

Article Type : Invited Review

Title: **Obesity and atopy**

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12435

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Key-words : Asthma, obesity, allergy.

Abstract

The prevalence of obesity has increased worldwide and weight gain has been shown to influence the development and clinical expression of various conditions including asthma. The relationships between atopy and obesity remain uncertain, both in adults and children. Although there are physiopathologic mechanisms which could explain how obesity could influence the immune system and promote the process of sensitization, evidences in favor of a possible role of obesity on the development of atopy have been inconsistent. Furthermore, the bulk of evidence suggests that atopy does not mediate the relationship between obesity and asthma, although in some populations, particularly in children and women, such association has been reported. Such lack of relationship has also been found with rhinoconjunctivitis although it has been observed for atopic dermatitis. Several factors may explain these variable results, including populational or environmental characteristics, socioeconomic status, confounding factors, in addition to sample size and methodology of the performed studies. The possibility that obesity influences atopy through its effects on sex hormones is suggested by a more frequent link between atopy and obesity in women, particularly post-puberal. Further research should be conducted on the influence of weight gain on atopy and atopic diseases.

Introduction

Obesity is increasingly common and this problem has taken epidemic proportions worldwide [1, 2]. Such increase in body weight has numerous consequences, including reduced quality of life and promotion of the development or worsening of many diseases, and therefore resulting in a major burden to health systems [3, 4]. More recently, obesity has also been

considered to contribute to the development of conditions such as asthma and a specific phenotype of asthma has been described in obese individuals [5, 6]. The mechanisms linking asthma and obesity are however uncertain but factors such as developmental, hormonal, inflammatory or mechanical influences induced by weight gain have been proposed [7, 8].

Atopy is a known major factor in the development of asthma [9, 10]. It has been proposed that obesity could favor the development of atopy, and contribute to the relationship observed between asthma and obesity, although this is still debated. In the following lines, the data gathered on the relationship between atopy and obesity as well as the contribution of atopy in asthma in the obese will be reviewed. A *pubmed* search was conducted using the key-words “obesity”, “BMI”, “overweight”, “atopy”, “asthma”, “allergy” and “allergic diseases” without restriction in regard to age. References from these publications were also examined to look for additional studies.

Is there a relationship between obesity and atopy

Positive studies

A number of studies have suggested that overweight and obesity, defined as a body mass index (BMI) of 25-29.9 and ≥ 30 kg/m² respectively, could be considered as a potential risk factor for atopy or that obesity could increase the effects of allergy on the airways. I will describe studies in children first, then in adult or mixed populations.

Initial studies included a report from Huang et al. [11], who looked at the association between BMI and atopy in 1,459 students from 7 junior high schools (mean age : 13.6

years). The prevalence of atopy was 42% in boys and 27% in girls. BMI was a significant predictor of atopy, allergic symptoms and airway hyperresponsiveness (AHR, a common physiological feature of asthma but also sometimes found in subjects with allergic rhinitis) in teenage girls. The more obese female children had a higher prevalence of atopy and rhinitis and the BMI-rhinitis association was related to the BMI-atopy interaction. Von Mutius et al. [12] also reported an analysis of data gathered from the National Health and Nutrition Examination Study III (NHANES III), indicating that the prevalence of atopy in children increased significantly with increasing quartiles of BMI. Furthermore, Visness et al [13] reported a higher geometric mean total immunoglobulin E (IgE) levels in obese and overweight children compared to normal-weight children and adolescents from 2 to 19 years old. The odds ratios for atopy were increased in the obese children compared with normal weight children, an association largely driven however by allergic sensitization to foods. Finally, in a study of 486 schoolchildren out of whom 98 were overweight or obese [14], obesity was not associated with atopy, while a subgroup analysis suggested that cockroach sensitization was more frequently observed in obese or overweight males.

Gender differences in regard to the obesity-atopy relationship were also observed in other studies. In this regard, Castro-Rodriguez [15] looked at a birth cohort of 1246 children enrolled between 1980 and 1984 in the longitudinal Tucson Children's Respiratory Study. They observed a trend in women only for an association between change in BMI status and the prevalence of atopy defined as the presence of at least one positive skin test to local allergens at six years of age. Indeed, 54.2% of females who became overweight or obese were allergy skin-test-positive at age six compared with 35.9% of females who remained with a normal weight ($p=0.08$, Men: 51.5% versus 48.0%, NS). However, there was no relationship between changes in BMI status and the prevalence of at least one positive skin test to local allergens at year 11 for either sex.

A subsequent study by Schachter et al [16] combined data from seven epidemiologic studies of Australian children and reported that, in girls, a higher BMI was significantly associated with a higher prevalence of atopy. This was not observed in boys. The authors suggested that a higher BMI was a risk factor for atopy in girls. Hancox et al. [17] also looked at gender differences in the relationship between BMI, asthma and atopy in a New Zealand birth cohort of close to 1,000 individuals tested on repeated occasions between ages 9 and 26 years. Associations were found between BMI and atopy assessed by skin-prick test and serum IgE in females but there was no convincing evidence of an association between BMI and asthma or atopy in males. The relationship between BMI and atopy seemed to increase with age.

In adolescents, Yoo [18] reported an increased risk of atopy in obese subjects compared with those of normal weight, even after adjusting for sex, age and other covariates. Overweight subjects had more frequent wheezing episodes (11.5 vs. 6.3%, $p = 0.02$), currently or in the previous 12 months compared to normal-weight subjects, especially in boys. Atopy was more common among overweight adolescents than among those of normal weight (61.5 vs. 49.2%, $p = 0.002$), also especially in boys (65.0 vs. 52.8%, $p = 0.005$). Overweight subjects had higher blood eosinophil counts, especially boys. The presence of AHR was however more common only among overweight girls (32.8 vs. 18.0%, $p = 0.028$). Overweight status was a significant risk factor (odds ratio = 1.49; 95% CI 1.06-2.10) for the presence of atopy after adjusting for various confounders.

Xu et al. [19] also found atopy to be associated with current BMI in a large cohort of Finnish adults (analysis performed in 4719 subjects) followed since birth. Ponderal index at birth, expressed as weight (g) times 100 divided by the cube of the length at birth (cm^3), and obesity at the age of 31 were associated with atopy. The authors speculated that these relationships between obesity markers and atopy could possibly be related to common risk

factors, such as genetic determinants, hormonal, dietary and/or lifestyle factors.

In a small sample of adults, Vieira [20] et al. found that the prevalence of an atopic state, as indicated by the presence of specific IgE, was higher in obese compared to nonobese women. Although the frequencies of self-reported allergies and total IgE antibody concentrations were similar between the 2 groups of women, specific IgE were found in 62% of the obese women, compared to 28% of the nonobese women. Otherwise, Chen et al. [21] looked at the relationship between obesity and atopic sensitization in 1,997 Canadian residents aged 18-79 years. Overall, the prevalence of atopy was 33.3% among those with a BMI of at least 30, 28.2% among those with a BMI of 25.0–29.9 and 27.3% among those with a BMI of less than (p = 0.003). Waist circumference was significantly associated with atopy in both genders. The data suggested a significant association between obesity and atopy but it was unclear how obesity, atopy and asthma might be interrelated.

Other reports found an association between atopy or atopic disorders and obesity. Ciprandi et al. found BMI values to be significantly higher in patients with allergic rhinitis (P=0.0002) or allergic asthma (P<0.0001), compared to control subjects [22]. A significant association was also found between BMI and airway hyperresponsiveness (AHR) in both allergic rhinitis and asthma. Furthermore, in Harbin, China, Luo et al [23] studied 266 atopic subjects with a previous diagnosis of atopic disorders such as atopic dermatitis, rhinitis, asthma or food allergy, and a positive response to at least one allergen specific IgE tests to 16 common allergens. Each case was individually matched to two healthy non-atopic controls based on their age, sex, and residential regions. Obesity was significantly associated with the presence of atopic dermatitis and atopic rhinitis in both genders. Obesity was not significantly associated with atopic asthma.

More recently, Cibella et al. [24] reported that asthma and allergic sensitization were significantly more frequent among overweight/obese subjects compared to those with a normal weight (21.0 and 51.6 and 10.2 and 37.0%, respectively). Furthermore, in a retrospective, practice-based, case-control study of randomly sampled 414 children and adolescents, Silverberg et al. [25] showed that obesity predisposed to atopic dermatitis when obesity started under 5 years old only and when obesity was prolonged for more than 2.5 years. Obesity was associated with more severe atopic dermatitis. In their retrospective case-control study of 2090 adults, Silverberg et al. [25] found that obesity in adults was associated with increased atopic dermatitis but not nonatopic dermatitis ($p = 0.01$ compared to $p = 0.32$). The association between obesity and atopic dermatitis remained significant even when controlling for history of asthma, rhinoconjunctivitis and food allergies. Curiously, obesity was not associated with nonatopic asthma, atopic or nonatopic rhinoconjunctivitis, food allergies nor atopy itself.

Negative studies

A number of studies found no association between obesity and atopy, either in children or adults. In the Childhood Asthma Management Program (CAMP) database, Tantisira et al. found that BMI was associated with decreases in the forced expiratory volume in one second over forced vital capacity (FEV1/FVC) ratio, and that neither of the measures of atopy, IgE and eosinophil count, were significantly associated with BMI [26]. As mentioned above, Leung et al. [14] found that obesity status was not associated with asthma, allergic rhinitis or eczema. Atopy was not associated with age-adjusted BMI or waist circumference, and atopy and presence of allergen-specific IgE did not differ between overweight or obese children and those with normal BMI. Furthermore, Kattan et al. [27] studied 368 adolescents with moderate-to-severe asthma, aged 12-20 years, and found that there was no relationship between adiposity or adipokines and total IgE levels, blood eosinophil counts, and exhaled

nitric oxide levels.

Looking at data from 1971 white adults aged 17-73 years from three large pooled epidemiological studies, Schachter et al. found no association between BMI and atopy in adults [28]. In keeping with these results, Jarvis et al. [29], looking at the results from the European Community Respiratory Health Survey found no association between BMI and sensitization to any of tested allergens. Furthermore, Santamaria [30] found no differences in BMI between asthmatic and nonasthmatic subjects nor between atopic and nonatopic subjects in addition to find no increase in FeNO in obese asthmatic subjects. This was similarly found by Van Veen et al. [31], who reported that obese subjects did not differ from those with BMI < 30 with respect to atopy.

In regard to allergic diseases, in a large sample size analysis of 1,247,038 male conscripts born between 1952 and 1977 and enrolled in successive cohorts from the Swedish Military Service Conscription Register, Braback et al. [32] found that obesity was not associated with allergic rhinoconjunctivitis after multivariate analyses with adjustments for confounders. The odds ratios were similar in the three successive cohorts studied from 1952 to 1977. Furthermore, in a letter to the editor, Flexeder et al. [33] reported on 2533 adults aged 19-65 years in whom atopy was assessed by skin prick testing or allergen-specific IgE. The final analysis based on 1,840 individuals with valid data of BMI, skin prick tests, specific IgE and confounders, showed no relationship between atopy and BMI categories. Finally, in a recent study on the relationships between BMI and co-morbidities, Bruno et al. reported that neither eosinophils numbers nor atopy or IgE levels were associated with BMI and asthma severity in adults [34].

In conclusion, the evidence is still lacking to confirm a possible link between obesity and atopy although such relationship seems to exist in sub-groups of children and women.

Further studies on the relationship between obesity and asthma with or without other associated allergic diseases.

As I previously published a review on asthma and obesity in this Journal, I will only summarize some of the evidence on the possible role of atopy to explain the relationship between obesity and asthma, in addition to other allergic diseases.

In addition to previous cross-sectional studies, more recent prospective studies and meta-analyses have confirmed that obesity or BMI precede the development of asthma both in children and adults, suggesting that obesity could favor the development of asthma [35-38]. However, how obesity could influence asthma, both in regard to its development and clinical expression is still uncertain. Atopy was suggested initially as a possible link between the two conditions, although it does not seem to be the case for most asthmatic patients.

Positive studies

In a recent study by Forno et al., atopy was considered to play a role in the adiposity-asthma association in a population of Puerto Rican children. Allergic rhinitis accounted for 22% to 53% of the association with asthma, and sensitization to roaches mediated 29% to 42% of the association with emergency department visits for asthma [39]. Furthermore, in a study by von Kries et al., using questionnaire data collected from 9357 five and six year-old German children, the lifetime prevalence of doctor's diagnosed asthma in normal weight girls was 3.5%, while it was 5.8% for overweight and 10.3% for obese girls, whereas no relation to

weight was found in boys. Hay fever and eczema were unrelated to weight in girls and boys [40]. In regard to adults, in the above cited study by Silverberg et al [25], obesity was associated with increased atopic asthma but not with nonatopic asthma.

As part of International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three data analysis, Mitchell et al. reported an association between overweight and an even stronger one with obesity, and symptoms of asthma and eczema (only in males for this last) in children and adolescents, although this observation could not be extended to rhinoconjunctivitis [41]. In this last study however, atopic status was not recorded, and asthma, rhinoconjunctivitis and eczema are not necessarily allergic diseases [42]. So, their increasing prevalence may have little to do with allergy, especially in the developing world. The observation suggesting an relationship between overweight and persistent eczema was however in keeping with another report [43] showing that being overweight at age 3 years was significantly associated with late-onset or persistent wheeze and persistent eczema both in both boys and girls. The authors of this last study reported that there was no association between BMI and sensitization but that being overweight is associated with an increased risk of allergic disease in childhood, although the strength of the association varies with the gender, age and atopic phenotype.

Negative studies

Gilliland et al. [44] found a relationship between new onset asthma and overweight in non-allergic, but not in allergic children, and suggested that the association between obesity and asthma is related to factors other than atopic sensitization. In the report by Von Mutius et al. [12], the prevalence of asthma and atopy rose significantly ($p=0.0001$ and $p=0.05$ respectively) with increasing quartiles of BMI but there was no evident independent relation between BMI and atopy. The authors suggested that the effects of increased BMI on asthma

could be mediated by other factors such as mechanical properties of the respiratory system associated with obesity or by upregulation of inflammatory mechanisms rather than by allergic eosinophilic inflammation.

Otherwise, the relationship between breastfeeding, asthma, atopy, and child body mass index (BMI) was investigated by Oddy et al. [45] in a prospective birth cohort (n=2860) in Perth, Western Australia, including 2195 children followed up to age 6 years. Asthma was defined as doctor-diagnosed asthma and wheeze in the last year, and atopy was determined by skin prick test. A high BMI was a risk factor for asthma following adjustment for most known risk factors but a high BMI was not associated with atopy.

Furthermore, Visness et al. [37] found the association between BMI and the risk of asthma to be stronger in non-atopic children than in atopic children. Obesity was significantly related to current asthma among children and adolescents. In their study on 486 schoolchildren, Leung et al. [14] reported that obesity status was not associated with asthma, allergic rhinitis or eczema. Atopy was not associated with age-adjusted BMI or waist circumference. Atopy and allergen-specific IgE were similar in overweight and obese children and those with normal BMI.

In the previously cited study by Schachter et al. [28], after adjusting for atopy, age, sex, smoking history, and family history, severe obesity was a significant risk factor for asthma, wheeze and medication use in the previous 12 months, but not for AHR. The association between asthma and obesity was not related to atopy. Underweight subjects seemed to have more significant respiratory problems with a higher prevalence of symptoms.

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In the report from the European Community Respiratory Health Survey [29], a multicentre cross-sectional survey study of young adults showed a positive association between a high BMI and the risk of asthma attacks in women but the authors considered that this was unlikely explained by a higher risk of atopy in obese subjects, as there was no relationship between obesity and markers or manifestations of atopy. Furthermore, in a Swedish study [46], there was a significant association between both overweight, increased waist circumference and asthma but the increase in asthma morbidity in the overweight subjects was found almost exclusively in the non-atopic asthma patients. Also, in the study by Braback et al. [32], obesity was associated with asthma with or without allergic rhinoconjunctivitis

Chen et al. [47] showed that obesity appears more strongly associated with asthma in women than in men, although it was not significant in atopic subjects, suggesting a stronger association between obesity and asthma among nonatopic people than among atopic people. This was consistent with their previous report, [48] showing that the association between obesity and asthma was stronger in non-allergic than allergic adults. The adjusted odds ratios for obese compared to normal weight subjects were respectively 2.56 (95% CI: 1.07, 6.12) and 1.76 (95% CI: 1.04, 3.01) for those without and with a history of respiratory allergy. The authors suggested that the greater prevalence of nonallergic asthma in women could explain the stronger obesity-asthma association seen in women compared with men and children who have a greater prevalence of allergic asthma.

Furthermore, Van Veen et al. [31] showed that in 136 nonsmoking difficult-to-treat asthmatic adults with persistent symptoms despite high doses of inhaled or oral corticosteroids and long-acting bronchodilators, obese patients did not differ from those with BMI < 30 with respect to age, atopy, age of asthma onset and medication dose. Patients with a high BMI

had a lower percentage of sputum eosinophils and sputum neutrophils and lower FENO values as compared with patients with BMI <30.

In an Australian study of 4,060 men and women, Appleton et al. [49] also found an increased risk for asthma for those with central obesity measured by waist circumference and waist/hip ratio and who were non-atopic. When stratified by atopic status, the relationship between obesity markers and asthma was significant in both nonatopic men and women, but not in those who were atopic. Similarly, we also previously observed, looking at national data of the Canadian adult population, that there was a weaker association between obesity and asthma in individuals self-reporting suffering from allergies compared with those who did not, no significant relationship being observed between BMI and atopy in subjects with self-reported physician diagnosis of asthma [50].

Finally, in a general population sample of 3471 individuals aged 19-72 years, Fenger et al. reported that adiposity measures were associated with a higher risk of asthma but the adiposity-asthma associations were significantly stronger in non-atopic than in atopic subjects [51]. Increasing adiposity was associated with lower lung function independent of atopic status. Adiposity measures were not associated with atopy and not consistently associated with FeNO levels.

Finally, in a recent report on study including 18 617 participants aged 6 to 44 years old, Sybilski et al. stated that overweight and obesity were associated with an increased the prevalence of symptomatic asthma in adults, especially in women [52]. In children, overweight was associated with increased prevalence of clinically diagnosed asthma but only a trend towards atopy, while there was no correlation between BMI and sensitization to

aeroallergens. A higher BMI was negatively associated with the prevalence of allergic rhinitis only in overweight and obese man. Being overweight and obese were not significant factors in increased prevalence of atopy for either males or females.

How could we explain a possible relationship between BMI and atopy?

It is difficult to reconcile the above studies and the differences in their outcomes may possibly be related to variations in the population studied, genetic factors or other confounders.

a) Genetic influences

There seems to be links between genetic markers of asthma, atopy and obesity. For example, the β_2 -adrenergic (*ADRB2*) and the glucocorticoid (*NR3C1*) receptors genes have been involved in the development of asthma and obesity, both being located on chromosome 5q [53, 54]. Similarly, polymorphisms of the fractalkine receptor gene *CX3CR1* have been associated with asthma, atopy, and obesity [53, 54]. The possibility that common genetic traits could explain a positive relationship between atopy and obesity in some sub-groups should be further examined

b) Can obesity contribute to atopy and asthma in increasing inflammatory processes?

Obese subjects, with or without metabolic syndrome, are considered to be in a state of increased systemic inflammation, which could theoretically translate into significant airway inflammation. A role of obesity-related increase in systemic inflammation has been proposed but the contribution of such inflammatory process and asthma is still uncertain. Furthermore, despite some positive reports, the possibility that weight gain favors a TH2 type inflammation

is uncertain, at least in adults and children over 5 years old.

In regard to a possible role of systemic inflammation, in a British birth cohort, levels of the systemic inflammatory marker “C-reactive protein” levels were positively correlated with BMI, particularly among females and heavy smokers but the association between C-reactive protein and asthma prevalence was confined to nonatopics [55]. It was therefore considered unlikely that an inflammatory process related or not to atopy, could explain the development of asthma in the obese subject. However, Visness et al. had previously reported that C-reactive protein levels were associated with total IgE, atopy, and food sensitization [13].

Animal models suggest that there may be a close link between obesity and atopy. For example, in mouse models of asthma, obesity was shown to lower the threshold for allergic sensitization, with increased IgE, IL-5, and eosinophilia [56]. Ovalbumin challenge in obese mice resulted in a higher eosinophil accumulation both peri-bronchial and in bone marrow. Obesity was associated with markedly elevated serum leptin and lowered adiponectin levels while levels of interleukin (IL)-5, eotaxin, TNF α and IL-10 in bronchoalveolar lavage fluid of obese mice were higher than in lean mice [57].

In this regard, various chemokines such as adipokines with potential pro-inflammatory properties, including interleukin IL-6, eotaxin, tumor necrosis factor alpha (TNF- α), and leptin, are produced by adipocytes and have been considered to play a possible role in asthma. Adiponectin has anti-inflammatory properties while leptin increases IgE and airway responsiveness in murine models of allergic airway inflammation [58]. Leptin can promote the proliferation and activation of circulating monocytes and CD41 and CD81 T cells and shift immune response towards a more TH1 pattern. However, the production of mediators

by the fat tissue has been considered unlikely to explain the obesity-asthma interaction [7]. It remains possible that in a sub-type of obese subjects there is a role for increased IgE production in the development of asthma. Cluster analyses of asthma showed that some obese subjects have increased IgE levels and are atopic, although they seem to be a minority [59].

Finally, exhaled nitric oxide (FeNO), a marker of eosinophilic airway inflammation, and sputum eosinophils, were reduced in subjects with an increased BMI while sputum neutrophils were increased [31, 60, 61]. In non-obese subjects, Berg et al. [62] reported that wheezing was significantly associated with reduced FeNO in obese subjects, whereas there was a positive association between wheezing and FeNO among the non-obese, indicating a possible difference in asthma phenotype, based on body weight. Other mechanisms may play a role also in the relationship between inflammatory events and asthma in the obese, such as those related to oxidative stress [60]. The possible effect of obesity on TH2 responses is further discussed in the next section on hormonal influences.

c) Hormonal factors

Obesity can influence sex hormones and these last can possibly influence the development and expression of atopic disorders and asthma [63, 64]. In this regard, it is of interest to note that in many studies cited above, the relationship between obesity or BMI and atopy was predominant in women, mostly post-puberal [11, 15-17, 20]. The mechanisms by which obesity-related changes in hormonal profile could promote the development of asthma are however still uncertain.

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Estrogens may stimulate interleukins (IL) such as IL-3 and IL-4 secretion in monocytes and may promote a Th2 phenotype immune response while progesterone can show pro-inflammatory properties [65]. In the study by Vieira et al. [20], abdominal obesity in women was associated with higher plasma concentrations of free estradiol, a modulator of IL-4 secretion from CD4+ T helper cells. Peripheral blood mononuclear cells, isolated from mite allergen sensitized women were found to increase IL-4 secretion in a dose-response fashion when estradiol was added to the incubation medium. Plasma concentrations of 17 β -estradiol, the ratio of 17 β -estradiol to sex hormone-binding globulin, the fasting insulin resistance index, and C-peptide and leptin concentrations were higher in the obese than in the nonobese group after adjustment for oral contraceptive use. These authors suggested that this could indicate a direct relationship between adiposity and a Th2 immune response in women and that the relationship between atopy and obesity could be influenced by the increased production of 17 β -estradiol.

Hormonal changes in the obese may also possibly be related to the effect of aromatase, an enzyme contributing to the transformation of androgens to estrogens, which is present in high concentrations in fat, therefore possibly contributing to increase circulating levels of estrogen in the obese. Increased estrogen levels could therefore favor eosinophilic activation and in doing so, possibly contribute to asthma development and/or symptoms [66]. However, the contribution of hormonal influences to asthma and its relationship with obesity remain to be further studied.

d) Changes in the lipid metabolism?

Other metabolic alterations found in obese subjects can contribute to the development of atopy. In this regard, Ouyang et al. [67] looked at serum lipid profiles, often perturbed in obesity, in 1,187 rural Chinese twins (653 men) aged 18-39 years. They found no

association between obesity and allergic sensitization, defined as at least one positive response to nine foods and five aeroallergens tested. However, in this lean Chinese population, higher percent body fat, lower HDL and higher LDL were associated with increased risk of allergic sensitization in males. In men, the risk of allergic sensitization was increased with HDL<40 mg/dl and higher LDL quartiles. The authors suggested common genetic influences on these traits to explain these findings.

DISCUSSION

This overview suggests that obesity can influence the development of atopy in some populations although this unlikely explains the frequent association of asthma and obesity. Studies looking at a possible increase in prevalence of atopy in obese individuals have brought variable results, both in adults and children, although there seems to be a signal towards an increased prevalence of the atopic status in the obese, particularly children and women. The evidence for a positive relationship is however weak, and is probably affected by confounding factors and publication biases. Furthermore, there is a lack of longitudinal studies on this topic. Atopy does not however seem to mediate the relationship between obesity and asthma, either through an inflammatory mechanism or another obesity-related influence. This link could also be related to common genetic and environmental or lifestyle determinants, including the diet, without causal relationship, or to other factors such as changes in the microbiome.

Because atopy is an important risk factor for asthma, the relationship between BMI and atopy has been examined, as reported above, and possible underlying mechanisms have been reviewed [68]. Epidemiological studies suggest however that obesity is not a consistent risk factor for atopy, at least in adults and men [69]. Most data gathered also suggest that obesity is not a risk factor for allergic asthma. Studies have suggested an influence of BMI

on asthma, but this is less obvious on atopy and atopic diseases such as hay fever, eczema, and rhinoconjunctivitis [12, 26, 32, 40, 70]. Since atopy usually begins early in life, it may be that overweight or obesity in early childhood is important for the development of atopy, whereas weight gain as an adult is not [71, 72]. The more frequent report of atopy and atopic diseases in young obese children suggest that there may be an effect of obesity at an early age but not later on. This should be further explored. Why the association between BMI and asthma is more often observed in women is also unknown. It may be partially explained by the fact that for a given BMI, women have a greater percentage of body fat than men [49, 73]. However, as discussed above, hormonal influences may also play a role.

Several factors may be involved in these variable results, such as variable methods of analysis, self-report versus skin tests-confirmed atopic status, self-report or proven diagnosis of asthma, and sample size. It is also possible that geographic or populational factors, possibly involving genetic influences, explain these differences although other unknown causes are possible. Finally, we cannot exclude the possibility that there may be many phenotypes of obese asthma, related to different etiologies or contributing factors. Sub-phenotyping could lead to a better understanding of the real impact of obesity on atopy and allergic diseases [74, 75].

In conclusion, overall, although a positive relationship has been found between BMI and atopy in some studies, this observation is not universal and there may be subpopulations such as children or women, in whom obesity could contribute to the development of atopy. This relationship could be due to common genetic or environmental/lifestyle influences or other factors. In regard to the mechanism by which obesity could favour the development of asthma, the bulk of evidence is against the possibility that this could be mediated through atopy.

Disclosure of potential conflicts of interest of L.-P. Boulet

I consider having no conflict of interests in regard to this publication.

"General" conflicts of interests: **Advisory Boards:** GlaxoSmithKline, Novartis, AstraZeneca.

Conferences: AstraZeneca, GlaxoSmithKline, Merck Frosst, Novartis. **Sponsorship for**

investigator-generated research: AstraZeneca, GlaxoSmithKline, Merck Frosst, Schering.

Nonprofit Grants: Research funding provided to my center for participating in multicenter

studies: Altair, AllerGEN NCE, Amgen, Asmacure, AstraZeneca, Boehringer-Ingelheim,

Canadian Institutes for Health Research (CIHR), Genentech, GlaxoSmithKline, NIOSH,

Novartis, Ono Pharma, Pharmaxis, Schering, Wyeth **Support for the production of**

educational materials: AstraZeneca, Canadian Lung Association, GlaxoSmithKline, Merck

Frosst, Boehringer-Ingelheim, Novartis. **Governmental:** Adviser for the Quebec National

Health Institute. **Organisational:** Chair of the Global Initiative for Asthma (GINA) Guidelines

Dissemination and Implementation Committee. Laval University Chair on Knowledge

Transfer, Prevention and Education in Respiratory and Cardiovascular Health. Member of

various committees of the American College of Chest Physicians, European Respiratory

Society, American Thoracic Society, Canadian Respiratory Society and other medical

scientific organisations.

Acknowledgments

I would like to sincerely thank Marie-Eve Boulay and Sylvie Carette for their help in the preparation of this manuscript.

TABLE I. Overview of studies examining the relationships between atopy and obesity in children and adolescents.

Reference	Study population	Atopy assessment	Prevalence of atopy	Main findings
Studies showing a positive relationship between atopy and obesity				
Huang et al. 1999 [11]	1,459 students from 7 junior high schools in Taiwan	Skin prick tests	♂ = 42% ♀ = 27%	- Prevalence of atopy and rhinitis symptoms was increased in girls with higher BMI quintile. - In girls, BMI was associated with an increased risk of being atopic. - No relationship between BMI and atopy in boys.
Visness et al.	4,111 American children aged 2-19 years in NHANES 2005-2006 cohort	Questionnaire and serum total and specific IgE measurement	46.4% ♂ = 49.4% ♀ = 43.2%	- Higher total IgE levels in obese and overweight children compared to normal-weight children. - Increased odds ratios for atopy were observed in obese children as compared to normal weight children. - Relationship particularly driven by food allergy.
Leung et al. 2009 [14]	486 school children from the Hong Kong secondary school children survey.	Serum specific IgE measurement	♂ = 53.5% ♀ = 41.7%	- No association between age-adjusted BMI and atopy - No difference in atopy and presence of allergen-specific IgE between obese, overweight and normal-weight children.
Castro-Rodriguez et al. 2001 [15]	688 children from the Tucson Children's	Skin prick tests	Not reported	- Trend towards an increased prevalence of atopy in females overweight or obese at Yr6 compared to those who did not. - No relation between changes in BMI

		Respiratory Study. Longitudinal study of a birth cohort. Data at age 6 and 11.			status and the prevalence of atopy at Yr11 for either sex.
Schachter et al. 2003 [16]	5,993 children 7-12 years old from 7 studies in Australia	Skin prick tests	Reported as BMI quintiles		Higher BMI associated with a higher prevalence of atopy in girls.
Hancox et al. 2005 [17]	Birth cohort of 1,037 children from the Dunedin Multidisciplinary Health and development Study.	Skin prick tests and total serum IgE measurement	Not reported		Association between atopy assessed by skin prick tests and serum IgE and BMI in females but not in males.
Yoo et al. 2001 [18]	717 Korean adolescents (15-17 years old)	Skin prick tests and serum total IgE	53.3%		- Atopy more common in overweight adolescents than among normal-weight adolescents, particularly in boys. - No association found for overweight status and serum total IgE in either gender. - Multiple logistic regressions showed that overweight was a significant risk factor for the presence of atopy. - When separating by sex, overweight remained a risk factor for atopy only in boys.

	Cibella et al. 2011 [24]	708 1- to 16-year old schoolchildren in Palermo, Italy.	Skin prick tests	39.5%	Significant increased prevalence of allergic sensitization in overweight-obese children compared to non-overweight-obese children.	
	Murray 2011 (39C)	Birth cohort of 731 children followed up to 8 years old	Skin Prick tests	♂ = 34% ♀ = 23%	Being overweight is associated with an increased risk of allergic disease in childhood. However, the strength of the association varies with the gender, age and atopic phenotype.	

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Studies showing no relationship between atopy and obesity

Von Mutius et al. 2001 [12]	7,370 children aged 4-17 years in the NHANES III cohort	Skin prick tests	52.3%	- The prevalence of atopy increased significantly with increasing quartiles of BMI. - No relationship between BMI and atopy after controlling for confounding factors.
Tantisira et al. 2003 [26]	1,039 children aged 5-12 years from the Childhood Asthma Management program (CAMP)	Serum IgE and eosinophil counts	Not reported	Measures of atopy were not associated with BMI.
Kattan et al. 2010 [27]	368 adolescents aged 12-20 years from the Asthma Control Evaluation (ACE) study in 10 major urban area of the USA.	Skin prick tests and serum total IgE	Not reported	No relationship between adiposity, adipokines and total IgE levels.
Santamaria et al. 2007 [30]	50 obese children in Italy	Skin prick tests	58%	- No difference in BMI between atopic and non-atopic children. - Note: all subjects were obese.

TABLE II. Overview of studies examining the relationships between atopy and obesity in adults.

Reference	Study population	Atopy assessment	Prevalence of atopy	Main findings
Studies showing a positive relationship between atopy and obesity				
Xu et al. 2002 [19]	Longitudinal birth cohort study of 4,719 Finish adults (from birth to 31 years old).	Skin prick tests	30.9% at 31 years old	- Ponderal index at birth was independently associated with atopy at 31 years of age. - Obesity at the age of 31 years was associated with adult atopy.
Vieira et al. 2005 [20]	43 women (aged 18-41 years)	Serum specific IgE	62% in obese 28% in non-obese	The presence of specific IgE in obese women was 3 times that in non-obese women.
Chen et al. 2010	1,997 adults (18-79 years old) in Saskatchewan, Canada.	Skin prick tests	29.7%	- Prevalence of atopy was significantly increased with increasing BMI and this was only significant in women when analysis was separated by sex. - Multiple logistic regression showed that obesity was a significant risk factor for atopy, after adjusting for covariates and this was still significant only in women when analyses were separated by sex.
Ciprandi et al. 2009 [22]	300 adult Navy soldiers	Skin prick tests	Not reported	BMI values were significantly higher in rhinitic patients.
Luo et al.	266	Serum	100% in	Positive significant association

2013 [23]	atopic adults and 532 adult controls in China.	specific IgE	atopics and 0% in controls	between obesity and atopic dermatitis and atopic rhinitis.	
Studies showing no relationship between atopy and obesity					
Silverberg et al. 2012 [25]	2,090 adults from an allergy clinic in New York, USA.	Skin prick tests	80.8%	- Overweight and obesity were not associated with atopy. - Obesity, but not overweight, was associated with an increased risk of atopic dermatitis.	
Schachter et al. 2001 [28]	1,971 adults aged 17-73 years in Australia	Skin prick tests	Underweight = 52.8% Normal = 42.1% Overweight = 45.3% Moderate obesity = 47.2% Severe obesity = 41.4%	No difference in the prevalence of atopy between the different groups (underweight, normal, overweight, moderate obesity and severe obesity).	
Jarvis et al. 2002 [29]	Sample of 13,909 adults from the European Community Respiratory Health Survey	Serum specific IgE	Nos reported	No association between BMI and atopic sensitization.	

		(ECRHS)				
	Van Veen et al. 2008 [31]	136 adults from the outpatient pulmonary department of 10 hospitals in the Netherlands.	Self-reported	Non-obese = 55.8% Obese = 65.5%	No significant difference in the prevalence of atopy between obese and non-obese subjects.	
	Braback et al. 2005 [32]	1,247,038 male conscripts from the Swedish Military Service Conscript Register.	Self-reported allergic rhinoconjunctivitis used as proxy for atopy.	Not reported	Multivariate analyses showed no association between obesity and allergic rhinoconjunctivitis.	
	Flexeder et al. 2011 [33]	1,840 adults, aged 45-65 years, from the German ECRHS I study.	Skin prick tests and serum specific IgE	Not reported	After adjusting for confounding variables, no association was found between BMI categories and atopy.	

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