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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.

INTRODUCTION

It is well know 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..

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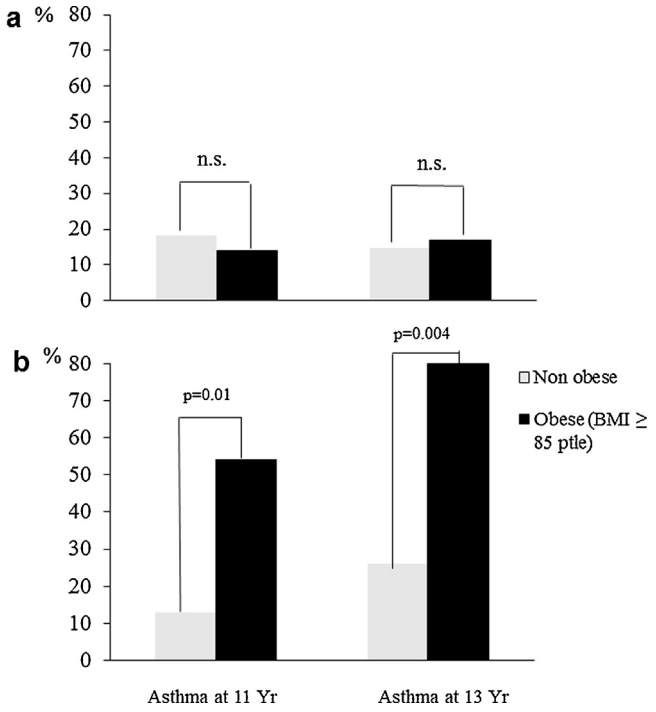

Figure 1. (a) Relation between overweight/obesity and asthma among females with menarche after 11 years of age in the Tucson Respiratory Study [20] (**b)** Relation between overweight/obesity and asthma among females with menarche by 11 years of age in the Tucson Respiratory Study [20].

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,

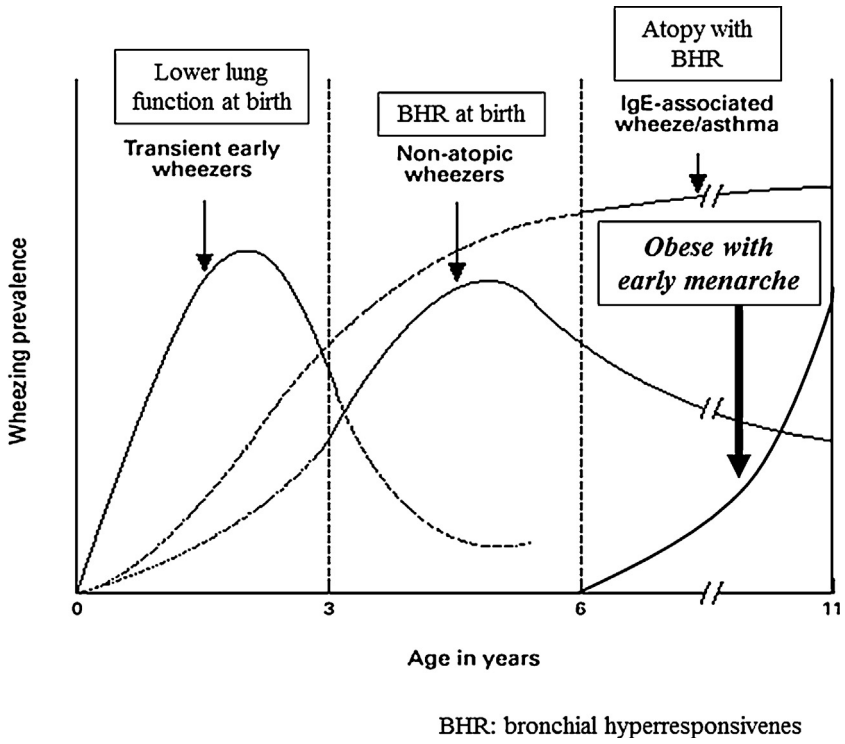

Figure 2. Obesity among girls with early menarche: a new asthma phenotype in childhood [1].

smoking habits and FEV1% predicted. Early menarche modified the relation of BMI quintiles to clinical score, and became significant in women with early menarche. The asthma severity score increased with increasing BMI among women with early menarche ($r = 0.49$, $p = 0.005$), suggesting the role of hormonal factors in asthma severity.

Later, in New Zealand, Hancox et al. [25], in a cohort study ($n = 1037$, survey age 9 to 26), reported that a larger BMI was associated with incidence of asthma in women but not in men. The population attributable fraction calculations estimate that 28% [95% CI: 7–45] of asthma developing in women after the age of 9 was due to overweight status. Also, they found an inverse relation between BMI and lung function (FEV1/FVC) among asthmatic females. However, even though no data on age of menarche were available, either in the manuscript or online repository, the authors state absence of a relation between asthma and age of menarche, and that age at menarche did not modify the relation between BMI and asthma.

Recently, Salam et al. [26], in a longitudinal study in southern California ($n = 905$ females, aged 13–38 years), reported that girls who had their menarche before 12 years of age were more likely (aHR: 2.08; [1.05–4.12]) to have developed asthma 1 or more years after puberty compared with women who had menarche after age 12 (after adjusting for age, race, BMI at cohort entry, education, living with spouse/partner, personal smoking status, exposure to second-hand smoke, oral contraceptive use, health insurance and mode of data collection).

In 2011 two epidemiological studies were published. In Canada, Al-Sahab et al. [27] ($n = 1176$ girls followed up from 8–11 to 18–21 years of age) reported that those attaining menarche at a young age ($<$ 11.6 years of age) were more likely to developed asthma (aOR: 2.34; [1.12–4.49]) than those who matured at the average age (12.7 years), after adjusting for all covariates (income, educational level, family type, smoking and family history of asthma). Using the European Community Respiratory Health Survey II ($n = 3354$), Macsali et al. [28], after excluding women with asthma before menarche, reported that those with early menarche ($\leq$10 years) had lower lung function (adjusted difference for FEV1 and FVC: -113 ml, [-196 to -33 ml] and 126 ml, [-223 to -28 ml], respectively) and more asthma symptoms (aOR: 1.80; [1.09–2.97]), asthma with BHR (aOR: 2.79; [1.06–7.34]), and higher asthma symptom score (adjusted mean ratio: 1.58; [1.2–2.21]) than those with menarche at 13 years, after adjusting for BMI, age, smoking intensity, education, order of siblings, height and center.

More recently, Fida et al. [29], in a cohort study in Seattle ($n = 3461$) after controlling for potential confounders (age, race, BMI, and socioeconomic status) showed that women who had early menarche ($<$ 12 years old) had a 60% higher risk of being diagnosed with adult onset asthma as compared with women who did not have early menarche ($\geq$ 12 years old) (aRR = 1.59; [1.19–2.13]). Menstrual irregularities or abnormal cycle length were not associated with risk of adult onset asthma. In addition, no significant interaction was observed between age at menarche or menstrual characteristics with BMI or physical activity (in adolescence) in relation to adult onset asthma. Hong et al. [30], in a longitudinal study of 1055 girls enrolled at 6–8 years of age in the USA, reported that asthma was associated with younger pubarche ($\leq$ 10 vs $>$ 10 years, aPR = 1.13, [1.01–1.25], after adjusting for BMI), but not thelarche. That was the first study to prospectively examine breast and pubic hair development, which typically occurs 2–3 years before menarche.

Therefore, from these epidemiologic studies we can conclude that those obese girls who had an early menarche ($\leq$ 11 years of age) are more prone to develop asthma and with more severity (Table 1). Moreover, a recent meta-analysis ($n = 22\,859$), including seven cohort and cross-sectional studies, with or without adjustment for confounders, showed that girls with early menarche ($<$ 12 years) had an increased risk of asthma relative to girls with late menarche (random effects OR = 1.37; [1.15–1.64], $p = 0.0005$, $I_2 = 55\%$) [31].

BASIC STUDIES

It is logical to assume that if girls have an early menarche they will experience long-lasting effects of oestrogens [32]. Girls who mature early are exposed to higher levels of the sex hormones oestrogen and progesterone than are girls with late onset of menarche. These hormones have been suggested to affect pulmonary inflammatory processes [26], smooth muscle [20], and the function of the immune system [24]. However, the

Table 1
Epidemiologic studies supporting the relation between obesity, early menarche and asthma

Authors (year)	Location	Type of study	*n* (aged)	Principal finding
Castro-Rodriguez (2001)	Tucson, AZ	Birth cohort	688 (0–13 years)	Girls with early menarche ($<$ 11 years) who became overweight/obese had higher risk for asthma incidence
Gold (2003)	Six cities, USA	School-based	9828 (6–14 years)	Excessive weight gain in girls is a risk factor for asthma incidence
Guerra (2004)	Tucson, AZ	Birth cohort	781 (6–16 years)	Early onset of puberty is an independent risk factor for asthma persistence during adolescence (trend for girls)
Herrera-Trujillo (2005)	Mexico	Population	7465 (11–14 years)	Obese girls with menarche $<$ 11 years had an increased risk of current wheezing
Varraso (2005)	France	Case-control	366 (36.8 years)	Women with early menarche ($<$ 11 years) had more severe asthma at adulthood
Hancox (2005)	New Zealand	Cohort study	1037 (9–26 years)	PAF = 28% of asthma developing in women after age 9 is due to being overweight
Salam (2006)	California, USA	Population-based	905 females (13–38 years)	Girls having menarche before 12 years is a risk factor for asthma incidence
Al-Sahad (2011)	Canada	National survey	1176 girls (8–21 years)	Girls having menarche at a young age (1 SD) is a risk factor for asthma incidence
Mascali (2011)	Europe	European survey	3354 women (27–57 years)	Women with early menarche ($\leq$ 10yrs) had lower lung function and more asthma symptoms at adulthood
Fide (2012)	USA	Retrospective cohort	3641 ($>$ 18 years)	Early menarche ($<$ 12 years old) led to 60% higher risk of being diagnosed with adult onset asthma, as compared with women who did not have early menarche (aRR = 1.59; [1.19–2.13]).
Gnatiuc (2013)	UK	National survey	4191 (7–31 years)	Asthma at 11 years was associated with early menarche ($\leq$ 12yrs) after adjusting for BMI

BMI = body mass index; SD = standard deviation.

association between the sex hormones and asthma is complex [33]. Hormonal fluctuations during the menstrual cycle are associated with worsening of asthma symptoms [34,35], as well as a predominance of Th2-over Th1-mediated immunity during the perimenstrual period [36]. Exogenous sex hormones in the form of oral contraceptive pill have been shown to blunt the Th2 immune response [36]. Salam et al. [26] showed that in women without asthma, oral contraceptive pill use was associated with higher risk of current wheeze (aOR: 1.75; [1.2–2.7]); in contrast, oral contraceptive pills use was associated with a markedly reduced prevalence of current wheeze in women with a history of asthma (aOR: 0.18; [0.06–0.56], $p = 0.003$ for interaction), and with significant trends with duration of oral contraceptive use (independent of health care, BMI, or concurrent use of asthma medication).

Among the numerous proteins associated with obesity, leptin plays the central role. Leptin is a 146-amino acid protein encoded by the obesity (ob) gene and a member of the IL-6 family of cytokines (pro-inflammatory). Secreted by adipocytes, the circulating level of leptin correlates with the amount of body fat and BMI and is a permissive factor for the initiation of pubertal events in both boys and girls [37]. In a population-based study [38], FEV1 was shown to decrease with an increase in leptin levels in non-obese subjects, which could reflect the pro-inflammatory role of leptin, but no information about asthma status was available. Higher leptin levels and higher insulin resistance in women with early menarche, influencing inflammation and innate immunity, could contribute to the association with adult lung health [39,40]. The association found between asthma and younger pubic hair, but not thelarche, independent of obesity [30], may indicate that the insulin/IGF-1 pathway plays a potential role since it was proposed to trigger the commencement of adrenarche, which precedes pubarche [41]. Thelarche is triggered by rising levels of oestrogen, which is synthesised in peripheral adipose tissue; oestrogen is less important for pubic hair, which is initiated by adrenal androgens.

GENETIC AND EPIGENETIC STUDIES

Some genetic studies suggest a relation between the timing of menarche with increased BMI, but not yet both conditions with asthma. Blell et al. [42] showed that the timing of menarche was associated with conditions in fetal and early life, such as gestational age, maternal age and BMI at age 9 years. Age at menarche signals the start of women's reproductive life and could be determined by environmental and genetic factors [43,44]. During the last 100 years the median age at menarche has decreased from 16–17 years to less than 13 years [43,45]. The only gene associated with pubertal height growth, *LIN28B* at locus 10, pleiotropically influences childhood growth, puberty and cancer progression. A recent meta-analysis on genome-wide association (GWA) from nine cohort studies ($n = 18\,737$ European samples) found that *ADCY3-POMC* at locus 10 was associated with both early puberty and increased childhood BMI [46]. Another meta-analysis on GWA in 32 studies (87 802 women of European descent with replication in up to 14 731) reported in addition to the known loci at *LIN28B* and *9q31.2*, 30 new menarche loci and suggestive evidence for a further 10 loci [47]. The new loci included four previously associated with BMI (in or near *FTO*, *SEC16B*, *TRA2B* and *TMEM18*), three in or near other genes implicated in energy homeostasis (*BSX*, *CRTC1* and *MCHR2*) and three in or near genes implicated in hormonal regulation (*INHBA*, *PCSK2* and *RXRG*).

Recently, a study with meta-analytical techniques to estimate the associations of 95 *a priori* and recently identified obesity-related (BMI, waist circumference, and waist/hip ratio) SNPs with age at menarche was performed in 92 116 women of European descent from 38 studies [48]. Six novel associations of BMI loci with age at menarche were identified and 11 adiposity loci previously reported to be associated with age at menarche were confirmed, but none of the central adiposity variants individually showed significant associations. These findings suggest complex genetic relationships between menarche and overall obesity, and to a lesser extent central obesity, in normal processes of growth and development. However, genetic studies that relate common SNPs for early menarche, obesity and asthma have not yet been carried out.

As we know, the transcription factor *GATA3*, located on chromosome 10, encodes a master regulator of Th2 cell differentiation that plays an important role in the production of cytokines. A recent epigenetic study [47] reported an interaction between genetic variation and DNA methylation of *GATA3* and the risk of asthma at 18 years, which is modified by the use of oral contraceptive pills and age at menarche. This suggests a potential pathway in which oral contraceptive pill exposure and age at menarche, presumably via sex hormones, can alter the DNA methylation of the *GATA3* CpG site, which subsequently, in conjunction with genetic variants, influences the risk of asthma at 18 years. An interaction between oral contraceptive pills use and SNP *rs1269486* was found to be associated with the methylation level of *cg17124583* (after adjusting for socioeconomic status, smoking at 18 years and BMI at 18 years). DNA methylation of this same CpG site was also influenced by the interaction between age at menarche and *rs1269486*. They also found that *cg17124583* modified the association of SNP *rs422628* with asthma risk at the age of 18 years.

CONCLUSIONS

These epidemiology and basic studies support that overweight/obese females with early menarche ($\leq$ 11yrs) correspond to another new asthma phenotype in childhood, as we first proposed more than 10 years ago (Figure 2). Hormonal and inflammatory mediators related with obesity (e.g. leptin, insulin/IGF-1 pathway) could play a role in this phenotype with genetic–environmental interactions. Genetic studies suggest a relation of the timing of menarche with increased BMI, but both conditions together with asthma are not described yet. Future studies need to be done in order to find the best control and treatment of this new asthma phenotype.

FUTURE RESEARCH DIRECTIONS

- Future studies should serve to define the best control and treatment modalities for this new asthma phenotype.
- Public health efforts should promote and implement healthy diet and physical activity strategies from early childhood.

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