

Is Obesity Associated with an Increased Risk for Airway Hyperresponsiveness and Development of Asthma?

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We investigated the association between airway hyperresponsiveness (AHR) and obesity in adults referred for confirmation of asthma diagnosis. Data were analyzed for obesity class I (body mass index [BMI] 30–34.9 kg/m²), class II (BMI ≥ 35–39.9 kg/m²), and class III (BMI ≥ 40 kg/m²). Of 861 subjects, 401 demonstrated AHR; the mean dose of methacholine was 4.16 ± 2.55 mg/mL. A significant association between obesity and AHR was evident for all subjects: the odds ratio was 1.37 (95% CI 1.02–1.82; *p* = .0317). One unit of increased BMI (1 kg/m²) was associated with a 3.1% increase in AHR risk (95% CI 1.01–1.05, *p* < .005). The odds ratio increased from 1.86 (95% CI 1.27–1.76; *p* = .0012) for class I to 2.61 (95% CI 1.48–4.60; *p* = .0006) for class III. Obesity was found to be associated with AHR and appears to be a risk factor for asthma.

Key words: airway hyperresponsiveness, asthma, obesity

Recently, asthma and obesity have evolved into two major health concerns in developed countries.¹ Over the past 20 years, obesity among adults and children has risen significantly in the United States. The latest data from the National Center for Health Statistics show that 30% of US adults 20 years of age and older (over 60 million people) and 16% of children and teens age 6 to 19 years (over 9 million young people) are obese.² In addition, current data overwhelmingly document the existence of a worldwide asthma epidemic, although individual studies remain controversial.^{3–6} The epidemic is thought primarily to involve persons with allergic asthma; numerous diverse theories, based on an immunopathologic understanding of the disease, have recently emerged to explain this involvement. Thus, it appears that during the past three decades, the prevalence of both asthma and obesity has increased concurrently in Western countries, therefore

suggesting a possible link between the two.⁷ Many publications have shown an association between asthma and obesity in adults and children.^{7–10}

Although obesity and asthma remain two of the fastest growing and most pervasive public health problems in developing countries, the question remains whether the relationship of asthma to obesity is a real connection with causal association or rather a misleading observation. Many, but not all, of the studies have shown that the association between obesity and the prevalence of asthma diagnosis is stronger in women than in men.^{9,10} Despite a number of epidemiologic studies supporting an association between asthma and obesity, controversy and inconsistency in the literature remain. The majority of studies support an association, but they are largely observational in design and failed to use objective clinical measures of asthma; therefore, they are susceptible to the diagnostic and recall bias. The few studies that incorporated objective measures did not find an association.^{10,11} Unfortunately, these studies included a relatively small number of patients, and this may have precluded finding an important difference. Additionally, confounding effects of asthma medications used in the obese cohort may have created a bias against an association being found. Although many studies have supported the possible association between obesity and asthma, the scientific literature remains divided regarding the association between airway hyperresponsiveness (AHR) and changes in body mass index (BMI). A recent cross-sectional study of 86,144

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Canadians examined the association between BMI and asthma prevalence. The study found that 1 unit of BMI increase was associated with an approximately 6% increase in asthma risk in women and a 3% increase in men. A stronger association between obesity and asthma was observed in non-allergic women than in allergic women.¹² No definite information on the BMI-adjusted trends in the prevalence of asthma has been published in adults, although data on asthma and BMI were obtained in the National Health and Nutrition Examination Survey (NHANES).¹³

To further investigate the association between obesity and asthma and its possible mechanisms, we investigated the relationship of AHR, a marker of asthma, to obesity in adult subjects. We hypothesized that in a large sample of patients with respiratory symptoms suggestive of asthma referred for confirmation of asthma diagnosis, a positive association exists between BMI and AHR.

Methods

We evaluated all subjects referred for confirmation of asthma by methacholine challenge test from 1999 to 2004 at the Pulmonary Function Tests Laboratory of St. Boniface General Hospital, Winnipeg. Appropriate Institutional Review Board and hospital approvals were obtained. Based on symptoms, a diagnosis of asthma was suspected by either the primary care physicians or pulmonary specialists. The laboratory database prospectively recorded demographic information, spirometry, and methacholine challenge test data. The chronicled demographic information included age, sex, race, height, weight, referring physician's diagnosis, smoking history, medications, and history of cardiac disease. Evaluation of all subjects and spirometric testing was done by experienced pulmonary technologists certified and licensed by the Canadian College of Respiratory Therapists and the Canadian Association of Cardio-Pulmonary Technologists. In addition, the technologists validated the information provided by the referring physician and documented asthma history as part of the previously established standard laboratory protocol. To minimize confounding by other conditions in which (AHR) has been reported (chronic obstructive pulmonary disease [COPD], sarcoidosis, bronchiectasis, and cardiac disease and β -blocking medications), we excluded these subjects. Additionally, subjects with a history of smoking (≥ 10 pack-years), chronic steroid use, and suspected restrictive pulmonary disease (forced vital capacity [FVC] $< 80\%$ predicted and

ratio of forced expiratory volume in 1 second [FEV₁] to FVC $\geq 80\%$) were excluded from the study.

Spirometry was performed according to American Thoracic Society criteria.¹⁴ Testing was done with the subjects seated, and a maximum forced exhalation was carried out for a minimum of 6 seconds. After 6 seconds, the test continued until zero flow was achieved (≤ 50 mL flow extrapolated over 30 seconds). At least three FVC manoeuvres were performed, two of which were reproducible within 5%. Spirometric measurements were made using the PFT Horizon System SensorMedics Corp. (Yorba Linda, CA, USA); the machines were calibrated daily with a 3 L volumetric syringe. All β_2 -agonist medications were withheld at least 6 hours before testing. The methacholine challenge test was performed in a standard fashion.¹⁵ FVC and FEV₁ were measured after inhalation of normal saline and after doubling concentrations of methacholine from 0.03 to 16.0 mg/mL in normal saline solution. The methacholine solution was delivered using a Wright twin nebulizer and inhaled by tidal breathing for 2 minutes with the nose clipped. FVC and FEV₁ were measured at 30 and 90 seconds after each dose. Doubling concentrations of methacholine were administered at 5-minute intervals until the FEV₁ decreased by 20% from the lowest value following saline solution FEV₁ or until a dose of 16 mg/mL was achieved. The provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) was calculated by linear interpolation of the last two points. The subjects with a fall in FEV₁ of 20% or more with less than 8 mg/mL methacholine were defined as having AHR.

Obesity was defined as [BMI = weight (kg)/height (m) squared ($ht \times ht$) ≥ 30 kg/m²]. Non-obese individuals were defined as BMI < 30 kg/m². Obese individuals were further classified as obesity class I, BMI from 30.0 to 34.9; obesity class II, BMI from 35 to 39.9; and obesity class III for BMI ≥ 40.0 .

Statistical Analysis

Continuous variables were expressed as mean \pm SD. Prevalence rates and mean values are reported with 95% confidence intervals. The χ^2 test was used to determine the significance of differences in prevalence across all BMI groups and between different BMI groups, determined by increasing cutoff values compared with their control groups. Odds ratios (ORs), relative risks (RRs), and attributable risks (ARs) (AR = risk ratio - 1/risk ratio) were estimated for AHR in the presence of obesity. Correlates of BMI and AHR were studied with analysis of variance (ANOVA) or Wilcoxon rank sum tests where

applicable. For all analyses, p values of $< .05$ were regarded as significant. The Cochran-Mantel-Haenszel test was also used to stratify the results by gender. Pearson correlation coefficient was used to assess the association between continuous BMI and airway responsiveness. Two-way ANOVA was used to analyze means of grouped data, and least-square means post hoc analysis using the pooled variance was also performed to correct for multiple comparisons when comparing specific groups. The Mantel-Haenszel trend test was performed as the data suggested that there might be a dose-response trend. Microsoft *Excel* and SAS version 9.1 (SAS Inc, Cary, NC) were used for the data analysis.

Results

The analysis included 861 subjects: 337 (39%) were obese and 401 (47%) demonstrated AHR (Table 1). The mean methacholine dose (PC_{20}) was 4.16 ± 2.55 mg/mL. Spirometric measurements of FVC, FEV_1 , and ratio of FEV_1 to FVC in methacholine-positive versus -negative subjects were not statistically different. The mean FVC (89.67 ± 14.88 vs 92.14 ± 15.40), mean FEV_1 (98.93 ± 15.34 vs 98.40 ± 16.17), and mean ratio of FEV_1 to FVC (85 ± 9.3 vs 81 ± 9.5) were measured within the two groups. There was a significant association between obesity and AHR for all subjects; the OR was 1.37 (95% CI 1.02–1.82; $p = .0317$). When used as a continuous variable in logistic regression models, one unit of increased BMI

(1 kg/m²) was associated with a 3.1% increase in AHR risk (CI 1.01–1.05; $p < .005$) in all subjects. For men, this risk was 3.4% (CI 1.01–1.06) for one unit of increased BMI (1 kg/m²) and for women 2% (CI 0.97–1.07), respectively.

The OR for point estimates of AHR risk in obesity was 1.09 (CI 0.76–1.54) for class I, 1.5 (CI 0.92–2.46) for class II, and 2.78 (CI 1.56–4.94) for class III (Table 2). The p values were .64 for class I, .10 for class II, and .0005 for class III. When different thresholds for obesity were used as cutoffs, the association became increasingly significant as the level of obesity increased from class I to class III. ORs for class I obesity were 1.86 (95% CI 1.27–1.76; $p = .0012$) and for obesity class III were 2.61 (95% CI 1.48–4.60; $p = .0006$) (Table 3). Likewise, the RR increased from 1.22 to 1.67 to 1.86 for obesity class I to class II and class III, respectively. The attributable risk for the entire group increased from 17.83 to 30.43 to 40.13% for obesity classes I, II, and III, respectively. Using multiple regression, for the positive methacholine challenge test, the age-adjusted OR for BMI ≥ 30 was 1.44 (95% CI 1.07–1.93; $p = .014$), for BMI ≥ 35 was 1.93 (95% CI 1.32–2.84; $p = .007$), and for BMI ≥ 40 was 2.71 (95% CI 1.54–4.79; $p = .0006$). The age-adjusted OR for the positive methacholine challenge for a 1 kg/m² change in BMI was 1.037 (95% CI 1.01–1.06).

On stratifying data according to sex difference, we found dissimilar results. For males, obesity class I did not appear to be a significant risk factor. However, for higher levels of obesity, classes II and III, there was a positive association between obesity and AHR. The OR was 2.75 (95% CI 1.21–6.20) and the AR was 41% for class II obesity in men, whereas the OR was 4.82 and the AR was 51% for males with class II obesity. In females, obesity was a significant risk factor for AHR at all levels of obesity. Class I obesity had an OR of 1.47 (95% CI 1.04–2.08) and an AR of 22%, whereas a higher risk was observed with obesity classes II and III, in which the ORs and ARs were 1.72 (95% CI 1.11–2.65) and 28% and 2.4 (95% CI 1.26–4.55) and 38%, respectively.

Table 1. Demographics of Total Evaluated and Included Patients

Characteristics	Number (%)
Number of subjects evaluated	1,372
Number of subjects included	861 (63%)
Number of subjects excluded	511
Reasons of exclusion	
COPD	293
Smoking history (> 10 pk-yr)	168
Restrictive lung disease	38
Congestive heart failure	12
Number of subjects with bronchial hyperresponsiveness	401 (47%)
Number with obesity > 30 kg/m ²	337
Mean FVC (% predicted) in subjects with AHR	89.67 ± 14.88
Mean FEV_1 (% predicted) in subjects with AHR	98.93 ± 15.34

AHR = airway hyperresponsiveness; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

Table 2. Point Estimates of Airway Hyperresponsiveness in All Patients When Grouped as BMI 30 to 34.9, BMI 35 to 39.9, and BMI ≥ 40 Compared with BMI < 30

BMI	Odds Ratio	95% CI	p Value
30–34.9	1.09	0.76–1.54	.64
35–39.9	1.50	0.92–2.46	.10
≥ 40	2.78	1.56–4.94	.0005

BMI = body mass index; CI = confidence interval.

Table 3. Relationship to Airway Hyperresponsiveness in All Patients Using a Cutoff Value for Body Mass Index at 30, 35, and 40

BMI	Age (yr)	% Methacholine		95% CI for Odds		Attributable		p Value
		Positive	Odds Ratio	Ratio	Relative Risk (CI)	Risk (%)		
< 30	44.5 ± 16.4	33.82	1.37	1.03–1.82	1.22 (1.02–1.45)	17.83	.0317	
≥ 30	49.1 ± 14.2	41.16						
< 35	45.7 ± 16.1	34.24	1.86	1.27–1.76	1.67 (1.17–1.76)	30.43	.0012	
≥ 35	49.1 ± 13.4	49.22						
< 40	46 ± 16	35.02	2.61	1.48–4.60	1.86 (1.31–2.13)	40.13	.0006	
≥ 40	49.5 ± 11.3	58.49						

BMI = body mass index; CI = confidence interval.

Discussion

We found obesity to be a significant risk factor for AHR in subjects suspected of having asthma. According to the Canadian Asthma Consensus Guidelines, asthma is defined as “a disease characterized by paroxysmal or persistent symptoms of dyspnea, chest tightness, wheezing, sputum production, and cough associated with variable airflow limitation and airway responsiveness to exogenous stimuli.”¹⁶ For epidemiologic purposes, asthma is defined as current symptoms of dyspnea and/or wheeze within the last 12 months, together with documented AHR.¹⁷ The PC₂₀ is usually interpreted in the context of pretest and posttest probability of asthma.^{18,19} The subjects in this study were referred for confirmation of asthma diagnosis because of respiratory symptoms, thus carrying a high pretest probability of asthma. Therefore, following a positive methacholine challenge test (mean PC₂₀ dose = 4.16 ± 2.55 mg/mL), a high posttest probability of asthma in these subjects exists. AHR

has also been reported in patients with COPD.²⁰ However, we excluded individuals with COPD based on spirometry and smoking history. When analyzing data for sex differences, similar to other published studies, we found obesity to be a significant risk factor for AHR at all levels of obesity for females but only for higher levels of obesity for men.^{11,21,22}

Literature Review

Previous observational studies support an association between AHR and asthma and obesity. Based on Canadian National Population Health Survey data from 1994–1995, Chen and colleagues found that BMI values were positively associated with prevalence of asthma in women.⁸ The adjusted OR was 1.52 for women with a BMI of 28.0 kg/m² or more compared with those with a BMI of 20.0 to 24.9 kg/m². Shaheen and colleagues found that the

Table 4. Sex Differences for Airway Hyperresponsiveness Prevalence with Body Mass Index

Patient Attribute	Prevalence of AHR in Subjects with BMI < 30 or ≥ 30				Prevalence of AHR in Subjects with BMI < 35 or ≥ 35				Prevalence of AHR in Subjects with BMI < 40 or ≥ 40			
	Female		Male		Female		Male		Female		Male	
BMI	< 30	≥ 30	< 30	≥ 30	< 35	≥ 35	< 35	≥ 35	< 40	≥ 40	< 40	≥ 40
Total number of subjects	382	230	153	96	496	100	234	31	555	41	250	15
% Methacholine positive	33	42	36	39	34	47	35	59	35	56	35	73
Odds ratio (CI)	1.47 (1.04–2.08)		1.17 (0.70–1.98)		1.72 (1.11–2.65)		2.75 (1.21–6.20)		2.40 (1.26–4.55)		4.82 (1.25–18.6)	
p Value	.03		.54		.01		.01		.006		.01	
Relative risk	1.27		1.12		1.38		1.71		1.61		2.04	
Attributable risk (%)	22		10		28		41		38		51	

AHR = airway hyperresponsiveness; BMI = body mass index; CI = confidence interval.

ORs for the prevalence of asthma among 8,960 British adults were higher in overweight women.⁹ ORs were 1.51 in those with a BMI of 25.0 to 29.9 kg/m² and 1.84 in those with a BMI of at least 30.0 kg/m² compared with those with a BMI less than 25.0 kg/m². Luder and colleagues reported similar associations between BMI and physician-diagnosed asthma based on data from 5,527 adults living in New York State.¹⁰ Several longitudinal epidemiologic studies have yielded similar results.^{8–12} Findings from the Nurses' Health Study suggest that a 25 kg weight gain was associated with a 2.5-fold increase in the risk for diagnosis of asthma compared with no significant weight gain.¹¹ In a cross-sectional analysis of 18,000 children aged 4 to 11 years, Figueroa-Munoz and colleagues showed that asthma diagnosis and BMI were positively associated (OR = 1.29, 95% CI 1.13–1.47).²¹ Gilliland and colleagues showed that the risk of new-onset asthma was higher among obese children (RR = 1.60, 95% CI 1.08–2.36) and found this effect to be stronger in boys.²²

Other investigators did not find such an association and thus speculated that asthma might be overdiagnosed in obese subjects. Schachter and colleagues studied 1,971 Australian adults in a cross-sectional epidemiologic study and found that obesity was a significant risk factor for diagnosis of asthma (OR = 2.04), wheeze, and asthma medication use (OR = 2.83) but not for AHR, atopy, or airflow obstruction.²³ Despite more symptoms consistent with asthma and use of more asthma medications in severely obese subjects, the level of AHR and airflow obstruction did not support higher prevalence of asthma. Sin and colleagues examined data from NHANES III and showed that the most obese participants (BMI > 31 kg/m²) had the greatest risk of self-reported asthma, dyspnea, and bronchodilator use but paradoxically were found to have lower risk for airflow obstruction.¹³ Obese subjects used more bronchodilators than non-obese subjects without objective evidence of airflow obstruction, and asthma was overdiagnosed in this obese population. In a cross-sectional study of 86,144 Canadians who were 20 to 64 years of age, a stronger association between obesity and asthma was observed in non-allergic women than in allergic women, with the adjusted ORs being 2.53 (95% CI 2.11–3.04) and 1.57 (95% CI 1.36–1.82), respectively.¹²

Biological Plausibility

To establish causality between obesity, asthma, and BHR, plausible biological mechanisms must be proved to

support this hypothesis. Obesity may directly affect individuals with asthma predisposition by direct mechanical effects, by immune response enhancement through related genetic mechanisms, and by sex-specific hormones.²⁴ Since obesity is intricately linked to environmental factors such as physical activity, diet, and birth weight, these environmental influences, in combination with genetic predilection, may then lead to enhanced susceptibility to asthma. Undoubtedly, obesity is known to produce symptoms of dyspnea and wheezing; whether asthma and airflow obstruction are responsible for these symptoms has not been conclusively ascertained. The reduced chest wall compliance in obesity causes a substantial elastic load on inspiratory muscles and increases the work and the energy costs of breathing.^{25,26} Obesity induces a reduction in functional residual capacity (FRC) and decrements in tidal volume, which fail to increase during exercise.²⁷ Thus, waning FRC and tidal volumes may result in alterations in the airway smooth muscles and hence increased airways resistance and methacholine reactivity. Therefore, obese patients complain of more dyspnea and asthma-like symptoms than leaner patients and may be incorrectly diagnosed with asthma.^{28,29} In addition, obesity has been associated with decrements in forced expiratory flow (FEF) in the midportion of FVC (FEF_{25–75}). The ratio of FEF_{25–75} to FVC has also been independently associated with methacholine responsiveness of the airways.³⁰ Gastroesophageal reflux (GER) is commonly seen in patients with asthma; the prevalence of GER is estimated to be 60 to 80%.³¹ Since obesity has been frequently cited as an independent risk factor for GER, one may speculate that GER might mediate the relationship between asthma and obesity.

Asthma and obesity are both inflammatory states.¹⁶ Allergic asthma is characterized by elevation of the cytokines interleukin (IL)-4 and IL-5, which are responsible for the inflammatory cells infiltrating the airways.³² Tumour necrosis factor α (TNF- α), IL-1 β , and IL-6 are also increased in asthmatics. Obesity is also a chronic inflammatory state.³³ Fat cells (adipocytes) are an important endocrine organ that produces a number of compounds that regulate inflammation such as IL-1 β , IL-6, TNF- α , leptin, and adiponectin.³⁴ Animal studies indicate that elevations in IL-6 may contribute to upregulation of inflammation in airways, independent of an allergic mechanism. IL-6 increases production of prostaglandin E₂ (PGE₂), stimulating the humoral immune system and production of T-helper 2 (Th2)-associated cytokines.³⁵ PGE₂ does this by modulating

professional dendritic cells, by acting on their differentiation, maturation, and ability to secrete cytokines.³⁶ PGE₂ is a potent inducer of IL-10 in bone marrow-derived dendritic cells, and this cytokine displays both immunostimulatory and immunoregulatory activities.³⁷ PGE₂ can also act on immature dendritic cells to trigger local Th2 recruitment via control of cytokine production.³⁸ The hormone leptin of the IL-6 family has effects on inflammation, including the release of IL-6 from macrophages and lymphocytes.^{39,40} Leptin levels in adulthood are higher in women than in men, along with a higher prevalence of asthma.⁴¹ But the specific role of leptin and the recently described adipocytokines, such as adiponectin, resistin, and visfatin, remains undefined.⁴²

Interestingly, in most but not all studies, BMI has not been independently related to atopy, so the effects of obesity, other than immune mechanisms, are mediated through hormonal influences. The study by Huang and colleagues showed that girls in the highest BMI quintile had a significantly higher prevalence of atopy and rhinitis symptoms than girls in the lowest BMI quintile.⁴³ In contrast, Jang and colleagues and Jarvis and colleagues found no association between BMI and atopy.^{44,45} In a study of children with a mean age of 5.9 years, Guler and colleagues found that atopic asthmatics had significantly higher leptin levels for a similar BMI than non-atopic asthmatics, but this did not correlate with skin test reactivity.⁴⁶ An explanation for these disparities may come from the study of Vieira and colleagues, who found that in healthy obese and non-obese women, specific immunoglobulin E (IgE) was three times higher in obese compared with non-obese subjects, as were plasma 17 β -estradiol, fasting insulin resistance, C-peptide, and leptin concentrations.⁴⁷ All of these factors correlated with fat mass, which was the only positive predictor of specific IgE. Thus, female sex hormones may also play a role, given the increased risk of asthma development in women.⁴⁸ The effect of female hormone levels may also be related to our findings of significant BHR in obesity class I compared with men. Obesity may reduce progesterone, which would reduce β_2 -receptor function, which may reduce bronchial smooth muscle relaxation and worsen asthma control. Weight loss increases progesterone and adrenoceptor density and improves lung function in obese females with asthma. Although some effect of estrogen levels on airways responsiveness is seen in animal models, it is not clear which airway cells express estrogen receptors and/or if signalling pathways via estrogen receptors interact with airway inflammation in asthma.^{49,50}

Implications of Obesity and Asthma Causality

Our and other epidemiologic investigations denote a significant temporal relationship between alterations in body mass and asthma. This association is probably multifactorial; however, the potential independent effects of biomechanics, inflammation, genetics, and sex-specific effects contradict this association. Research is urgently needed to further elucidate this relationship and understand the causal mechanisms of obesity and asthma association. From a public health standpoint, these studies have substantial implications. If asthma were added to the list of conditions related to obesity, then reducing the prevalence of obesity could be expected to produce even greater public health benefits than are currently estimated. It may be too early to incorporate weight reduction strategies in efforts to reduce the health and economic burden of asthma; however, current evidence mandates that such interventions should not be delayed either.

Limitations of Our Study

Ours is an observational cohort study that includes inherent limitations, such as the lack of an age- and sex-matched control group, its retrospective nature, relatively small sample size, and inability to categorize clinical asthma severity. All patients included in this study were referred to a tertiary care centre for evaluation of respiratory symptoms, therefore creating a selection bias. Despite these limitations, our study attained some important observations, which can have potential implications in designing future health policies.

Conclusion

In summary, obesity and asthma are the two fastest growing health problems worldwide; there appears to be a genuine association between the two. Our study established obesity as a risk factor for new diagnosis of asthma, the risk increasing with higher levels of obesity. These findings should be the basis for future controlled investigations to further establish this association and discover the biological mechanisms for their association.

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