

Review

A new childhood asthma phenotype: obese with early menarche



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EDUCATIONAL AIMS

The reader will come to appreciate that:

- A new asthma phenotype is proposed, affecting obese girls with menarche before the age of 12 years.
- Synergistic interactions between hormones, inflammatory mediators and environmental/epigenetic and genetic factors are suggested to be responsible.

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SUMMARY

Three concomitant phenomena occur in the later years of childhood: increases in the incidence of asthma, obesity and early menarche. This article is an overview of the current epidemiologic, basic, genetic and epigenetic evidence about this relationship. As a consequence we propose that obese girls who have an early menarche (≤ 11 years of age) constitute a new asthma phenotype in childhood. Future studies need to be carried out in order to find the best control and treatment of this new asthma phenotype.

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INTRODUCTION

It is well known that asthma is a heterogeneous disease with several phenotypes described in childhood [1]. Curiously, the prevalence of asthma in the first two decades of life has been suggested to have a sex-modified mechanism [2]. During childhood, asthma is more prevalent in boys; however, asthma rates increase and become higher for girls during adolescence and adulthood [2,3]. Also, bronchial hyperresponsiveness (BHR) is found to be more severe among post-pubertal girls than among boys [4]. During the menstrual cycle, a rise in the level of oestrogen has been associated with an increase in symptoms and a decrease in pulmonary function among asthmatic women [5]. Change in asthma prevalence among girls can be attributed to a higher

incidence of asthma in early adulthood, in particular around puberty. Moreover, the worldwide increase in asthma prevalence and the downward trend in the age of menarche – a surrogate measure of puberty – emphasises the importance of asking if there is an association between early menarche and asthma [6–8]. Finally, there is evidence that age at menarche is decreasing in the world, and as child obesity is associated with earlier menarche, this change may be partly explained by the global obesity epidemic. Whether this association (early menarche, obesity and asthma) is causal or not needs to be addressed.

Over the last decade a significant and concomitant increase in the prevalence of both asthma and obesity has occurred worldwide. An association of asthma incidence with body mass index (BMI) and weight gain has been reported in women [9–12] but not in men in most, but not all, studies [13–15]. Therefore, obesity may be influenced by female sexual hormones, because these can act as promoters for the development of adipose tissue [16]. The increase in the peripheral availability of oestrogen and the production of leptin by the adipose tissue may be implicated in the association between sexual maturation and obesity [17]. Therefore, it is possible that an interaction exists between age of puberty, obesity and asthma [18,19]. In this article we review the current

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Abbreviations: aOR, adjusted odds ratio; aHR, adjusted hazard ratio; BHR, bronchial hyperresponsiveness; BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GWA, genome-wide association; PR, prevalence ratio; SNP, single nucleotide polymorphism.

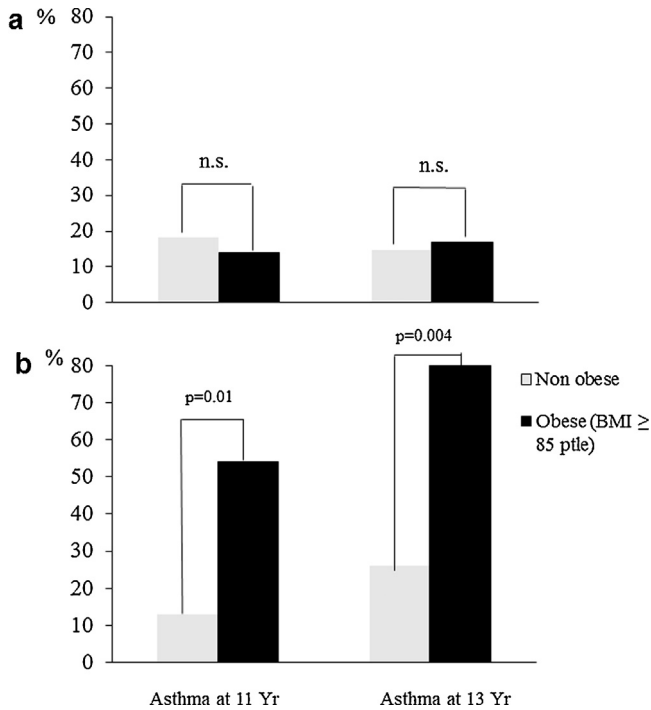


Figure 1. (a) Relation between overweight/obesity and asthma among females with menarche after 11 years of age in the Tucson Respiratory Study [20] (b) Relation between overweight/obesity and asthma among females with menarche by 11 years of age in the Tucson Respiratory Study [20].

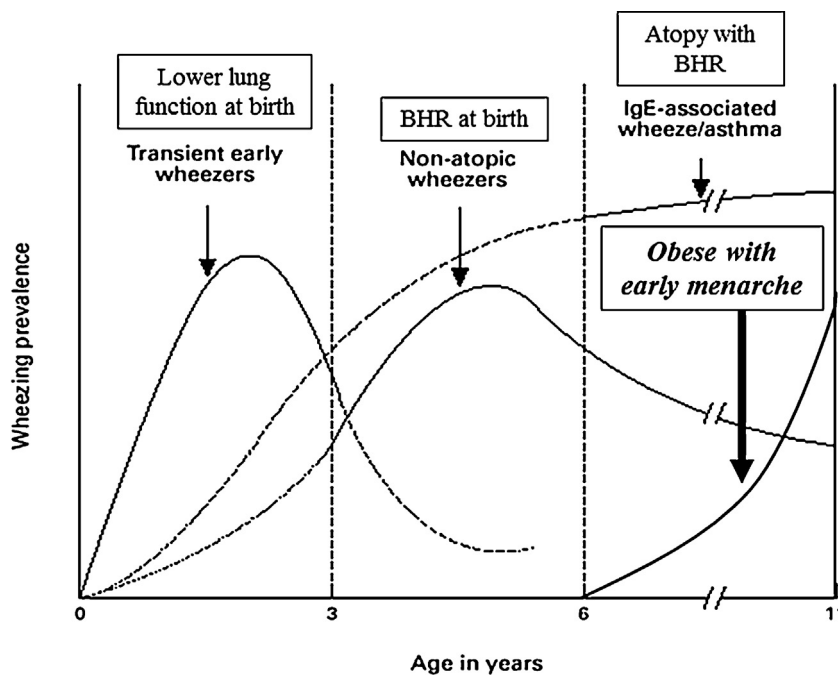
epidemiologic, basic, genetic and epigenetic evidence for this relation between asthma, obesity and early puberty.

EPIDEMIOLOGIC STUDIES

In 2001 Castro-Rodriguez et al. [20], using the birth cohort Tucson Children's Respiratory Study ($n = 688$), reported, for the

first time, that obesity was related to the incidence of wheezing in girls but not in boys. However, it was true only among girls with *early menarche* (< 11 years – Figures 1a and 1b). After adjusting for skin test and parental BMI, girls who became overweight (BMI ≥ 85 to < 95 percentile) or obese (≥ 95 percentile) between 6 and 11 years of age were more likely to develop new infrequent (aOR: 6.8; 95% CI [2.4–19.4], $p = 0.0001$) and frequent (aOR: 5.5; [1.3–23.3], $p = 0.015$) wheezing episodes than those who did not become overweight or obese. Moreover, Guerra et al. [21] in the same cohort found that, obesity and *early onset of puberty* were independent risk factors (aOR: 8.9; [1.7–46.8] and aOR: 0.64; [0.44–0.93], respectively) for persistence of asthma during adolescence (up to 16 years of age), with a trend for girls. Later, Gold et al. [22], in a prospective, school-based study in six US cities ($n = 9828$ children, aged 6–14 years) reported that excessive annual weight gain during the elementary and middle school years added to the risk of asthma incidence among girls. Unfortunately, the influence of menarche was not reported.

In 2005 two epidemiological studies worldwide confirmed the association between obesity and asthma among women with early menarche. In Mexico, Herrera-Trujillo et al. [23], in a study population ($n = 7465$ females, aged 11–14 years) reported that obese girls (BMI ≥ 95 percentile) had an increased risk of current wheezing – in the last 12 months (OR: 1.19; [0.97–1.46]) compared with those with normal BMI. After stratifying by age of menarche, the increased risk was only present in girls with menarche at 11 years old or younger (OR: 1.31; [1.01–1.73]). Similar results were observed after adjusting for age, total calorie intake, physical activity and socioeconomic level. The strength of this study is the large sample, which reinforces evidence for the modifying effect of age at menarche on the association between obesity and asthma. In France, Varraso et al. [24], in a case-control study ($n = 366$ asthmatic with an average age of 36.8 years), found that women with *early menarche* (at 11 years or earlier) had a significantly more severe clinical score of asthma than those with menarche after 11 years. The association between BMI and severity of asthma remained for women after taking into account age,



BHR: bronchial hyperresponsiveness

Figure 2. Obesity among girls with early menarche: a new asthma phenotype in childhood [1].

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