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The epidemiology of obesity and asthma

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The prevalences of asthma and obesity have increased substantially in recent decades in many countries, leading to speculation that obese persons might be at increased risk of asthma development. In adults cross-sectional, case-control, prospective, and weight-loss studies are in the aggregate consistent with a role for obesity in the pathogenesis of asthma. In children 3 of 4 prospective studies also show a significant association between excess weight and asthma incidence. Because of the methodologic shortcomings of many studies, these findings are inconclusive, however. Population surveys do suggest that persons with asthma are disproportionately obese compared with persons who have never had asthma. Weight-loss studies on the basis of behavioral change and bariatric studies have shown substantial improvements in the clinical status of many obese patients with asthma who lost weight. Clarifying the nature of the relationship between obesity and asthma incidence and the role of weight management among patients with asthma are both critical areas with important ramifications for the prevention and treatment of asthma. (J Allergy Clin Immunol 2005;115:897-909.)

Key words: *Asthma, obesity*

Many countries have witnessed large increases in the prevalences of obesity and asthma during the last several decades.^{1,2} In the United States the prevalence of obesity has increased from 13.4% among US men aged 20 to 74 years in 1960 through 1962 to 27.6% in 1999 through 2002 and from 15.8% to 33.2% among women.³ From 1980 through 1996, the prevalence of self-reported asthma increased 73.9%.⁴ The concurrent increases in these 2 conditions raises the possibility that the two might be connected.

In this review I will consider the issue of excess weight and asthma from 2 vantage points. The first is whether excess weight increases the risk for development of asthma.

Abbreviations used

FVC: Forced vital capacity

NHANES: National Health and Nutrition Examination Survey

The second is whether obesity, aside from any causative connection to asthma, affects the course of this disease and what this might mean for the treating physician.

CROSS-SECTIONAL STUDIES

Numerous, but not all, cross-sectional studies in different countries show an excess of obesity among adults with asthma compared with those without asthma.⁵⁻²⁵ Most of these studies used self-reported asthma, whether diagnosed by a physician or not. Furthermore, all studies used body mass index as the principal anthropometric measure, although there was some variability in how categories of body mass index were created. In a few studies that examined differences by sex, a stronger association was reported among women than men.^{17,22} In 2 other studies, however, there was no significant effect modification by sex,^{9,24} although in one of these studies there was a sex difference for the underweight category but not the overweight and obesity classes.²⁴

In children and adolescents the results of cross-sectional studies are less consistent in linking measures of excess weight to asthma.²⁶⁻⁴⁰ In most studies the definition of asthma was based on physician-diagnosed asthma reported by the respondent or a parent. Body mass index was commonly used as the principal anthropometric measure, although several studies have also used other anthropometric measures. In the majority of studies, the determination of body mass index was based on measured weight and height, and categories of body mass index were generally calculated on the basis of age and sex. In at least one study, a significant association was limited to female subjects. In several other studies, however, no statistical evidence was found to suggest that associations between body mass index and asthma differed by sex. In addition, several case-control studies provided inconsistent results.⁴¹⁻⁴⁴

Because the presence of obesity and asthma are determined simultaneously in cross-sectional studies, cause

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TABLE I. Prospective studies of obesity and asthma incidence among adults

Reference	Study	Follow-up (y)	Period	Age (y)	Sample size	Asthma no.	Asthma diagnosis
Shaheen et al, ⁹ 1999	1970 British Cohort Study, UK	26	1970-1996	Birth	2892 M, 3528 F	714	Self-reported asthma-wheeze
Camargo et al, ⁴⁶ 1999	Nurses' Health Study II, US	4	1991-1995	26-46	85911 F	1596	Self-reported physician-diagnosed asthma; 2 stricter definitions as well.
Beckett et al, ¹⁶ 2001	Coronary Artery Risk Development in Young Adults Study, US	10	1985-1986 to not reported	18-30	2049 M, 2498 F	310	Self-reported asthma medication use or diagnosis by doctor or nurse
Chen et al, ⁴⁷ 2002	National Population Health Survey, Canada	2	1994-1995 to 1996-1997	20-64	9149 M F 4266 M 4883 F	176 49 127	Self-reported health professional-diagnosed asthma
Xu et al, ¹⁸ 2002	Finnish birth cohort from 1966, Finland	31	1966-1997	Birth	4719 M F	About 189	Self-reported physician-diagnosed asthma
Guerra et al, ⁴⁸ 2002	Tucson Epidemiologic Study of Airways Obstructive Diseases, US	20	1972-1973 to 1992	≥20	1577 M F	102	Physician-confirmed asthma
Huovinen et al, ⁴⁹ 2003	Finnish Twin Cohort, Finland	9	1982-1990	25-52	9671 M F 4449 M 5222 F	149	Self-reported physician-diagnosed asthma
Ford et al, ⁵⁰ 2004	NHANES I Epidemiologic Follow-up Study, US	10	1971-1975 to 1982-1984	25-74	9456 M F 3621 M 5835 F	317 102 215	Self-reported physician-diagnosed asthma

RR, Relative risk; BMI, body mass index.

TABLE I. (Continued)

Anthropometric measure	RR estimate	95% CI	Adjusted for:
BMI (measured weight and height) at age 10 y	Not associated		Not reported
BMI (self-reported weight and height)			Age, race, US region, smoking, physical activity, total energy intake, hysterectomy status, birth weight, duration of breast-feeding
<20.0	0.9	0.7-1.1	
20.0-22.4	1.0		
22.5-24.9	1.1	1.0-1.3	
25.0-27.4	1.6	1.3-1.9	
27.5-29.9	1.7	1.4-2.0	
≥30	2.7	2.3-3.1	
BMI (measured weight and height) quintiles			Age, sex, race, center, education
Lowest	1.39	0.97-1.99	
2	1.00		
3	1.07	0.73-1.58	
4	1.19	0.81-1.75	
Highest	1.60	1.12-2.30	
BMI (self-reported weight and height)			Age, smoking, pets, immigrant status, allergy history, income adequacy, alcohol
Men	Not associated		
Women			
<20	0.62	0.24-1.62	
20-24.9	1.0		
25-29.9	1.25	0.72-2.18	
≥30	1.92	1.90-3.41	
BMI (self-reported weight and height) at 14 y			Maternal age, BMI before pregnancy, smoking during pregnancy, parity, paternal social class, parental allergic disorders, month at birth, sex, gestational age, smoking, physical activity, professional training
<85th percentile	1.00		
85th-<95th percentile	1.32	0.82-2.14	
≥95th percentile	2.09	1.23-3.57	
BMI (measured weight and height): ≥28 vs <28	2.80	1.75-4.48	Age, sex, atopic status, smoking
BMI (self-reported weight and height): ≥30 vs 20-<25	3.00	1.64-5.50	Age, atopy, respiratory symptoms
Men			
Underweight	0.39	0.05-2.82	
Normal	1.00		
Overweight	1.06	0.60-1.85	
Obese	3.13	1.41-6.97	
Women			
Underweight	1.53	0.85-2.75	
Normal	1.00		
Overweight	1.41	0.80-2.50	
Obese	1.70	0.66-4.39	
BMI (measured weight and height)			Age, sex (except sex-specific models), race or ethnicity, education, smoking status, recreational physical activity, and nonrecreational physical activity
18.5-<25	1.00		
25-<30	0.95	0.68-1.33	
30-<35	1.28	0.83-1.96	
≥35	1.87	1.12-3.13	
Men			
18.5-<25	1.00		
25-<30	0.79	0.47-1.34	
30-<35	1.52	0.82-2.82	
≥35	1.98	0.60-6.54	
Women			
18.5-<25	1.00		
25-<30	1.13	0.73-1.75	
30-<35	1.10	0.64-1.89	
≥35	1.87	1.05-3.33	

and effect cannot be determined. These studies are thought provoking, however, and at least suggest the possibility that obesity could increase the risk of asthma development.

PROSPECTIVE STUDIES

The results of 8 prospective studies that have reported on whether excess weight raises the risk of asthma development in adults are shown in Table I.^{9,16,18,45-50} Among 6420 participants in the 1970 British Cohort Study, of whom 714 reported having asthma at age 26 years, body mass index at age 10 years was not significantly associated with asthma at age 26 years.⁴⁵ Birth weight was inversely associated with incident asthma in this study. In the Nurses' Health Study II, of 85,911 women aged 26 to 46 years who were followed for 4 years, 1596 had asthma.⁴⁶ A positive association was found between body mass index and asthma incidence, and the strength of the association increased as the definition of asthma became stricter. Among 4547 men and women aged 18 to 30 years who participated in the Coronary Artery Risk Development in Young Adults study and were followed for 10 years, 310 had asthma.¹⁶ Obesity was associated with asthma among women only. In the National Population Health Survey in Canada, among 9149 participants aged 20 to 64 years who were followed for 2 years, 49 men and 127 women had asthma. Baseline body mass index was associated with self-reported asthma incidence among women but not men.⁴⁷ A study of 4719 Finnish participants born in 1966 (about 189 had asthma) showed that obesity at age 14 years increased the risk of having adult asthma at age 31 years.¹⁸ Adjusting obesity during adolescence for obesity during adulthood attenuated the association. Participants who were obese at both 14 and 31 years of age, however, had more than 2 times the odds of having asthma at age 31 years as those who were not obese at either age. In addition, the ponderal index at birth showed a U-form association with adult onset of asthma. Using a nested case-control study design, investigators of the Tucson Epidemiologic Study of Airways Obstructive Diseases found that participants with a body mass index of ≥ 28 kg/m² had an increased risk of subsequently being given a diagnosis of asthma.⁴⁸ A stronger association was found among women than men, and the form of the association differed also. More recently, a 9-year follow-up of 9671 adult Finnish twins (139 had asthma) showed that obese participants had a substantially higher risk of asthma development than participants with a normal body mass index.⁴⁹ In addition, an analysis of data from 9456 participants in the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Followup Study found a moderately increased risk for asthma development among obese adults aged 25 to 74 years who entered the study between 1971 and 1975 and were followed through 1982 to 1984.⁵⁰

Seven of the 8 prospective studies in adults found a positive association between body mass index at

baseline and the subsequent development of asthma (Table I), thereby providing considerable support for the thesis that excess weight might be causally related to asthma incidence. An important aspect of these studies is that obesity anteceded the development of asthma. The measures of relative risk have ranged from 1.6 to about 3.0, and in several studies there was a dose-response relationship. The associations have not been consistent between men and women in all studies, however.

Several prospective studies have been conducted among children and adolescents (Table II).⁵¹⁻⁵³ In a study of 3415 British boys and 3329 British girls aged 5 to 6 years, obese children had an increased risk of asthma development after 4 years.⁵¹ However, the authors concluded that the increasing prevalence of increased body mass index was not responsible for the increasing prevalence of asthma because trends in the prevalence of asthma among children aged 8 to 9 years were unaffected by adjustment for standard deviation score of body mass index. Rather, they postulated that lifestyle changes common to both conditions were the reason for their apparent association in cross-sectional studies. Among 3792 participants in the Children's Health Study aged 7 to 18 years who were followed from 1993 through 1998, the risk of asthma development increased among overweight and obese boys but not girls.⁵² Finally, among 9828 children aged 6 to 14 years from 6 US cities, body mass index was positively associated with the risk of asthma development among female subjects.⁵³

WEIGHT-CHANGE STUDIES

In at least 4 of the prospective studies conducted among adults, the effect of weight change on the future risk of incident asthma was examined. In the Nurses' Health Study, increases in self-reported weight strongly predicted asthma incidence.⁴⁶ In the Coronary Artery Risk Development in Young Adults study, participants in the highest quintile of change in body mass index showed an increased risk for asthma development when compared with participants in the second quintile of change in body mass index.¹⁶ In the National Population Health Surveys, however, changes in weight and body mass index were not predictive of incident asthma during 2 years of follow-up.⁴⁷ In addition, an increase in weight of more than 10 kg was associated with a nonsignificant increase in asthma incidence in the Finnish Twin Cohort study.⁴⁹ Finally, the annual change in body mass index *z* score was significantly associated with incident asthma among girls but not boys from 6 US cities.⁵³

WEIGHT-LOSS STUDIES

If excess weight does cause asthma, then weight loss could be expected to have the opposite effect or at least improve the clinical status of patients with asthma. Thus

studies that examine the effect of weight loss in overweight and obese persons with asthma on the status of their disease could provide critical evidence that excess weight could be causally related to asthma. The results from bariatric surgery show impressive improvements in the clinical status of many morbidly obese patients with asthma.⁵⁴⁻⁵⁸ In these studies the mean or median body mass index among morbidly obese patients before surgery was about 45 kg/m² and about 30 kg/m² up to 4 years after surgery. In up to half of patients with asthma, their condition resolved.^{54,57} Parameters such as the number of attacks, medication use, hospitalization, and severity score improved for up to 90% of patients. In addition, an analysis of data from the Swedish Obese Subjects Intervention Study found substantial reductions in the cost for medications to treat asthma in a surgically treated group but not in a conventionally treated group of obese patients.⁵⁹

The results from bariatric studies are intriguing. However, these studies did not include control groups, and thus they constitute quasiexperimental studies. Even so, the inclusion of control groups is unlikely to have affected the conclusions of these studies. Furthermore, it is difficult to assess how rigorously asthma was assessed. Other measures, such as medication use, were perhaps more objective measures of asthma, but some percentage of obese patients might have been using asthma medication to treat symptoms such as cough or breathlessness rather than true asthma. Thus any reduction in medication use among these patients could have reflected an improvement in respiratory symptoms rather than in asthma. None of the studies included data from tests of pulmonary function or bronchial reactivity. Because important changes occurred not only in energy intake but also in dietary composition after the surgery, some have argued that a change in dietary composition rather than weight loss could have been responsible in part or whole for the improvements in respiratory health.^{54,60} An additional possibility is that the improvements in asthma or asthma parameters were due to reductions in gastroesophageal reflux.⁵⁴ Finally, to qualify for bariatric surgery, a patient should be morbidly obese (body mass index ≥ 40 kg/m²) or have a lower body mass index (≥ 35 kg/m²) accompanied by comorbidities. Thus the results of bariatric studies have limited generalizability to the larger population of persons with asthma.

Several studies have examined the effects of weight loss achieved through diet modification or diet modification plus other behavioral change on asthma status or related relevant parameters. In a randomized clinical study of 38 obese patients with asthma (previously diagnosed with a spontaneous diurnal variation of $\geq 15\%$ or a bronchodilator response of $\geq 15\%$) were placed on a very-low-calorie diet for 8 weeks.⁶¹ Persons in the experimental group lost, on average, 14.5% of their weight, which was accompanied by favorable changes in FEV₁, forced vital capacity (FVC), dyspnea, use of rescue medication, number of exacerbations, and health status at the end of 8 weeks and 1 year. In a second pre-post study, 14 obese

patients with a clinical diagnosis of asthma were also treated with a very-low-calorie diet for 8 weeks and lost, on average, 14% of their pretreatment weight.⁶² The weight loss in this group was accompanied by improvements in diurnal and day-to-day variation in peak expiratory flow, FEV₁, FVC, ratio of forced midexpiratory flow rate to FVC, functional residual capacity, expiratory reserve volume, and resting minute ventilation. In a third uncontrolled study, 58 obese women, of whom 24 had a history of physician-diagnosed asthma, completed a program that consisted of a 900 kcal/d diet for 6 or 12 weeks depending on the degree of obesity and received counseling and weekly follow-up for 6 months.⁶³ The program included an exercise component as well. The mean weight loss was 17.4% of baseline weight. Improvements in FEV₁, FVC, and total lung capacity were seen, but no significant change in bronchial reactivity was found in the overall group or in the subgroup of women with a history of physician-diagnosed asthma.

DISCUSSION

The issue of whether the increase in obesity has caused an increase in the incidence and prevalence of asthma has been controversial. The results from cross-sectional, case-control, prospective, and weight-loss studies in the aggregate provide tantalizing, although inconclusive, evidence in support of a causative role of excess weight in the onset of asthma in adults. Prospective studies conducted among adults are fairly consistent in finding that excess weight is associated with asthma. Of the 8 prospective studies, all but one have reported a positive association in either men, women, or both. Furthermore, weight gain is associated with an increased risk of asthma in several studies. The majority of large cross-sectional studies show that measures of excess weight (usually on the basis of body mass index) are positively associated with the likelihood of having asthma, although in some studies the risk appears to be stronger among women than men. The situation in children is perhaps more complex. Cross-sectional studies in this age group do not consistently show a significant association between excess weight and asthma. At least 3 cohort studies, however, provide some evidence that excess weight in children might increase their chances of asthma development, especially among female subjects. Furthermore, mechanisms that potentially link excess weight to asthma are discussed elsewhere.^{46,60,64-66}

Although the observation that obesity could be causally related to asthma incidence is an intriguing thought, alternative explanations have been invoked. These will be discussed in the following order: methodologic inadequacy of many studies, obesity as an epiphenomenon, and miscellaneous explanations.

Methodologic inadequacies

A barrage of critiques has been leveled at the studies of obesity and asthma. Concerns include the definitions of

TABLE II. Prospective studies of obesity and asthma incidence among children and adolescents

Reference	Study	Follow-up (y)	Period	Age (y)	Sample size	Asthma no.	Asthma diagnosis
Chinn and Rona, ⁵¹ 2001	National Study of Health and Growth, UK	12	1982-1994	5-6	6744 M F 3415 M 3329 F	~285	Self-reported asthma
Gilliland et al, ⁵² 2003	Children's Health Study, US	4	1993-1998	7-18	3792 M F 1799 M 1993 F	288	Self-reported physician- diagnosed asthma
Gold et al, ⁵³ 2003	6 communities, US	5	1974-1979	6-14	9828 M F 4970 M 4858 F	—	Parental report of physician-diagnosed asthma with wheeze

RR, Relative risk; *BMI*, body mass index; *SDS*, standard deviation score.

asthma (including the issue of whether studies measured asthma-like symptoms rather than true asthma), use of anthropometric measures (especially use of self-reported weight and height), directionality of causation (an issue for cross-sectional and case-control studies primarily), diagnostic or detection bias, and incomplete accounting of confounding by variables, such as diet and physical activity. In addition, some have suggested that gastroesophageal reflux and sleep-disordered breathing might confound associations between obesity and asthma. Others, however, have suggested that these conditions might be part of the chain of causation, in which case adjustment for these conditions would be inappropriate.⁶⁰ Thus clarifying the mechanisms by which obesity might cause asthma is important. One factor that is difficult to quantify is the degree of publication bias.

In epidemiologic studies definition of the dependent and exposure variables is of critical importance. Diagnosing asthma is not always a straightforward endeavor. According to the National Asthma Education and Prevention Program, the diagnosis of asthma should be

based on the presence of episodic symptoms of airflow obstruction along with the demonstration of airflow obstruction that is at least partially reversible.⁶⁷ In addition, other possible diagnoses should be excluded. How well or consistently physicians diagnose asthma is unknown.

Not surprisingly, definitions of asthma have varied considerably across studies. Almost all prospective studies have relied on some form of self-reported asthma, especially that diagnosed by physicians. Some of the definitions have added other elements, such as symptoms or medication use. Although the validity and reliability of self-reported asthma are acceptable, some have suggested that self-reported asthma might not reflect true asthma in many instances but rather that it reflects a variety of respiratory symptoms, such as cough and breathlessness, that are unrelated to asthma. Although the variability in case definitions among studies might be viewed as a problem on one hand, on the other hand, the relative consistency among prospective studies in adults adds confidence to the findings.

TABLE II. (Continued)

Anthropometric measure	RR estimate	95% CI	Adjusted for:
BMI SDS (measured weight and height)			None stated
Male			
Underweight	0.87	0.59-1.28	
Normal	1.00		
Overweight	1.10	0.65-1.89	
Obese	4.74	2.23-10.09	
Female			
Underweight	0.92	0.58-1.45	
Normal	1.00		
Overweight	1.50	0.78-2.89	
Obese	4.09	1.40-11.93	
BMI percentiles (measured height and weight)			Race, community, allergy, history of wheezing
Male			
>85th vs ≤85th percentiles	2.06	1.33-3.18	
>95th vs ≤95th percentiles	2.29	1.35-3.88	
Female			
>85th vs ≤85th percentiles	1.25	0.83-1.88	
>95th vs ≤95th percentiles	1.10	0.60-2.05	
BMI quintiles (measured height and weight)			Age, race, city, parental education, air-conditioning, being only child, single-parent family, maternal smoking
Male			
1	1.00		
2	0.42	0.21-0.83	
3	1.01	0.59-1.73	
4	1.13	0.67-1.91	
5	1.04	0.60-1.82	
Female			
1	1.00		
2	1.37	0.69-2.70	
3	1.83	0.95-3.53	
4	1.76	0.89-3.46	
5	2.24	1.14-4.40	

Estimating the validity of self-reported asthma or self-reported physician-diagnosed asthma is complicated by the lack of a true gold standard for defining asthma.⁶⁸ In the case of a physician's diagnosis of asthma, the path of how such a diagnosis is made to the time it is reported by a survey participant involves numerous steps.⁶⁹ Several approaches have been used to estimate validity. Self-reported (physician-diagnosed) asthma has been compared with the results of tests for bronchial hyperreactivity, with clinical diagnoses, medical records, administrative databases, and results from other questionnaires. Each of these gold standards has its weaknesses. Testing of bronchial hyperreactivity is hampered by the fact that a considerable proportion of persons who are thought to have asthma do not have bronchial hyperresponsiveness, and a considerable proportion of persons who have positive results on such a test are asymptomatic.⁷⁰⁻⁷³ This overlap in the results from testing of bronchial hyperresponsiveness is particularly striking in population-based studies as opposed to clinical ones. When clinical diagnoses are used as the gold standard, they might

be compromised by inconsistency in the way clinicians diagnose asthma. Regardless of the choice of a gold standard, the interpretation of results from validation studies is further complicated by the setting in which they were conducted (ie, clinical or population settings). In addition, international differences in the diagnosis of asthma and changes in diagnostic criteria over time also complicate the interpretation and generalization of validation attempts.

Limited efforts at validating the case definition of asthma used in the 8 prospective studies were made in only 2 of the studies.^{46,49} Earlier studies had shown that about 49% to 64% of reported asthma from interviews was consistent with asthma determined from clinical examination, insurance report, or physician records.⁷⁴ In another study of 247 children that used a clinical examination as the benchmark, the sensitivity of self-reported physician-diagnosed asthma was 81%, and the specificity was 95%.⁷⁵

When challenge tests are used as a gold standard, the sensitivity of self-reported asthma has been on the low side because not all persons with a positive challenge test result

have been given a diagnosis of asthma.⁶⁸ In studies that compared self-reported physician-diagnosed asthma with results from testing of bronchial hyperresponsiveness, sensitivities ranged from 12% to 100%, and specificities ranged from 52% to 100%.⁷⁶ Pulmonary function tests have also been used as an indirect measure of validity. In a study of 1413 participants from Saskatchewan, persons with asthma defined from a questionnaire had lower values of FEV₁, forced expiratory flow, and FEV₁/FVC ratio than persons without asthma.⁷⁷

In principle, epidemiologic studies are subject to some degree of misclassification. With respect to asthma status, there are 2 sources of misclassification. First, asthma tends to be underestimated (sensitivity). Second, persons might be determined to have asthma when they actually do not have it (specificity). The effect of misclassification on measures of association depends on its extent and whether it was differential or nondifferential with respect to the measure of exposure. If the misclassification is nondifferential, the likely effect is to bias the magnitude of the measures of association to the null hypothesis of no association. Some data suggest, however, that misclassification might be nondifferential.

An issue of potential concern in prospective studies of obesity and asthma incidence is the possibility that asthma might be diagnosed more frequently among the obese rather than truly occurring more frequently. Such diagnostic or detection bias could occur if obese persons are more likely to come into contact with the health care system. Studies on the basis of self-reported asthma would be especially susceptible to such bias. Unfortunately, little is known as to whether the percentage of persons who have undiagnosed asthma varies with body mass index. Among Danish children aged 12 to 15 years, body mass index was positively associated with the odds of having undiagnosed asthma.⁷⁸ In contrast, 15% of obese Australian adults had undiagnosed asthma versus 21% of participants with a body mass index of ≤ 30 kg/m².⁷⁹ In addition, researchers have examined whether persons who are obese are more likely to have airway hyperresponsiveness; studies have produced inconsistent findings.

Several early studies showed that a higher percentage of obese children than children who were not obese had bronchial hyperreactivity induced by an exercise challenge.^{32,80} Since then, studies in children and adolescents have generally failed to show that the prevalence of bronchial hyperreactivity varies directly as a function of the degree of excess weight. Among 1459 eighth-grade students from Taiwan, neither girls nor boys in the highest quintile of body mass index were more likely to have bronchial hyperresponsiveness, as measured by an abbreviated methacholine challenge test, than leaner reference participants.³⁵ Among Mexican children aged 8 to 16 years, obese children showed greater decreases in FEV₁ after an exercise challenge, regardless of asthma status.⁸¹ In a study of 5993 Australian children aged 7 to 12 years, higher body mass index was not significantly associated with airway hyperresponsiveness measured with the rapid histamine inhalation test in either boys or girls.⁴⁰ In

a study of 670 Korean children aged 10 to 13 years, body mass index was not a significant predictor of airway hyperresponsiveness determined from a methacholine challenge test.⁸² In a case-control study of children aged 11 to 13 years from Sweden, no significant association was found between high body mass index and bronchial hyperresponsiveness determined from a hypertonic saline provocation test.⁴⁴ Excessive weight gain between the ages of 6 and 11 years, however, was associated with increased bronchial responsiveness to albuterol administration at age 11 or 13 years.⁸³

Among adults, study results are divided. In a study of 1971 British participants aged 17 to 73 years, a body mass index of ≥ 25 kg/m² was not significantly associated with airway hyperresponsiveness measured with a histamine challenge.¹³ In a study of 3386 men and 3723 Chinese women aged 18 years or older, quintiles of body mass index showed a U-form relationship to symptomatic airway hyperresponsiveness determined from a methacholine challenge.¹⁵ In a study of 305 men aged 21 to 80 years who participated in the Normative Aging Study and were followed for 4 years, both low and high body mass indexes were associated with an increased risk for bronchial hyperresponsiveness development determined from a methacholine challenge.⁸⁴ A subsequent study reported a significant adjusted association between body mass index and bronchial responsiveness to a methacholine challenge among 5899 male but not 5354 female participants aged 20 to 44 years in the European Community Respiratory Health Survey.⁸⁵ Finally, weight loss did not result in a change in the percentage of 58 obese women who had bronchial reactivity determined from a methacholine challenge.⁶³

Some data might allow us to speculate on how differential misclassification caused by underdiagnosis might have affected risk estimates.⁷⁹ Let us assume that the true cumulative incidence of asthma in a hypothetical cohort study is identical (5%) for participants in each of 3 weight categories (normal, overweight, and obese). Because in an Australian study the authors did not separate those with normal weight from those who were overweight, we have to make an assumption about the degree of undiagnosed asthma and will assume that this was about 25% among those who were of normal weight, 20% among those who were overweight, and 15% among those who were obese. The observed hypothetical cumulative incidence would then be 3.75%, 4%, and 4.25% for the 3 weight classes, respectively, and the resulting estimates of relative risk would be 1.07 and 1.13 for the overweight and obese classes, respectively. This suggests that an extreme degree of differential misclassification would be necessary to explain away the results from the prospective studies. The effect of wrongly assigning a diagnosis of asthma to a participant who did not truly have asthma is more difficult to estimate. A specificity that is higher among participants who are not obese compared with those who are obese could go a long way in accounting for a positive association between obesity and asthma. If we extend the above example to now vary

the specificity as follows (normal weight, 99%; overweight, 98%; obese, 97%), the estimates of relative risk change to 1.26 and 1.51 for the overweight and obese classes, respectively.

Other evidence casts doubt on an obesity-asthma association. Obese participants from NHANES III reported having more asthma and dyspnea on exertion and were more likely to use bronchodilators than those who were not obese, yet they were less likely to show airway obstruction than nonobese participants.⁸⁶ The authors concluded that a substantial percentage of participants who claimed to have been given a diagnosis of asthma probably did not have this disorder and were being treated inappropriately with bronchodilators.

There are many ways to measure excess weight. Most studies in adults have used body mass index, which is based on measurements of weight and height. Use of body mass index to establish obesity has been endorsed by the World Health Organization and the National Institutes of Health.^{87,88} In addition, body mass index in children has received endorsement by major organizations.^{89,90} Clearly, numerous other measures could be used, such as waist circumference, waist/hip ratio, relative weight, skin folds, percentage of body fat calculated from dual-energy x-ray absorptiometry, bioelectrical impedance, underwater weighing, and abdominal fat from computed tomographic scans. Many of these measures show a high degree of correlation, especially in increasingly fat societies. Thus it is unclear whether results from the existing studies on the basis of body mass index would have produced findings that differed in important ways if anthropometric measures other than body mass index had been used. Four of the 8 prospective studies in adults used self-reported weight and height to calculate body mass index.^{18,46,47,49} Because height tends to be overestimated and weight tends to be underestimated (especially among the obese), misclassification with respect to body mass index class would have likely estimates of attenuated relative risk. In the remaining 4 studies, however, body mass index was calculated from measured height and weight, and in 3 studies a significant positive association between body mass index and asthma incidence was observed.

Choosing an appropriate set of confounding variables is not an easy matter. To be a confounder, a variable has to be related to both the outcome and exposure variable, and it is not clear what should constitute a minimal set of such variables. Several sociodemographic measures, such as age, sex, race, or ethnicity, and measures of socioeconomic status, such as education or income, should certainly be considered. Because smoking is directly associated with asthma and inversely associated with weight, it should be included as a potential confounder. Both smoking by a study participant and exposure to other sources of smoking should be considered. Whether there is a need to include family history of asthma might depend on whether this variable is associated with obesity. Researchers have also used various measures that attempt to adjust for possible environmental differences. Generally, dietary measures have not been included as potential

confounders in studies of asthma. Only one prospective study adjusted for total energy intake.⁴⁶ In addition, few prospective studies have adjusted for physical activity.^{18,46,50} Other variables that researchers have included in their multivariate models are birth weight, breast-feeding information, exposure to pets, allergy history, atopic status, pregnancy-related factors (maternal age, body mass index before pregnancy, smoking during pregnancy, parity), and parental medical histories). Finally, a distinction needs to be made between a variable that is a confounder and one that is potentially in the causal pathway. In the first instance control for the variable is appropriate. In the latter instance adjusting for such a variable might lead to an incorrect interpretation of the data.

Issues of sample size and power are important in evaluating studies. However, all the prospective studies are of sufficient size that statistical power issues are of little concern.

Is obesity an epiphenomenon?

In epidemiologic studies the possibility that a factor, known or unknown, might have accounted for both the outcome and exposure variables, thereby creating a spurious relationship, cannot always be dismissed. Two such factors are a reduction in physical activity and dietary aspects.

Untangling the independent contributions of energy intake and expenditure to a particular health outcome and the contributions that are mediated through excess weight is not an easy matter because these variables are difficult to measure accurately and are highly interrelated. If the level of physical activity rather than obesity was causally related to asthma, then persons who were sedentary or reduced their activity would increase their chances of asthma development. Furthermore, if these persons did not compensate by reducing their energy intake, they would likely gain weight, and thus it might appear that obesity is causally associated with asthma incidence. The level of physical activity has been shown to be inversely related to asthma incidence in men but not women in at least one study,⁴⁹ but in 2 other prospective studies, no significant association was found.^{16,46} In 3 prospective studies attempts were made to adjust for differences in physical activity among participants.^{18,46,50} Measuring physical activity accurately is notoriously difficult, however, and the possibility of residual confounding remains a possible explanation. Furthermore, the effect of physical activity on a health outcome might be mediated through an effect on obesity, but physical activity might also affect a health outcome independent of obesity.

In a similar vein differences in dietary intake of various foods or nutrients that lead simultaneously to obesity and asthma could induce an artificial association between obesity and risk for asthma development. A number of nutrients and foods might influence the pathogenesis of asthma.⁹¹⁻⁹⁶ Thus far, no prospective study has attempted to adjust for differences in intakes of nutrients or foods among study participants.

Miscellaneous explanations

Use of medications, particularly corticosteroids, has been suggested as an explanation for the reported associations between obesity and asthma, particularly from cross-sectional studies. The consistent associations reported from prospective studies and other data undermine the plausibility of this explanation, however.¹²

SEX, OBESITY, AND ASTHMA

Whether the relationships between excess weight and asthma differ by sex has elicited a great deal of discussion. In adults one of the first prospective studies of obesity and asthma incidence was conducted in women, perhaps setting the stage for the debate.⁴⁶ In a subsequent study from the Coronary Artery Risk Development in Young Adults Study, change in body mass index was significantly associated with asthma incidence among women but not among men.¹⁶ When a Canadian prospective study showed that obesity was a risk factor for asthma among women but not among men,⁴⁷ the conventional wisdom that obesity was a risk factor among women but not among men gained a foothold. And among participants in the Tucson Epidemiologic Study of Airways Obstructive Diseases, the form and strength of the associations differed between men and women. The confidence limits for the estimates overlapped considerably, however.

At least 3 other studies in adults do not support the conventional wisdom.^{18,49,50} In a birth cohort of 4719 Finns who were followed for 31 years, the associations between obesity and asthma were not statistically different between men and women.¹⁸ In the Finnish Twin Cohort study, risk estimates were far stronger among men than women.⁴⁹ In the NHANES I Epidemiologic Followup Study, risk estimates were very similar between men and women.⁵⁰ Finally, associations between obesity and the prevalence of asthma from cross-sectional studies do not differ consistently by sex.

The first prospective study in children aged 5 to 6 years showed an association between obesity and asthma that was perhaps a little stronger in boys than in girls but unlikely to be significantly so.⁵¹ In a subsequent prospective study, the relative risk estimates were also higher among boys than girls, a difference that was of borderline significance.⁵² In a third study, however, risk estimates were higher among girls than boys.^{52,53}

Thus it is far from settled that obesity is a stronger risk factor for asthma among women than men. More research will be needed to clarify the issue of whether sex modifies the association between obesity and asthma. Such studies should examine whether there might be differences in the ways that asthma is reported by men and women. This might be especially pertinent to studies that have used self-reported information for establishing asthma incidence. Furthermore, the form of the association between obesity and asthma for men and women deserves more attention. For example, the value of an anthropometric measure at

which the risk of asthma development is lowest might differ between the 2 sexes. Finally, the possibility that the likelihood of reporting of asthma or asthma-like symptoms in function of excess weight might differ between men and women should be considered. Although the existing literature is insufficient to assess this possibility, some data show that diagnosis of asthma might differ by sex. For example, in one study 37.3% of patients with diagnosed asthma but 46.4% of patients with undiagnosed asthma were men.⁷⁹

EFFECT OF OBESITY ON PATIENTS WITH ASTHMA

At least in the United States, large population-based surveys have shown since the 1970s that the prevalence of obesity among persons with self-reported asthma is considerably higher than that among persons without this condition.⁹⁷ Cross-sectional studies are subject to the methodologic limitations outlined above, however. Thus the case definition of asthma in many surveys is based on self-report, often of a physician's earlier diagnosis. In some studies body mass index is based on self-reported height and weight. Potential confounders might not have been included in the study, and detection bias could explain the results.

Assuming, for the sake of argument, that a disproportionate percentage of persons with asthma are obese, at least 3 possibilities could explain this high proportion. First, persons with asthma could consume more calories than those without asthma. There is little evidence to support overeating as an explanation, however. For example, in the Third NHANES (1988-1994), the mean energy intake was 2178 kcal/d among 739 adults aged ≥ 20 years with current self-reported physician-diagnosed asthma and 2183 kcal/d among 14,872 persons without asthma ($P = .936$). Second, persons with asthma could be less active than those without asthma. Two large population-based studies do not show large differences in participation in physical activity between persons with and without asthma.^{98,99} Still, if the energy balance is tipped even slightly in favor of energy intake, weight gain can accumulate over time. Finally, some medications might cause patients to gain weight. The use of medications to treat asthma is not thought to be associated with weight gain.¹² On the other hand, patients with asthma show a high prevalence of depressive symptoms.¹⁰⁰ Because use of some antidepressant medications can lead to weight gain, their use could account for some proportion of the excess obesity among asthmatic patients.

The question deserves to be asked whether and how a person's asthma might be affected by excess weight. Some evidence suggests that obesity indeed affects the respiratory health status of patients with asthma. Compared with nonobese asthmatic children, obese children aged 4 to 9 years with asthma were more likely to use multiple medications and oral steroids, had a higher mean number of days that they wheezed, and were more likely to visit an emergency department.¹⁰¹ In another

study 20.7% of Swedish patients with asthma on sick leave were obese on the basis of self-reported weight and height compared with 6.5% of a general population sample.¹⁰² The authors concluded that weight management should be part of the care of asthmatic patients. In a more recent study of 572 patients who presented to the emergency department with acute asthma, however, obesity was not a determinant of severity, as reflected by history of steroid use, hospitalizations, intubations, number of emergency department visits, or hospital admissions.¹⁰³

The intervention studies discussed above strongly suggest that obese asthmatic patients benefit substantially from weight loss. Some might experience a complete resolution of their disease. Others might enjoy improvements in the severity of their disease, have fewer symptoms, do better on pulmonary function tests, need less medication, or attain better health status. Although not studied thus far, they might also be likely to report improved quality of life because body mass index is a significant predictor of quality of life among these patients.¹⁰⁴ The mechanisms responsible for the improvements in clinical status of these patients deserve greater attention. More and larger randomized clinical trials of the effects of weight loss on respiratory health, asthma status, and quality of life are needed. Such studies should use rigorous definitions of asthma and try to disentangle the contributions of dieting and exercise on a wide range of parameters. Any differential effect of weight loss on patients with minimal, moderate, or severe asthma is worthy of study. In addition, the existence of any differences by age, sex, or race or ethnicity should be examined.

Many of these patients might not be appropriately counseled about weight loss and physical activity, and a large percentage of obese patients with asthma who are trying to lose weight are not using recommended means to do so.¹⁰⁵

Because respiratory symptoms, such as cough and breathlessness, occur more frequently among obese persons than others, resulting perhaps in an excess of diagnosed asthma, several researchers have raised the possibility that some proportion of obese persons who do not have asthma might be using asthma medications inappropriately.^{13,86} Thus clinicians should attempt to diagnose asthma as strictly as possible.

CONCLUSIONS

Although a considerable number of studies using different study designs indicate that excess weight might increase the risk of asthma development, the topic remains controversial because of potential methodological limitations inherent in many of these studies.¹⁰⁶ Given the trends in the prevalence of obesity and asthma, clarifying this still opaque area is of considerable urgency, because if a consensus was to be reached that obesity indeed causes asthma, new options for preventing and treating this disease could be vigorously pursued. Calculation of the

population-attributable fraction, assuming a prevalence of obesity of 30% among US adults and estimates of relative risk ranging from 1.6 to 3.0, suggests that about 15% to 38% of asthma in adults might be caused by obesity and thus might be preventable. Unless prospective studies are better able to define asthma incidence accurately and address potential sources of bias, additional prospective studies are unlikely to resolve any outstanding doubts. In addition, most studies have used body mass index as the principal anthropometric measure. Examining whether body mass distribution or other indicators of excess weight, such as total fat mass, might yield additional insights into this evolving arena. Large randomized clinical trials of weight loss, including bariatric studies, might yield valuable insights into the obesity-asthma relationship, especially if rigorous definitions of asthma are used. Whether weight-loss programs need to be tailored to patients with asthma deserves consideration. Because the combination of energy restriction and increased energy output produces the most consistent long-term weight loss, good control of asthma is a necessity to allow many patients with this disorder to increase their level of physical activity. Health care professionals can help to dispel any lingering doubts among most asthmatic patients about their ability to engage in adequate physical activity. Clearly, many aspects of obesity and asthma deserve further research.⁶⁶

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