

Does obesity weigh heavily on the health of the human airway?

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“When the world was a simpler place, the rich were fat, the poor were thin and right-thinking people worried about how to feed the hungry. Now, in much of the world, the rich are thin, the poor are fat, and right-thinking people are worrying about obesity.”—*The Economist*, December 13, 2003

In the United States the prevalence of obesity has more than doubled, from 13.4% in 1960 to 1962 to 27.6% in 1999 to 2002 among men and from 15.8% to 33.2% among women.¹ Although there are many causes, the increase in obesity is, in part, a result of the progressive decrease in levels of physical activity and adoption of a more sedentary lifestyle. As reviewed by Brisbon et al² in this issue of the Journal, this change in lifestyle has been accompanied by lack of access to safe areas for physical activity; increased use of television, computer, and video games; and sprawling residential neighborhoods that have increased reliance on the automobile for transportation.

Somewhat parallel to the increase in obesity has been the increase in the prevalence of asthma. From 1980 through 1996, the prevalence of self-reported asthma for all ages increased by 74% in the United States.³ The concurrent increase in these two conditions raises the possibility that the two might be connected to each other. The results from cross-sectional, case-control, prospective, and weight-loss studies of obesity indices and asthma

Abbreviations used

BHR: Bronchial hyperreactivity

BMI: Body mass index

outcome measures have been reviewed by Ford⁴ in this journal. The majority of these studies show that measures of excess weight (usually based on body mass index [BMI]) are positively associated with the likelihood of having asthma, although in some studies the risk appears to be stronger among women than men.⁴ Ford has also very elegantly addressed the potential for methodological flaws within these studies, such as the various definitions of asthma (including whether studies measured asthma-like symptoms rather than true asthma), inadequate differentiation of multiple obesity phenotypes, diagnostic or detection bias, and incomplete accounting of confounding by variables, such as diet and physical activity.⁴

Whether the increase in obesity might actually have caused an increase in the incidence and prevalence of asthma is controversial. To analyze causality between an exposure and outcome variable, the association between the variables must fulfill the following criteria⁵: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biologic gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy.

Does the association between obesity and asthma reviewed in this journal meet the above-mentioned causal criteria?

STRENGTH OF ASSOCIATION

A strong association, such as a 5- to 10-fold increase in risk, as is seen between cigarette smoking and lung cancer, is more likely to be causal than a weak association. A weak association is more likely to be spurious, arising from bias, confounding, or chance, although it does not rule out causality. The association between asthma and obesity is modest, with measures of relative risk described ranging from 1.5 to 3.0 in most studies, which raises concerns that it might not be causal.

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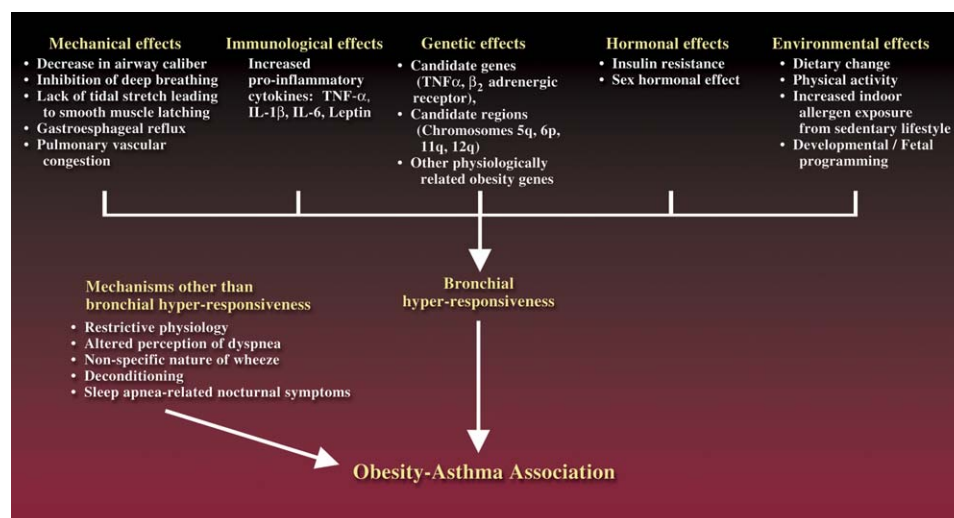


FIG 1. Proposed mechanisms for the association between obesity and asthma.

CONSISTENCY OF ASSOCIATION

If the association is repeatedly observed in different populations in different settings, it is more likely to be causal than an isolated observation. The obesity-asthma association has been observed in both children and adults, in various races and ethnic groups, as well as in different parts of the world. In most studies asthma was clinically defined as a physician diagnosis of asthma, presence of asthma symptoms, use of asthma medications and hospitalizations, or emergency department visits related to asthma. However, when the definition of asthma is revised to include the presence of bronchial hyperreactivity (BHR), the association is far less consistent, with several large studies showing contradictory results.⁴ Further, most studies have not included measures of airway inflammation to define the asthma phenotype.

Some, but not all, studies have found this association in women but not in men.⁴ Part of the explanation for this heterogeneity in the findings might be in study size and methodology. A statistically significant interaction between sex and asthma status is required to conclude a different effect in men and women. It is not sufficient to observe a statistically significant relation in one group and not in the other, but studies might lack the power to detect such an interaction. Therefore evaluation of the evidence for or against a sex difference is quite difficult.⁶

SPECIFICITY OF ASSOCIATION

This relates to a single cause leading to a single effect. This might be a holdover from infectious disease thinking and does not necessarily apply to complex disease traits, such as asthma (which more often than not have multifactorial causation). Such effect specificity is clearly lacking in this association because obesity has also been

shown to cause various diseases other than asthma, such as Type II diabetes mellitus and coronary heart disease.

TEMPORALITY OF ASSOCIATION

This postulates that a cause must precede an effect in time. It was previously argued that asthma leads to physical inactivity and subsequent weight gain and obesity. Several prospective studies have now found a positive association between weight gain and subsequent development of (incident) asthma, thereby providing considerable support for the thesis that obesity in fact antecedes the development of asthma.⁷

BIOLOGIC GRADIENT

The presence of a dose-response gradient (ie, more of a dose leads to more of an effect) supports the idea of causality. A modest dose-response relationship has in fact been described in various studies whereby the risk of asthma increases with the severity of overweight-obese status. However, several studies have also described another interesting observation that the association between BMI category and asthma risk might have a U- or J-shaped curve whereby the underweight category (or those with the lowest BMI status) might also have a significantly higher risk of asthma.⁷

PLAUSIBILITY OF ASSOCIATION

According to this postulate, the idea of causation must be biologically plausible. A host of mechanistic pathways have been suggested to explain this association, and these are summarized in Fig 1.⁸⁻¹⁰ However, these pathways might not be mutually exclusive, and the dominant

mechanism among them is yet to be singled out.¹⁰ Some believe that asthma-like symptoms in obese patients might be due to reasons other than BHR, such as increased work of breathing associated with thoracic restriction, deconditioning, misdiagnosis of nocturnal symptoms caused by obstructive sleep apnea, altered perception of dyspnea, or the lack of specificity of the question regarding the presence of wheeze in the obese. Others have suggested that the mechanical effect of obesity on airway caliber, lack of deep inspiration or lack of tidal stretch causing latching of airway smooth muscle, and/or conditions such as gastroesophageal reflux might result in increased BHR. Obesity might also be associated with other environmental factors such as a sedentary lifestyle, leading to increased exposure to indoor aeroallergens, different dietary nutrient intake that might affect respiratory status, and developmental factors leading to different fetal programming of the airway. Influence of insulin and sex hormones on the airway might also play a role. The genetic polymorphisms outlined in Fig 1 might both predispose to obesity and modify asthma severity. Furthermore, gene-environment interactions might be important, such as the effect of physical activity on certain genetic polymorphisms. Furthermore, there is an increased recognition that obesity might be a proinflammatory state.⁸ Adipose tissue produces T_H2-type cytokines and leptin, which might have a proinflammatory effect on the airway.⁸

COHERENCE OF ASSOCIATION

The idea of causation must accord with other relevant observations. For instance, there is at least one article examining data from the National Health and Nutrition Examination Survey that suggests that unadjusted prevalence of atopy increases significantly with increasing obesity.¹¹

EXPERIMENTAL EVIDENCE FOR ASSOCIATION

Supporting data for this association from animal experiments are limited. Fredberg and Shore,¹⁰ in their review in this journal, have quite rightly commented that “the majority of studies published on this topic are epidemiological investigations; the paucity of basic research on the possible role of adipose tissue in modulating asthma susceptibility and symptoms is quite striking.” It has now been shown that ozone-induced BHR and airway inflammation in mice that are obese (ob/ob) is higher than that seen in lean wild-type (C57BL/6J) mice.¹² Shore et al¹³ have also shown that exogenous administration of leptin increases BHR induced by ovalbumin aerosol challenge in ovalbumin-sensitized mice. Clearly, a lot more basic research on the mechanistic basis for this association is needed, and a recent workshop by the National Heart, Lung, and Blood Institute has developed

several complex recommendations for further research in this area.¹⁴

ANALOGY

Like obesity, other environmental factors are also associated with asthma. An example of such a factor is the popular hygiene hypothesis that has been described in the rostrum by Platts-Mills.¹⁵ This hypothesis proposes that decreased exposure to infections, decreased exposure to farm animals-endotoxin, or increased antibiotic use in early life results in dominance of T_H2 responses, which might also partly explain the increase in asthma prevalence.

So is the association between obesity and asthma causal? At this stage, the association between obesity and asthma is tantalizing, but the body of literature is insufficient to make a determination of cause and effect. Cross-discipline collaboration between investigators interested in asthma and those interested in obesity is needed to accelerate progress in research on this area.¹⁴

What message does the physician extract from this barrage of confusing information? First, the diagnosis of asthma in the obese on clinical grounds alone might lack specificity, and therefore bronchoprovocation testing to confirm the diagnosis might be desirable. Second, weight-reduction studies in obese patients with asthma show improvements in their clinical parameters, such as the number of attacks, medication use, hospitalizations, symptom severity score, and cost of care (although not extent of BHR). Physicians should therefore not delay weight-optimization measures in obese patients with asthma while the research community argues over the mechanisms for the obesity-asthma association. Third, a prescription for exercise should be part of the treatment plan of all asthmatic subjects, even though it is still unclear whether prolonged physical activity protects against persistent wheezing. Fourth, physicians should simultaneously counsel against aggravation of underweight status, which itself might be associated with a higher risk of asthma for unclear reasons.

To summarize, it appears that our mother's advice about maintaining our weight away from extremes and exercising regularly might still be an appropriate way to optimize the health of our airways.

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