagen City Heart Study Leisure Time Physical Activity Questionnaire, which has been extensively validated [36]. Still it is a limitation that we used only self-reported information on physical activity. However, the intensity was reported in the form of relative intensity, which is considered a more appropriate measure than absolute intensity when the age-span is large and when the participants have wide differences in levels of physical fitness [37]. Furthermore, we used only baseline data on physical activity. Ignoring longitudinal changes in physical activity may lead to misclassifications causing the true association to be underestimated [37]. Women with early menarche were, on average, 1.4 years younger when answering the questionnaire compared to women with later menarche. This may explain the significant effect of physical activity. Notably, the significant effect of physical activity on the risk of asthma disappeared when adjusting for age. Also, confounding from socioeconomic position may play a role although we did adjust for this (in the form of educational level) in the analyses. It has been shown that, particularly among women of Caucasian descent, unlike women of African descent, early age at menarche is associated with low socioeconomic position [38].

Another shortcoming was the use of self-reported definitions of menarche and asthma. Although diagnostic survey questions on menarche and asthma have proven to have a reasonable accuracy this method may have given rise to recall bias [39,40] and particularly to an overestimation of the number of new-onset asthma cases in the follow-up period. However, in a subsequent clinical examination of a selected sample of the twins used in the present study we estimated that the misclassification rate of asthma was only approximately 12%, with a sensitivity of the asthma screening question of 88% and a specificity of 89% [41].

Furthermore, we performed sensitivity analysis excluding possibly misclassified cases; i.e. those who at baseline (in 1994) denied a history of asthma, but whom at the follow-up survey (in 2002) reported an age at onset of asthma before 1994. This analysis showed an even stronger association between early menarche and risk of asthma. Also, including only women aged above 20 years in the analysis confirmed this finding.

Lastly, the findings of the present study are based on a twin cohort. Although twins resemble singletons in most aspects, twins are on average born three weeks prior to term with an average birth weight 1000 g below that of singletons and do experience more obstetric complications and caesarean sections than singletons [42]. Low birth

weight and caesarean section have been associated with a higher risk of asthma [33,43], and low birth weight has been associated with early menarche [34]. However, whether this could lead to an altered relationship between menarche timing and risk of asthma in twins is not clear.

Conclusion

Our study supports the hypothesis that early age at menarche is associated with an increased risk of asthma. The association between age at menarche and asthma seems to be non-causal, and possibly mediated via complex innate and non-genetic mechanisms. Future twin studies within larger populations and with more robust and objective definitions of exposure and outcome, and with more elaborate confounder control, are warranted to confirm these findings.

Conflict of interest

The authors have no real or perceived conflicts of interest in relation to this work.

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