Overweight, Obesity, and Incident Asthma

A Meta-analysis of Prospective Epidemiologic Studies

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Rationale: Although obesity has been implicated as an asthma risk factor, there is heterogeneity in the published literature regarding its role in asthma incidence, particularly in men.

Objectives: To quantify the relationship between categories of body mass index (BMI) and incident asthma in adults and to evaluate the impact of sex on this relationship.

Methods: Online bibliographic databases were searched for prospective studies evaluating BMI and incident asthma in adults. Independent observers extracted data regarding annualized asthma incidence from studies meeting predetermined criteria, within defined categories of normal weight (BMI < 25), overweight (BMI, 25–29.9), and obesity (BMI ≥ 30). Data were analyzed by inverse-variance-weighted, random-effects meta-analysis. Stratified analysis between BMI categories and within sex was performed.

Results: Seven studies (n = 333,102 subjects) met inclusion criteria. Compared with normal weight, overweight and obesity (BMI ≥ 25) conferred increased odds of incident asthma, with an odds ratio (OR) of 1.51 (95% confidence interval [CI], 1.27–1.80). A dose-response effect of elevated BMI on asthma incidence was observed; the OR for incident asthma for normal-weight versus overweight subjects was 1.38 (95% CI, 1.17–1.62) and was further elevated for normal weight versus obesity (OR, 1.92; 95% CI, 1.43–2.59; p < 0.0001 for the trend). A similar increase in the OR of incident asthma due to overweight and obesity was observed in men (OR, 1.46; 95% CI, 1.05–2.02) and women (OR, 1.68; 95% CI, 1.45–1.94; p = 0.232 for the comparison).

Conclusions: Overweight and obesity are associated with a dose-dependent increase in the odds of incident asthma in men and women, suggesting asthma incidence could be reduced by interventions targeting overweight and obesity.

Keywords: risk factors; epidemiology; body weight; respiratory tract diseases

The increasing prevalence of asthma and obesity has suggested an association between the two conditions (1). Age-adjusted prevalence data from the National Health and Nutrition Examination Survey show that 65% of United States adults are overweight or obese, with an increase of 10% from 1988–1994 to 1999–2000 (2, 3). Although asthma is less prevalent than obesity, it affects approximately 7% of the adult population in the United States (4).

Many cross-sectional epidemiologic investigations have shown a modest association between obesity and prevalent asthma (5–8), and a comprehensive qualitative review of this literature has been published (9). Using differing definitions of obesity, the relative risk of asthma in obesity ranges from 1.0

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Although obesity has been implicated as an asthma risk factor, there is heterogeneity in the published literature regarding its role in asthma incidence, particularly in men.

What This Study Adds to the Field

Asthma incidence increases by 50% in overweight/obese individuals. There is a dose-response relationship between body weight and asthma, and female sex does not disproportionately affect the obesity–asthma relationship.

(no effect) to 3.0, and some studies have shown this risk to be greater in women than in men. The strength of these studies is their ability to examine large numbers of subjects, and some have characterized obesity objectively using measured height and weight (5, 7, 8). However, even though these reports frequently control for confounding by socioeconomic status, age, activity levels, and diet, causation in the obesity–asthma relationship cannot be determined conclusively from cross-sectional data alone. Although many investigators have interpreted these data to suggest that obesity increases the risk of asthma, one cannot rule out that asthma may contribute to obesity, perhaps due to inactivity or side effects of systemic corticosteroids.

Prospective epidemiologic studies have the advantage of clarifying the direction of this relationship and have suggested that antecedent obesity leads to an increase in the incidence of a new diagnosis of asthma. For example, Camargo and colleagues showed that in a group of women participating in the Nurses' Health Study, the relative risk for incident asthma increased with increasing body mass index (BMI) up to 2.7 for a BMI ≥ 30 (p for trend < 0.001) (10). However, there is heterogeneity in the magnitude and significance of this relationship across studies. Reported odds ratios (ORs) or risk ratios for incident asthma in obese or extremely obese compared with normal-weight individuals range from 1.0 to 3.5. Although these studies are prospective adult investigations using reported or measured BMI at baseline and self-reported new diagnosis of asthma or asthma symptoms, there are differences in duration of follow-up, study size, sex distribution, age distribution, range of BMI, and other variables that could explain some of the differences in point estimates. For example, the role of sex in the obesity–asthma relationship is controversial, and there is considerable heterogeneity among studies reporting incidence data stratified by sex, with some demonstrating that the relationship between obesity and asthma is significant and similar for men and women (11, 12), others failing to show a significant relationship in men (5, 13) or reporting that the relationship in men is weaker than

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in women (14), and still others demonstrating significant findings only in men (15).

The primary objectives of this meta-analysis were (1) to determine a precise numerical estimate of the impact of overweight and obesity on the annual odds of developing asthma in adults, (2) to determine whether there is a dose-response effect of elevated BMI on asthma incidence, and (3) to determine whether sex alters the odds of incident asthma in overweight or obese adults. We hypothesized that overweight and obesity would increase the odds of incident asthma in a dose-dependent manner and that this effect would be more pronounced in women than in men. Some of the results of this study have been reported previously in the form of an abstract (16).

METHODS

This meta-analysis was conducted and reported according to recommendations of the Meta-analysis of Observational Studies in Epidemiology group (17). Targeted studies were those in which the relationship between BMI and incident asthma was evaluated. MEDLINE, Cumulative Index to Nursing and Allied Health Literature, International Pharmaceutical Abstracts, and all Evidence-Based Medicine Reviews (EBMR) (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials) were searched between a date range of 1966 to May 2006, crossing keywords "overweight" and "asthma," "obesity" and "asthma," "body mass index" and "asthma," "body weight" and "asthma," and "anthropometry" and "asthma." Reference lists were searched for additional articles, and discussions were held with experts in the area of investigation to identify additional published or unpublished data.

Two investigators independently reviewed each study. Predetermined inclusion criteria included (1) adult subjects, (2) primary outcome of incident asthma, (3) use of BMI as a measure of overweight or obesity, (4) minimum 1-year follow-up, (5) follow-up of at least 70%, and (6) data that could be categorized by standard ranges of BMI obtained at study inception. It was anticipated that all studies would use new, self-reported, physician-diagnosed asthma or new symptoms and/or medication use compatible with asthma as the criteria for incident asthma diagnosis. Normal weight was defined as BMI < 25, overweight was defined as BMI between 25 and 29.9, and obesity was defined as BMI ≥ 30. Study data sources were examined to ensure that every included dataset was unique.

Data were extracted into contingency tables to facilitate calculation of the odds of incident asthma over the study period. To standardize the differing follow-up periods between studies, asthma incidence data were expressed in an annualized fashion by assuming a constant rate of incident asthma over the follow-up period and dividing the number of new asthma cases by the number of years of follow-up. These contingency tables were used to further stratify asthma incidence in three BMI and two sex categories. Specific comparisons were made to allow determination of ORs comparing overweight subjects with normal-weight subjects, obese subjects with normal-weight subjects, and overweight and obese subjects with normal-weight subjects. These comparisons were performed in men and women separately.

Stata 7.0 (Stata Corporation, College Station, TX) (18) was used to generate summary ORs using inverse, variance-weighted, random-effects meta-analysis (19, 20). Random effects methodology was chosen to account for within-study and between-study variation. Heterogeneity of data was evaluated using the *Q* statistic (19). Summary ORs were represented as a point estimate and 95% confidence intervals (CIs) on a forest plot (21), and publication bias was evaluated (22, 23). A plan was established *a priori* to perform sensitivity analyses in the case of identified issues relating to study quality, if necessary, rather than applying weights to studies in the meta-analysis based simply on quality scoring criteria (17).

RESULTS

The systematic search (Figure 1) yielded 2,006 total references, of which 1,569 were unique. Using the prespecified inclusion

Figure 1. Results of systematic literature search.

criteria, a title review rejected 1,474 references, yielding 95 candidate abstracts. A subsequent abstract review rejected 82 of these references, yielding 13 candidate studies. After each of these studies was reviewed in its entirety, seven studies (10–15, 24) were found to meet the prespecified inclusion criteria.

A total of 333,102 unique subjects were included in the analysis (Table 1). Study populations included were well-characterized cohorts in the United States, Canada, and Europe. Two studies included only women (10, 24). One of the seven articles stratified BMI by decile (24), and attempts to obtain primary data for categorization according to the aforementioned criteria were unsuccessful. Because one of the BMI decile cutoffs in this study approximated 25 (24.62), this article was included in an analysis that grouped overweight and obesity into a single category (BMI ≥ 25). All included studies were observational and of similar design; thus, quantitative measures of quality were not used to weight the studies in the meta-analysis (17).

Antecedent obesity was associated with significantly increased annual odds of a new diagnosis of asthma. The summary OR for 1-year incident asthma in overweight and obese versus normal-weight men and women was 1.51 (95% CI, 1.27–1.80) (Table 2, Figure 2). A dose-response effect to this relationship was observed, with increasing BMI being associated with increasing odds of incident asthma (Table 2), such that the annual OR of incident asthma in overweight versus normal-weight individuals was 1.38 (95% CI, 1.17–1.62), with the annual OR of incident asthma in obese versus normal-weight individuals being further increased at 1.92 (95% CI, 1.43–2.95) (Table 2, Figure 3), with a $p < 0.0001$ for this trend.

Sex did not seem to be a significant modifier of the strength of relationship between overweight and obesity and asthma incidence. When overweight and obese subjects were compared with normal-weight subjects, the ORs of asthma over 1 year of follow-up were 1.46 (95% CI, 1.05–2.02) for men and 1.68 (95% CI, 1.45–1.94) for women (Table 2, Figure 4), with a $p = 0.2$ for the comparison. The dose-response relationship between increasing BMI and odds of incident asthma remained evident when stratified by sex (Table 2). There was no evidence of significant publication bias (Egger $p = 0.09$).

TABLE 1. INCLUDED STUDIES

Study	Population	n	Time (yr)	Reported OR and	Annualized OR and
				95% CI (BMI > 30)	95% CI (BMI > 30)
Camargo and colleagues (10)	Nurses' Health II	85,911	4		
	Men	0		N/A	N/A
	Women	85,911		2.7 (2.3–3.1)	2.5 (2.0–3.2)
Chen and colleagues (13)	Canadian NPHS	9,149	2		
	Men	4,266		1.0	0.7 (0.2–2.1)
	Women	4,883		1.9 (1.1–3.4)	2.1 (1.2–4.0)
Ford and colleagues (11)	NHANES I	9,546	10		
	Men	3,621		1.5 (0.9–2.6)*	1.6 (0.3–8.8)
	Women	5,925		1.4 (1.0–1.9)*	1.4 (0.5–4.1)
Gunnbjörnsdóttir and colleagues (12)	ECRHS	16,191	7.9 [†]		
	Men	7,604		2.1 (1.4–3.2)*	2.2 (0.7–6.7)
	Women	8,587		1.6 (1.1–2.1)*	1.4 (0.6–3.7)
Huovinen and colleagues (15)	Finnish Twin Cohort	9,671	9		
	Men	4,449		3.5 (1.6–7.7)	4.4 (0.6–33)
	Women	5,222		2.3 (0.96–1)	4.5 (0.7–31)
Nystad and colleagues (14)	Norwegian Health Surveys	135,405	21 [†]		
	Men	66,723		1.8 (1.4–2.3)	2.3 (0.9–6.3)
	Women	68,682		2.0 (1.7–2.4)	1.9 (1.0–3.7)
Romieu and colleagues (24)	French E3N Cohort	67,229	3		
	Men	0		N/A	N/A
	Women	67,229		2.2 (1.4–3.2) [‡]	1.4 (1.0–2.2)

Definition of abbreviations: BMI = body mass index; CI = confidence interval; ECRHS = European Community Respiratory Health Survey; N/A = not applicable; NPHS = National Population Health Survey; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio.

* Study did not report this comparison, so primary data were extracted into a 2 × 2 table comparing BMI > 30 with BMI < 25, and OR was calculated.

[†] Mean follow-up.

[‡] Reported OR comparing BMI ≥ 27 to the reference BMI category 20.2–21.4.

DISCUSSION

This meta-analysis has provided a precise estimate of the odds of incident asthma for individuals who are overweight or obese, suggesting that the odds of incident asthma are increased 50% in overweight or obese individuals as a whole. Our findings also demonstrate a clear dose–response relationship between BMI and asthma, suggesting that asthma risk increases further as body weight increases. In addition, we have shown that female sex does not seem to disproportionately affect the obesity–asthma relationship, given that the odds of incident asthma in overweight and obese men and women were similar.

On the basis of these findings, overweight and obesity seem to be significant risk factors for asthma, and if they can be considered to be modifiable risk factors, interventions that effect weight loss could be associated with a decrease in asthma incidence. Survey data suggest that two-thirds of the adult population of 220 million in the United States are overweight or obese (2). Assuming that approximately 12% of these overweight or obese individuals have asthma (25, 26) and assuming that 6% of the remaining adult population has asthma, approximately

200 million United States adults are free of asthma but at risk of developing it. Studies suggest that new asthma cases in the general adult population occur at a rate of approximately 0.5% per year (27, 28), and presumably this rate is influenced by contributions from the lean and overweight/obese subgroups of the population in the ratio described previously (1 lean:2 obese/overweight). If significant weight loss could be achieved in the population of overweight and obese individuals, it could be estimated that the number of new asthma cases in United States adults might fall by as much as 250,000 per year (from 0.5 to 0.375% per year). If these rates of increase can be extrapolated to the pediatric population, where the annual incidence of asthma is as much as five times higher (24 per 1,000 person-years [29]), the effect of even small changes in mean population BMI may translate into significant increases or decreases in asthma incidence in children and adults.

This analysis has a number of potential limitations. First, many of the studies included in this meta-analysis relied on self-reported, rather than measured, weight and height to determine BMI. If there were large and systematic differences in reporting of weight and height by sex or BMI, then these results could be

TABLE 2. ODDS RATIOS AND 95% CONFIDENCE INTERVALS OF INCIDENT ASTHMA AFTER 1 YEAR OF FOLLOW-UP IN VARIOUS CATEGORIES OF BODY MASS INDEX IN AGGREGATE AND STRATIFIED BY SEX

Comparison	Total		Men		Women	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Overweight vs. normal BMI	1.38 (1.17–1.62)	< 0.001	1.44 (1.01–2.04)	0.042	1.42 (1.18–1.72)	< 0.001
Obese vs. normal BMI	1.92 (1.43–2.59)	< 0.001	1.63 (0.92–2.89)	0.094	2.30 (1.88–2.82)	< 0.001
Overweight and obese (BMI ≥ 25) vs. normal BMI	1.51 (1.27–1.80)	< 0.001	1.46 (1.05–2.02)	0.025	1.68 (1.45–1.94)	< 0.001
Obese vs. overweight	1.49 (1.20–1.85)	< 0.001	1.17 (0.66–2.07)	0.590	1.58 (1.25–1.99)	< 0.001

Definition of abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.

Figure 2. Point estimate for the summary odds of incident asthma at 1 year of follow-up, comparing obese and overweight men and women versus normal-weight men and women. Superscript numbers indicate reference number.

confounded by a classification bias. We believe this is unlikely to have affected our results. Of the seven studies included in this analysis, two (11, 14) used measured and not self-reported height and weight, and these studies found that the relationship between obesity and asthma was significant and was similar between men and women, which is consistent with our results. In addition, a recent study by Hu and colleagues validated self-reported with measured weight among 184 participants in the Nurses' Health Study (30). Self-reported weight was highly correlated with measured weight ($r = 0.96$; mean measured weight

Figure 4. Point estimate for the summary odds of incident asthma at 1 year of follow-up, comparing overweight and obese men versus normal-weight men (top) and overweight and obese women versus normal-weight women (bottom). Superscript numbers indicate reference number.

Figure 3. Point estimates for the summary odds of incident asthma at 1 year of follow-up, comparing overweight men and women versus normal-weight men and women (top) and obese men and women versus normal-weight men and women (bottom). Increasing body mass index (BMI) is associated with an increased odds of incident asthma at 1 year of follow-up. Superscript numbers indicate reference number.

was 1.4 kg greater than self-reported weight). This analysis was performed in a study cohort included in this meta-analysis (10).

BMI may not be the best measure of adiposity, particularly when looking at the effect of obesity on lung disease. There may be sex differences in muscle mass and body fat distribution that could make BMI a misleading indicator of the degree of adiposity, and measures of abdominal adiposity are better predictors of alteration in pulmonary function than body weight or BMI (31, 32). Although future research in obesity and lung disease may benefit from the use of alternative measures of adiposity, for practical purposes we were constrained to use BMI because it is by far the most commonly used measure of obesity in this literature.

It is possible that asthma may be overdiagnosed in an obese population or that the phenotype of asthma seen with overweight and obesity is unique regarding clinically meaningful parameters, such as the nature or perception of symptoms, specific physiologic impairments (33), or response to therapy (34). Although the data on which our analysis is based do not allow evaluation of these factors in the combined study population, previous reports suggest that asthma associated with obesity may differ phenotypically from asthma in normal-weight individuals. Obesity in the absence of asthma causes physiologic impairments in lung function, including reduction in lung volumes (35), chest wall restriction (36), and increased oxygen cost of breathing (37), and contributes to comorbid conditions such as gastroesophageal reflux (38, 39) and sleep apnea; these can result in dyspnea and wheezing, which might be mistaken for asthma by patients and clinicians (33, 40). It has also been reported that although lung volumes are reduced and asthma symptoms are increased in obesity, airflow obstruction and airway hyperresponsiveness are not altered (41). Weight loss studies have shown improvements in lung function and asthma symptoms (42) but not necessarily

in airflow obstruction or airway hyperresponsiveness (43). These reports cast some doubt on the validity of self-reported asthma (even if it is also "physician diagnosed") in large epidemiologic studies. It is reasonable to believe that some of these patients with "asthma" may have respiratory symptoms due to obesity but may not meet rigorous objective physiologic criteria for asthma (40). This type of classification bias is difficult to address in a large epidemiologic investigation without having independent clinical and physiologic data for each subject and may have falsely inflated the number of new cases of asthma in obese subjects, leading to an overestimate of the OR, a phenomenon that might contribute to the overdiagnosis of asthma in reports in which conclusions are drawn from epidemiologic data using self-reported asthma as the primary criterion for diagnosing asthma, without supporting physiologic evaluation.

Alternatively, the calculated ORs may have been underestimated due to the grouping together of underweight and normal-weight subjects. Being underweight has been shown to be a risk factor for asthma, with the relationship between asthma risk and BMI having a J-shape such that very low BMI has been reported to be associated with elevated asthma risk (15). By defining "normal" BMI as less than 25, we potentially included underweight individuals with a high incidence of asthma in the "normal" group, which elevates the group's asthma incidence and diminishes the relative odds of asthma due to obesity. Because three of the seven studies included BMI of less than 20 in their "normal" group, we were unable to rigorously exclude underweight individuals in our analysis.

Although the effect of obesity on asthma in this study was statistically significant and there was a clear dose-response relationship, the magnitude of the effect was modest, even if one assumes that all newly reported cases of asthma in these studies are asthma and not obesity-associated respiratory symptoms. However, to standardize data for our analysis, we determined the number of new cases of asthma per year; thus, the increased odds are elevated even over a relatively short time frame with regard to duration of overweight and/or obesity in many patients and when multiplied over many years are likely to be clinically significant.

Obesity is a well-established risk factor for diabetes, hypertension, sleep apnea, stroke, cardiovascular disease, arthritis, cancer, and many other diseases (44, 45). Our findings support adding asthma to this list and should provide yet one more piece of information to compel obese individuals to lose weight and to support the aggressive implementation of public health measures to support the attainment of this goal.

Conflict of Interest Statement: D.A.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.R.S. served as an advisor or consultant to Dey, GlaxoSmithKline, Pfizer, Talecris, and Schering-Plough and received lecture fees from IVAX and unrestricted investigator-initiated grant funding from Boehringer-Ingelheim and GlaxoSmithKline from 2003 to 2006.

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