

STATE-OF-THE-ART-REVIEW

The asthma–obesity link in childhood: open questions, complex evidence, a few answers only

P. M. Matricardi, C. Grüber, U. Wahn and S. Lau

Department of Pediatric Pneumology and Immunology, Charité – Universitätsmedizin, Berlin, Germany

Clinical and Experimental Allergy

Summary

Obesity and asthma are public health priorities in developed countries. Genes which may contribute to the control of both conditions include those encoding for the β_2 -adrenergic receptor, tumour necrosis factor- α (TNF- α) and the insulin-like growth factor 1 (IGF-1). Prospective studies consistently supported a link between obesity and reported wheezing or asthma diagnosis in children. However, there are still no clear explanations for such a link. On one hand, overweight asthmatic children may perceive their asthma as worse. On the other hand, atopic sensitization and bronchial hyper-reactivity do not explain the observed associations. After puberty, the association between asthma and obesity tends to be stronger in girls than in boys. It is conceivable that severe obesity in adolescent females may aggravate asthma through mechanisms different from those linking prepubertal obesity to unremitting asthma in males. Future studies should therefore address multiple age- and gender-specific hypotheses about the mechanisms that link obesity to asthma throughout childhood.

Correspondence:

Paolo Maria Matricardi, Department of Pediatric Pneumology and Immunology, Charité – Universitätsmedizin, Augustenburger Platz 1, D-13353 Berlin, Germany.
E-mail: paolo.matricardi@charite.de

Introduction

Paediatricians are well aware of the fact that obese children often complain about respiratory problems. Epidemiologists have reported that both obesity and asthma are 'endemic' in developed countries [1, 2] and 'epidemic' in developing countries undergoing their epidemiological transition phase [3]. Accordingly, the World Health Organization includes both obesity and asthma among the major chronic disorders representing world-wide public health priorities [4]. Thus, not only paediatricians but also public health experts are increasingly coping with these expanding phenomena. Their growing prevalence demands more research concerning the epidemiology and genetics of the asthma–obesity link, its causes and mechanisms, and the best prevention and therapeutic strategies to use against this dual morbidity [5].

A common belief is that asthmatic children have less tolerance for physical activity [6]; similarly, it is generally accepted that obesity can mechanically generate respiratory problems in children [7]. However, the asthma–obesity link seems to be far more complex [8]. More and more unexpected biological functions are being attributed to the adipose tissue [9]. For example, the discovery of the central

role of leptin in obesity [10], combined with evidence of its pro-inflammatory role [11], has added fuel to the hotly debated issue of how obesity may lead to asthma [8].

Aside from behavioural and environmental issues, co-expression of asthma and obesity phenotype raises the question of common traits. Epidemiological work suggests a genetic pleiotropy between asthma and obesity [12]. In fact, some genes have been identified that may contribute to the control of both asthma and obesity. The gene encoding for the β_2 -adrenergic receptor is located on chromosome 5q31–q32, and the same receptor polymorphism associated with lower airway reactivity in asthmatics [13] and increased levels of serum IgE [14] is also associated with obesity [15]. Similarly, the gene complex of the pro-inflammatory cytokine TNF- α is located on chromosome 6p21.3, and polymorphisms of this gene are associated with childhood wheezing, asthma, and bronchial hyper-responsiveness [16–18]; a linkage has also been found between obesity and a marker near the TNF- α locus [19]. Another example is given by the gene encoding the insulin-like growth factor 1 (IGF-1), which is located on chromosome 12q23; on the one hand, a polymorphism of this gene is associated with body mass index (BMI) [20], and on the other, IGF-1 secreted by

bronchial epithelial cells stimulates myofibroblast proliferation after injury [21] and may contribute to airway remodelling in chronic asthma. Further candidates for a common regulation of asthma and obesity include genes for glucocorticoid receptor, IL-6, and the IL-6 receptor.

This area of investigation is therefore still in its infancy; hence, although the list of questions around the asthma–obesity link in childhood is quite long (Box 1), the list of answers is much shorter.

BOX 1. Open questions on the asthma–obesity link in childhood

1. Is the evidence of a reported asthma–obesity link consistent enough in children?
2. Which asthma phenotypes are involved?
3. Which comes first: asthma or obesity?
4. Is there a gender effect in the association?
5. Does obesity cause asthma or simply make it worse?

Many reviews have elucidated comprehensive and general [22, 23] or specific [5, 8, 24–30] aspects of this subject, but none, to our knowledge, has been exclusively focused on the paediatric age. Other reviews have thoroughly discussed methodological problems [23], underlying mechanisms [5, 8, 26], and studies in adults on the asthma–obesity link (reviewed in [23]). We have focused here on the evidence from epidemiological studies in paediatric populations that reveals an association between asthma and obesity, and we briefly discuss some perspectives for further paediatric clinical and epidemiological research and for public health measures.

The evidence

Epidemiological studies on asthma and obesity in children can be roughly classified into five major categories:

1. Cross-sectional population studies [31–46] (Table 1).
2. Case–control studies [47–53] (Table 2a).
3. Observational studies in patients [54–57] (Table 2b).
4. Prospective population studies (including birth cohort studies) [58–62] (Table 2c).
5. We were unable to identify intervention studies focused on weight loss in asthmatic children.

A wide range of definitions, methodologies, study designs, and study populations has been utilized through a large series of studies. Several problems arise due to the heterogeneity of the approaches, study design, definitions, and methods; thus, we acknowledge that this review is not intended to be a meta-analysis based on Cochrane methodology. We have tried, however, to isolate the evidence robust enough to persist across most relevant and reliable studies, to provide tentative answers to a few questions,

and to comment about future perspectives for further epidemiological research in this area.

Questions on the asthma–obesity link in childhood

1. Is the evidence of a reported asthma–obesity link strong and consistent enough in children?

Periodically, associations between exposure and disease raise enthusiasm and many hypotheses about disease causes and mechanisms, environmental or behavioural risk factors, and new preventive and therapeutic strategies. Most of the population-based, cross-sectional, and case–control studies, as well as all the prospective studies examined in this review, have consistently supported a link between obesity and reported wheezing or asthma diagnosis in children (Tables 1–3). The association was consistent across a long list of high-income countries, but its strength was rather low, with a relative risk rarely overcoming 2.5 in general-population studies. However, odds ratios up to 9 were recorded when considering peculiar population subsets [59].

Thus, in the likely event that the asthma–obesity association is a rather specific phenomenon, low or negative outcomes may result from a ‘dilution’ or the absence of the relevant subset within the population sample examined. For example, obesity was not associated with asthma in a rather small case–control study among primarily African-American adolescents [50]. Similarly, no association between overweight and a maternal report of current, diagnosed asthma was found among over 11 000 Canadian children, whose upper age range, however, was limited to 11 years [35]. Finally, among Italian children, BMI-SDS was even inversely associated with asthma [47]. These three ‘negative’ studies, however, have a cross-sectional design. By contrast, all the longitudinal studies focusing on obesity and asthma in children have confirmed that obesity is indeed associated with asthma [58–62] (Table 2c). The following additional questions can help clarify the nature of the observed association.

2. Which asthma phenotypes are involved?

To understand the relationship between asthma and obesity, it is useful to check what kind of asthma (e.g. allergic or non-allergic, with or without bronchial hyper-reactivity) is more frequently associated with a higher BMI. Many studies have focused on the association of obesity with atopic sensitization or bronchial hyper-reactivity. Their results are important to exclude that asthma and obesity have solely a common genetic basis and little to do with these intermediate phenotypes.

2A. Is the obese and asthmatic child also atopic?

An allergic background is highly prevalent among asthmatic children, especially at school age and in

Table 1. Cross-sectional studies on obesity and asthma

Author, ref, PY, country	Sample size (n); age (years); setting	Main positive outcomes	Main negative outcomes
Saha, 2005 [31] (USA)	2544; 5–18 y; primary health care	Asthma (doctor's diagnosis) associated with overweight (BMI percentile > 95) in female subjects (OR 1.8) than in male subjects (OR 1.6)	
Sulit, 2005 [32] (USA)	788; 8–11 y; community based	Wheeze associated with obesity (OR 1.57; CI 1.10, 2.44)	
Wickens, 2005 [33] (NZ)	871 (in 1989), 894 (in 2000); 12 y; community based	Increasing BMI-SDS associated with current wheeze ($P = 0.002$), inhaled steroid use ($P = 0.004$), and the use of any medication ($P = 0.001$)	No gender effect. Significant increases in the prevalence of wheeze and asthma between 1989 and 2000 were not explained by a concurrent increase in the prevalence of obesity
Bibi, 2004 [34] (ISR)	5984	Obese vs. non-obese children had more wheezing (14.5% vs. 10.5%; $P < 0.038$), asthma (physician diagnosis) (7.2% vs. 3.9%, $P < 0.008$), inhaler use (15.9% vs. 8.8%, $P < 0.001$)	BHR significantly greater among the non-obese than obese asthmatic (51.4% vs. 27.8% ($P < 0.001$))
To, 2004 [35] (CAN)	11199; 4–11 y		The OR for asthma, comparing the highest and lowest BMI categories, was 1.02 (99% CI, 0.70–1.46) for boys and 1.06 (99% CI, 0.67–1.69) for girls
Rizwan, 2004 [36] (UK)	1171 in 1991, 2368 in 1993, 1964 in 1998; 5–11 y; community based	Obesity associated with doctor-diagnosed asthma (OR 1.74, 95% CI, 1.29–2.37) and cough, wheeze, and breathlessness (OR 1.88, 95% CI, 1.21–2.90).	
Schachter, 2003 [37] (AUS)	5993; 7–12 y; community based	BMI associated with wheeze ever (OR 1.06, $P = 0.007$) and cough (OR 1.08, $P < 0.001$). In girls, but not in boys, a higher BMI associated with atopy ($P < 0.005$), wheeze ever ($P < 0.001$), and cough ($P < 0.001$)	BMI not associated with recent asthma (OR 1.02, $P = 0.43$) or airway hyper-responsiveness (OR 0.97 $P = 0.17$)
Rodriguez, 2002 [38] (USA)	12 388; 0–16 y; general US population	Asthma associated with a higher BMI (> 85 percentile) (OR 1.94; CI 1.09–3.46)	
von Kries, 2001 [39] (GER)	9357; 5–6 y; community based	Asthma in girls associated with overweight (OR 2.12; 95% CI 1.22–3.68) and obesity (OR 2.33; 95% CI 1.13–4.82)	No relation between asthma and weight in boys. Hayfever and eczema were unrelated to weight in girls and boys
von Mutius, 2001 [40] (USA)	7505; 4–17 y; US general population	BMI associated with asthma (adjusted OR 1.8, 95% CI 1.4–2.2 between the highest and lowest quartiles of BMI)	No independent relation between BMI and atopy or eosinophilia. No effect modification by sex or ethnic group
Chinn, 2001 [41] (UK)	6740 in 1982 and 9356 in 1994; 8–9 y; representative of the general population		Asthma prevalence increased from 1982 to 1994. Unadjusted and adjusted ORs per year for asthma, wheeze, and 'asthma or bronchitis' were virtually identical both in boys and in girls
Figueroa-Munoz, 2001 [42] (UK)	14 908; 4–11 y; representative of the general population	BMI (10th vs. 90th centiles) associated with asthma (OR 1.28, 95% CI 1.11–1.48)	The sum of skinfolds was unrelated to asthma symptoms in most analyses
Epstein, 2000 [43] (USA)	5154; 6–16 y; representative of the US general population	BMI (20.9 vs. 19.4) and prevalence of obesity (1.53; 1.25–2.46) higher in children with asthma	
Huang, 1999 [44] (Taiwan)	1459; 13–15 y; community based	BMI (highest quintile) associated with atopy (adjusted OR 1.77; 1.15–2.73) in girls; BMI (lowest quintile) inversely associated with BHR (OR 0.40; 0.20–0.81)	No association between BMI and atopy or BHR was found in boys
Schwartz, 1990 [45] (USA)	6839; 6 mo–11 y; representative of the US general population	Frequent wheeze associated with triceps skinfold thickness (increase in odds of asthma for 2 SD increase in skinfold, OR 1.6)	
Somerville, 1984 [46] (UK)	7800; 5–11 y	Weight for height was associated with bronchitis, 'chest ever wheezy', and 'colds usually going to the chest'	

OR, odds ratio; BMI, body mass index; CI, confidence interval; mo, months, BHR, bronchial hyper-responsiveness.

Table 2. Case–control and longitudinal studies on obesity and asthma

Author, ref, PY, country	Sample size (n); age (years)	Main positive outcomes	Main negative outcomes
<i>a. Case–control studies</i>			
Vignolo, 2005 [47] (Italy)	554 asthma, 625 controls; 2–16 y	BMI-SDS higher in controls than in asthmatics ($P = 0.04$). BMI-SDS was lower in those not treated with inhaled corticosteroids (IGCs) ($P = 0.02$)	Overweight/obesity (BMI-SDS ≥ 2) similar in controls and in asthmatic patients ($P = 0.08$)
Calvert, 2005 [48] (South Africa)	380 with exercise-induced bronchospasm, 393 controls; 8–12 y	BMI associated with exercise-induced bronchospasm and with a greater strength of association between specific IgE and the corresponding skin test	
Mai, 2003 [49] (Sweden)	161 current wheeze, 296 controls; 12 y	Current wheeze associated with overweight (adjusted OR 1.9, 1.0–3.6). Asthma severity (wheezing episodes last 12 months) associated with high BMI (adjusted OR 2.0, 1.0–4.0)	
Brenner, 2001 [50] (USA)		The prevalence of obesity in the asthmatic group was 20% compared with 17% in the control group	Overweight similar in asthmatics (16%) and controls (15%). Obesity not different in moderate to severe asthmatics (21%) in mild asthmatics (19%) or controls (17%)
Gennuso, 1998 [51] (USA)	85 asthma, 86 controls; 4–16 y	A very high BMI (> 95 percentile) more frequent in children with asthma (30.6%) than in controls (11.6%) ($P = 0.004$)	Asthma severity was not related to obesity
Luder, 1998 [52] (USA)	209 asthma, 1017 controls; 2–18 y	Overweight associated with moderate to severe asthma and more severe asthma symptoms	
Mai, 2004 [53] (Sweden)	74 very low birth weight, 64 normal birth weight	In the VLBW group, overweight associated with current asthma (adjusted OR 5.8, 1.2–27)	
<i>b. Patient series</i>			
Tantisira, 2003 [54] (USA)	1039; 5–12 y	BMI associated with worse bronchodilator response	BMI not related to school absence, ER visits, hospital admissions, doctor's visits, days on steroids, physical education restriction, cough/wheeze at rest, eosinophil count, total IgE, or methacholine sensitivity.
Pianosi, 2004 [55] (Canada)	64; 8–12 y	Overweight or obese children reported greater limitation of physical activity and asthma-impairment scores, which were related to greater medication needs	Appropriate-weight, overweight, or obese (defined by BMI) children all had similar results for maximum aerobic power and level of habitual activity. Standard measures of pulmonary function were no different among groups
Belamarich, 2000 [56] (USA)	1322; 4–9 y	Obese children were more likely to have used oral steroids (30% vs. 24%), a higher mean number of days of wheeze per 2-week period (4.0 vs. 3.4), and unscheduled ED visits (39% vs. 31%)	There were no differences between groups in terms of baseline PEF scores. There were no differences between the groups in terms of frequency of hospitalization, or in nocturnal awakening
Blandon, 2004 [57] (Spain)	100	QOL (PAQLQ) was lower in obese asthmatic patients	Overweight and normal weight had no effect on QOL
<i>c. Longitudinal studies</i>			
Hancox, 2005 [58] (USA)	DMHDS; birth cohort; 1972–1973; 26 y; $n = 1037^*$	In females, a higher BMI after puberty associated with new onset of asthma in females, lower FEV ₁ /FVC, and higher total IgE	No association between BMI and asthma, lung function, or total IgE in males
Guerra, 2004 [59] (USA)	TCRS Study; birth cohort; 1980–1984; 16 y; $n = 781$	Overweight or obesity at 11 y associated with unremitting asthma after puberty both in subjects with infrequent wheezing (OR 5.2; 1.6–17.1) and those with asthma (OR 8.9; 1.7–46.8) in the pre-pubertal period; early onset of puberty in both groups was also significantly associated with persistence of wheezing after puberty onset ($P = 0.022$; $P = 0.019$, respectively)	

Table 2. Continued

Author, ref, PY, country	Sample size (n); age (years)	Main positive outcomes	Main negative outcomes
<i>c. Longitudinal studies*</i>			
Gilliland, 2003 [60] (USA)	Children's Health Study; prospective; 1993–1996; age at entry 7–18; follow-up: 4 y; n = 3792	New-onset asthma associated with overweight (RR 1.52, 1.14, 2.03) or obesity (RR 1.60, 1.08, 2.36). Overweight effect greater in boys (RR 2.06, 1.33–3.18) than in girls (RR 1.25, 0.83–1.88), and in non-allergic children (RR 1.77, 1.26–2.49) than in allergic children (RR 1.16, 0.63–2.15)	
Gold, 2003 [61] (USA)	Six-city Study; prospective; 1974–1979; age at entry <10 y in 90%; mean f.u. 5 y; n = 9828	New asthma onset associated with higher BMI at entry into the study ($P = 0.009$) and with a greater increase in BMI during follow-up ($P = 0.0003$) in girls only	New asthma diagnosis not associated with higher BMI in boys
Castro-Rodriguez, 2001 [62] (USA)	TCRS Study; birth cohort; 1980–1984; 13 y; n = 708	In females, overweight or obesity at 11 y associated with current wheezing at 11 and 13 y but not at 6 or 8 y. Effect strongest if menarche <11 y. In females, overweight or obesity between 6 and 11 y associated with a seven times higher likelihood of new asthma at 11 or 13 y ($P 0.0002$), increased peak flow variability and bronchodilator responsiveness	BMI at 6 y not associated with wheezing. No association seen in males between pre-pubertal overweight/obesity and new asthma symptoms or BHR in early adolescence

*Study acronym; design; birth years and follow-up; sample size (n); age (years).

OR, odds ratio; BMI, body mass index; QOL, quality of life, FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; BHR, bronchial hyper-responsiveness.

westernized countries. Thus, it would be of interest to know whether obesity is associated not only with asthma but also with an atopic background. This hypothesis is not inconceivable, considering that the adipocyte is a well-recognized source of inflammatory cytokines [8, 9] and that raised plasma levels of eotaxin have recently been found in obese adults [63].

Unfortunately, only a minority of studies have also tested atopy-related parameters; they led to totally conflicting conclusions (Table 3). In a study of 9000 German schoolchildren aged 5–6 years, doctor-diagnosed asthma, but not hayfever and eczema, was related to overweight in girls, suggesting that the obesity–asthma association is related to factors other than atopic sensitization at this early age [39]. Similarly, a significantly positive association between BMI and asthma was found, whereas no independent relation between BMI and atopy or eosinophilia was evident among over 7500 children aged 4–17 participating in an NHANES-III study [40]. In another study of 12-year-old New Zealand children, BMI was associated with wheezing but not with bronchial hyper-responsiveness (BHR) or atopy [33]. In a case–control study among Italian children, BMI-SDS was higher in controls rather than asthmatic subjects, independent from atopic sensitization and comorbidity with other allergic symptoms [47]. Most importantly, in the Children Health Study, the risk of new-onset asthma during about 4 years after recruitment was higher among children who were

overweight or obese at recruitment. However, the effect of being overweight was limited to non-allergic children (RR = 1.77%, 95% CI: 1.26, 2.49) and absent in allergic children (RR = 1.16%, 95% CI: 0.63, 2.15) [61].

By contrast, among 7–12-year-old Australian girls, but not in boys, a higher BMI was very significantly associated with a higher prevalence of atopy, wheezing, and cough [37]. Similarly, among girls participating in the Dunedin cohort study, those who became both asthmatic and obese after puberty were also more frequently atopic [58]. In this latter study, total IgE was associated with a higher BMI [58]. An association between obesity and atopy was also found among Taiwanese girls [44].

Conclusions on the association between obesity and atopy and the role of atopy in the obesity–asthma link can hardly be drawn from these conflicting data. This scenario is even further complicated by recent data showing that increasing BMI was associated with skin sensitization but not with the corresponding serum IgE antibodies among 380 South African schoolchildren (age 8–12) with exercise-induced bronchospasm, as well as in 393 age-matched controls [48].

2B. Is wheezing in the obese child associated with BHR?

Obese people experience dyspnoea more often, which is often interpreted as a sign of asthma and referred to as wheezing. Obesity may be associated with a lack of fitness and may contribute to breathlessness, which could lead to asthma over-reporting and to diagnostic confusion

Table 3. Summary of evidence on the link between obesity and asthma in children (numbers indicate references)

	Yes (ref.)	No (ref.)
1. Is asthma linked to obesity?		
Cross-sectional population studies	[31–34, 36, 38–46]	[35]
Case–control studies or studies in patients	[48–53]	[47]
Prospective studies	[58–62]	
2. Are the obesity and asthma epidemics interrelated?		
Serial cross-sectional population studies	[36]	[33, 41]
3. Which asthma phenotypes are involved?		
Respiratory symptoms (wheeze, cough, breathlessness)	[34, 54]	
Lower FEV ₁ /FVC	[58]	
BHR		[34, 49, 54, 58]
Other allergic diseases		[61]
Atopic sensitization	[37, 39, 44, 48, 58]	[33, 39, 40, 42, 49, 54]
Eosinophilia		[37, 40]
Total IgE	[58]	[37]
4. Does obesity precede asthma?		
Prospective studies	[58–62]	
5. Is there a gender effect in the association?		
Cross-sectional population studies	[31(f), 39(f), 44(f), 54(f)]	[33–38, 40]
Case–control studies		[47, 48, 51]
Prospective studies	[58(f), 60(m), 61(f), 62(f)]	[59]
6. Is BMI causally linked to asthma severity?		
Case–control studies	[49]	[50, 51]
Cross-sectional in patients	[55, 57]	[55]
Prospective		[58]

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; BHR, bronchial hyper-responsiveness; BMI, body mass index; IgE, immunoglobulin E.

between wheeze and asthma. In these cases, is the wheezing associated with bronchial inflammation and BHR? The available evidence is unequivocal and negative on this point (Table 2c).

In one study, a large population of almost 6000 Israeli children, obese children tended to wheeze more than non-obese children: 14.5% vs. 10.5%, respectively ($P < 0.038$). Asthma (physician diagnosis) was also much more frequent among obese children than non-obese children: 7.2% vs. 3.9%, respectively ($P < 0.008$). In addition, inhaler use was more prevalent among obese children than non-obese children: 15.9% vs. 8.8%, respectively ($P < 0.001$). However, BHR was significantly greater among the non-obese than obese asthmatics: 352 (51.4%) vs. 10 (27.8%), ($P < 0.001$). This suggests that a high BMI

Table 4. Major mechanistic explanations of the obesity–asthma link (26)

1 Obesity reduces lung tidal volume and functional residual capacity
2 Obesity enhances gastroesophageal reflux, thus leading to bronchoconstriction
3 Obesity is linked to a higher production of pro-inflammatory cytokines (TNF, IL-6, IL-1b)
4 Leptin, an obesity-related hormone, may act directly on the lung or through the SNS
5 Genetic polymorphisms may be important for both asthma and obesity
6 Oestrogen-dependent, gender-specific genetic effects may link obesity and steroid-resistant asthma in females
7 Physical activity and diet during pregnancy can influence programming of fetal asthma- and obesity-genes
8 Low intake of anti-oxidants or ω -3 fatty acids and a high total caloric intake may underly both obesity and asthma
9 High birth weight might be associated with both obesity and asthma later in life

among children is a risk factor for obesity-related chest symptoms that mimic asthma [34]. Similarly, a higher BMI was not associated with methacholine sensitivity but with a lower post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) ratio among asthmatic children participating in the CAMP study [54]. Among females participating in the Dunedin study, obesity was associated with asthma appearing after puberty but not with BHR [58].

Taken together, these studies have shown that asthma occurring in obese children is less often accompanied by BHR than asthma occurring in children with a normal weight.

3. Which comes first: asthma or obesity?

Temporality is one major criterion for attributing causality and directionality to an association. Obviously, a cause must precede its effect. Five prospective studies, completed in four different populations (including two birth cohorts), have clearly allowed to exclude that asthma may cause obesity. On the contrary, the Dunedin study has shown that girls with asthma at 9 years of age had a significantly lower BMI at 26 years of age [58].

All the five studies suggested that overweight and obesity can precede asthma or its worsening (Table 2c). In the Tucson birth cohort study, overweight or obesity at 11 years was highly independently associated with unremitting asthma after the onset of puberty both in subjects with infrequent wheezing and those with asthma in the pre-pubertal period [59]. In the same Tucson birth cohort, females who became overweight or obese between 6 and 11 years of age were seven times more likely to develop new asthma symptoms at age 11 or 13 [62].

Two other prospective studies reinforce the evidence from the birth cohort studies. In the Children Health

Study, the risk of new-onset asthma was higher among children who were overweight or obese at recruitment. Boys had an increased risk associated with being overweight in comparison with girls. The effect of being overweight was greater in non-allergic than in allergic children [60]. In the six-city study, an increased risk of a new asthma diagnosis in girls was associated with a higher BMI at entry into the study as well with a greater increase in BMI during follow-up [61].

The evidence from the Dunedin study is different. In this study, a raised BMI after puberty is associated with new onset of asthma in women. This is the only study attempting to calculate the population's fraction of asthma attributable to obesity: it was estimated that among females who developed asthma after age 9, the cause may have been overweight in 28% (95% CI 7–45). In this study, a higher BMI was also associated with lower FEV₁/FVC in women, independently from asthma. However, it was not possible to establish whether obesity preceded asthma or whether they emerged simultaneously in the same participants [58]. Indeed, subjects were examined at only four time-points between 14 and 26 years of age (15, 18, 21, 26) [58]; thus, the length of the inter-observational periods (range 2–5 years) and the definition of asthma used in this study (a self-report of diagnosed asthma with symptoms in the previous year) prevented a more precise analysis of the timing and sequence of events in the development of the association.

4. Is the link limited to girls only?

Cross-sectional studies provide conflicting data as to whether the association of BMI with asthma-related outcomes is affected by gender. In many valuable studies, including one birth cohort study, these associations are stronger in girls than in boys; by contrast, no major differences among sexes were observed in a similar number of valuable cross-sectional and prospective studies as well (Table 3). The gender issue is even more complicated by a single prospective study clearly showing that among overweight children, the risk of new-onset asthma was evident among boys (RR = 2.06%, 95% CI: 1.33, 3.18) but not in girls (RR = 1.25%, 95% CI: 0.83, 1.88) [60].

However, these differences are not always in reciprocal conflict, as positive and negative outcomes are often related to different parameters and coexist in the same study. For example, in the Tucson birth cohort study, females, *but not* males, who became overweight between 6 and 11 years of age were seven times more likely to develop new asthma symptoms at age 11 or 13 [62]. Menarche before the age of 11 was also a risk factor for asthma symptoms. By contrast, in this same cohort, overweight or obesity among wheezers at 11 years predicted unremitting asthma after puberty in *both* males and females, thus excluding a gender effect in this outcome [59].

When referring to a gender effect in the relation between asthma and obesity in childhood, it is therefore important to specify not only the parameter taken into consideration but also the age at which the effect is to be observed, as some associations might be seen only in certain 'window periods' of development.

5. Does obesity cause asthma or simply make it worse?

By common sense, being slightly overweight may not affect the severity of asthma, but a high degree of obesity could indeed be very relevant. Several studies have been aimed at distinguishing whether obesity is an amplifier of symptoms in asthmatic patients (Table 3). Among 161 Swedish children (age 12) with current wheeze, the number of wheezing episodes during the previous 12 months was significantly higher among overweight vs. children with a normal weight [49]. In the NCICAS prospective study among children with inner-city asthma, obese children had a higher mean number of days of wheeze per 2-week period and of unscheduled ED visits. There were no differences, however, between obese and non-obese children in the hospitalization frequency, or in nocturnal awakening [56].

A very interesting observation has been made regarding 64 asthmatic Canadian children, showing how opposite outcomes can be obtained in the same study without being in conflict. In this rather small cohort, normal weight, overweight, or obese children all had similar results for maximum aerobic power and level of habitual activity. However, overweight or obese children reported greater limitation of physical activity. Their asthma-impairment scores were higher than the scores of appropriate-weight peers, although standard measures of pulmonary function were not different among groups. The higher asthma-severity scores were related to greater medication needs in the overweight or obese children with asthma. The authors concluded that lower maximum aerobic power in asthmatic children is related more to how capable they perceive themselves than to real asthma severity. Overweight asthmatic children may perceive their asthma as worse and experience greater limitation of physical activity. They receive more prescriptions of medication, although by standard measures of asthma severity they are very similar to normal-weight peers with asthma [55]. Accordingly, among 100 Spanish children with asthma, an index of quality of life (QOL) (PAQLQ) revealed a significantly lower QOL in obese asthmatic patients, while overweight and normal weight had no effect on QOL [57].

Weight-loss and bariatric surgery studies among adults with asthma have rather clearly shown that reduction of severe or moderate obesity is helpful in improving objective lung function parameters and both the frequency and severity of respiratory symptoms [23]. No such studies, to our knowledge, are yet available in children.

Conclusions: research and public health implications

The present analysis of the epidemiological literature in children suggests that different explanations may underlie the association of asthma with obesity at different ages and genders. It is conceivable that severe obesity in adolescent females may aggravate asthma through mechanisms different from those linking pre-pubertal obesity to unremitting asthma in males. It is important therefore that future paediatric studies take advantage of the available hypotheses of the specific mechanisms linking obesity to asthma. These hypotheses have been thoroughly discussed elsewhere [5, 8, 26] and are briefly summarized in Table 4.

More specific questions should be addressed, and longitudinal, observational studies may focus not only on reported diagnosis of asthma but also on objective markers of intermediate phenotypes of asthma (lung function, bronchial hyper-reactivity, atopic sensitization, etc.). The follow-up of these studies should combine objective evaluation of anthropometric measures and a high evaluation frequency. The latter is also essential to establish the exact time of asthma onset and therefore to investigate accurately whether obesity precedes asthma onset. In parallel, longitudinal studies should also monitor a wider set of confounders and in particular both diet and physical activity to ascertain their respective role in the interaction.

A public health perspective is relevant: over-perception of respiratory symptoms and over-prescription of anti-asthmatic drugs among obese children should be carefully tested. On the other hand, obesity should be reconsidered as an important co-factor to be addressed by therapeutic and prevention guidelines for childhood asthma. Needless to say, the enormous burden of chronic diseases linked to the epidemic trend of obesity calls for further expansion of public health efforts to promote and implement healthy diet and physical activity strategies from early childhood on.

References

- Woolcock AJ. Evidence for the increase of asthma worldwide. *Ciba Found Symp* 1997; **206**:122–34.
- World Health Organization. *Obesity: preventing and managing the global epidemic*. WHO Technical Report Series 894. Geneva, Switzerland, WHO, 2000.
- World Health Organization. *Risk factors*. World Health Report 2002. Geneva, Switzerland: WHO, 2002.
- World Health Organization. *Preventing chronic diseases: a vital investment*. Geneva, Switzerland: WHO, 2005.
- Weiss ST, Shore S. Obesity and asthma. Directions for research. *Am J Respir Crit Care Med* 2004; **169**:963–8.
- Wirrell E, Cheung C, Spier S. How do teens view the physical and social impact of asthma compared to other chronic diseases? *J Asthma* 2006; **43**:155–60.
- Deane S, Thomson A. Obesity and the pulmonologist. *Arch Dis Child* 2006; **91**:188–91.
- Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001; **56**:64–74.
- Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Low-grade-systemic inflammation in overweight children. *Pediatrics* 2001; **107**:E13–8.
- Maffei M, Halaas J, Ravussin E *et al.* Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1995; **1**:1155–61.
- Loffreda S, Yang SQ, Lin HZ *et al.* Leptin regulates pro-inflammatory immune responses. *FASEB J* 1998; **12**:57–65.
- Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol* 2005; **116**:1235–41.
- Hall IP, Wheatley A, Wilding P, Liggett SB. Association of Glu 27 beta2-adrenoceptor polymorphism with lower airway reactivity in asthmatic subjects. *Lancet* 1995; **345**:1213–4.
- Dewar JC, Wilkinson J, Wheatley A *et al.* The glutamine 27 beta2-adrenoceptor polymorphism is associated with elevated IgE levels in asthmatic families. *J Allergy Clin Immunol* 1997; **100**:261–5.
- Meirhaeghe A, Helbecque N, Cottel D, Amouyel P. Beta2-adrenoceptor gene polymorphism, body weight, and physical activity. *Lancet* 1999; **353**:896.
- Albuquerque RV, Hayden CM, Palmer LJ *et al.* Association of polymorphisms within the tumour necrosis factor (TNF) genes and childhood asthma. *Clin Exp Allergy* 1998; **28**:578–84.
- Moffatt MF, James A, Ryan G, Musk AW, Cookson WO. Extended tumour necrosis factor/HLA-DR haplotypes and asthma in an Australian population sample. *Thorax* 1999; **54**:757–61.
- Bilolalikar H, Nam AR, Rosenthal M, Davies JC, Henderson DC, Balfour-Lynn IM. Tumour necrosis factor gene polymorphisms and childhood wheezing. *Eur Respir J* 2005; **26**:637–46.
- Norman RA, Bogardus C, Ravussin E. Linkage between obesity and a marker near the tumor necrosis factor-alpha locus in Pima Indians. *J Clin Invest* 1995; **96**:158–62.
- Garenc C, Perusse L, Chagnon YC *et al.* HERITAGE Family Study. Effects of beta2-adrenergic receptor gene variants on adiposity: the HERITAGE Family Study. *Obes Res* 2003; **11**:612–8.
- Zhang S, Smartt H, Holgate ST, Roche WR. Growth factors secreted by bronchial epithelial cells control myofibroblast proliferation: an *in vitro* co-culture model of airway remodeling in asthma. *Lab Invest* 1999; **79**:395–405.
- Chinn S. Asthma and obesity: where are we now? *Thorax* 2003; **58**:1008–10.
- Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005; **115**:897–909.
- Brisbon N, Plumb J, Brawe R, Paxman D. The asthma and obesity epidemics: the role played by the built environment – a public health perspective. *J Allergy Clin Immunol* 2005; **115**:1024–8.
- Sood A. Does obesity weigh heavily on the health of the human airway? *J Allergy Clin Immunol* 2005; **115**:921–4.
- Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol* 2005; **6**:537–9.
- Shaheen SO. Obesity and asthma: cause for concern? *Clin Exp Allergy* 1999; **29**:291–3.
- Chinn S. Concurrent trends in asthma and obesity. *Thorax* 2005; **60**:3–4.

- 29 Gold DR. Less childhood obesity – less persistence of wheeze in teenage girls and boys? *Am J Respir Crit Care Med* 2004; **170**:8–9.
- 30 Tasali E, Van Cauter E. Sleep disordered breathing and the current epidemic of obesity. Consequence or contributing factor? *Am J Respir Crit Care Med* 2002; **165**:562–3.
- 31 Saha C, Riner ME, Liu G. Individual and neighborhood-level factors in predicting asthma. *Arch Pediatr Adolesc Med* 2005; **159**:759–63.
- 32 Sulit LG, Storfer-Isser A, Rosen CL, Kirchner HL, Redline S. Associations of obesity, sleep-disordered breathing, and wheezing in children. *Am J Respir Crit Care Med* 2005; **171**:659–64.
- 33 Wickens K, Barry D, Friezema A *et al*. Obesity and asthma in 11–12 year old New Zealand children in 1989 and 2000. *Thorax* 2005; **60**:7–12.
- 34 Bibi H, Shoseyov D, Feigenbaum D *et al*. The relationship between asthma and obesity in children: is it real or a case of over diagnosis? *J Asthma* 2004; **41**:403–10.
- 35 To T, Vydykhan TN, Dell S, Tassoudji M, Harris JK. Is obesity associated with asthma in young children? *J Pediatr* 2004; **144**:162–8.
- 36 Rizwan S, Reid J, Kelly Y, Bundred PE, Pearson M, Brabin BJ. Trends in childhood and parental asthma prevalence in Merseyside, 1991–1998. *J Public Health (Oxford)* 2004; **26**:337–42.
- 37 Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. *Thorax* 2003; **58**:1031–5.
- 38 Rodriguez MA, Winkleby MA, Ahn D, Sundquist J, Kraemer HC. Identification of population subgroups of children and adolescents with high asthma prevalence: findings from the Third National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med* 2002; **156**:269–75.
- 39 von Kries R, Hermann M, Grunert VP, von Mutius E. Is obesity a risk factor for childhood asthma? *Allergy* 2001; **56**:318–22.
- 40 von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 2001; **56**:835–8.
- 41 Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax* 2001; **56**:845–50.
- 42 Figueroa-Munoz JI, Chinn S, Rona RJ. Association between obesity and asthma in 4–11 year old children in the UK. *Thorax* 2001; **56**:133–7.
- 43 Epstein LH, Wu YW, Paluch RA, Cerny FJ, Dorn JP. Asthma and maternal body mass index are related to pediatric body mass index and obesity: results from the Third National Health and Nutrition Examination Survey. *Obes Res* 2000; **8**:575–81.
- 44 Huang SL, Shiao GM, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy* 1999; **29**:323–9.
- 45 Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Association with social class, perinatal events, and race. *Am Rev Respir Dis* 1990; **142**:555–62.
- 46 Somerville SM, Rona RJ, Chinn S. Obesity and respiratory symptoms in primary school. *Arch Dis Child* 1984; **59**:940–4.
- 47 Vignolo M, Silvestri M, Parodi A *et al*. Relationship between body mass index and asthma characteristics in a group of Italian children and adolescents. *J Asthma* 2005; **42**:185–9.
- 48 Calvert J, Burney P. Effect of body mass on exercise-induced bronchospasm and atopy in African children. *J Allergy Clin Immunol* 2005; **116**:773–9.
- 49 Mai XM, Nilsson L, Axelsson O *et al*. High body mass index, asthma and allergy in Swedish schoolchildren participating in the international study of asthma and allergies in childhood: phase II. *Acta Paediatr* 2003; **92**:1144–8.
- 50 Brenner JS, Kelly CS, Wenger AD, Brich SM, Morrow AL. Asthma and obesity in adolescents: is there an association? *J Asthma* 2001; **38**:509–15.
- 51 Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. *Arch Pediatr Adolesc Med* 1998; **152**:1197–200.
- 52 Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr* 1998; **132**:699–703.
- 53 Mai X-M, Böttcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. *Pediatr Allergy Immunol* 2004; **15**:523–30.
- 54 Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Childhood Asthma Management Program Research Group. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax* 2003; **58**:1036–41.
- 55 Pianosi PT, Davis HS. Determinants of physical fitness in children with asthma. *Pediatrics* 2004; **113**:e225–9.
- 56 Belamarich PF, Luder E, Kattan M *et al*. Do obese inner-city children with asthma have more symptoms than nonobese children with asthma? *Pediatrics* 2000; **106**:1436–41.
- 57 Blandon Vijil V, del Rio Navarro B, Berber Eslava A, Sierra Monge JJ. Quality of life in pediatric patients with asthma with or without obesity: a pilot study. *Allergol Immunopathol (Madrid)* 2004; **32**:259–64.
- 58 Hancox RJ, Milne BJ, Poulton R *et al*. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005; **171**:440–5.
- 59 Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004; **170**:78–85.
- 60 Gilliland FD, Berhane K, Islam T *et al*. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol* 2003; **158**:406–15.
- 61 Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol* 2003; **36**:514–21.
- 62 Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmatic symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001; **163**:1344–9.
- 63 Vasudevan AR, Wu H, Xydakis AM *et al*. Eotaxin and obesity. *J Clin Endocrinol Metabol* 2006; **91**:256–61.