Prospective Study of Body Mass Index, Weight Change, and Risk of Adult-onset Asthma in Women

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Background: Obesity and asthma are common disorders, and their prevalence rates continue to rise. Although individuals with asthma may gain weight as a result of activity limitations, the relationship between body mass index (BMI), which is calculated as weight in kilograms divided by the square of height in meters, and risk of developing asthma is not known.

Methods: We performed a prospective cohort study of female US registered nurses in the Nurses’ Health Study II. In 1991, after excluding women who died with probable asthma or with incomplete data, there were 85,911 participants, aged 26 to 46 years. The main outcome measure was self-report of physician-diagnosed asthma with recent use of an asthma medication.

Results: From 1991 to 1995, we identified 1,596 incident cases of asthma. In a multivariate model controlling for 9 potential confounding factors (including age, race, smoking, physical activity, and energy intake), the relative risks of asthma for 6 increasing categories of BMI in 1991 were 0.9, 1.0 (reference), 1.1, 1.6, 1.7, and 2.7 (P for trend <.001). Stronger associations were found using stricter definitions for asthma, and the finding was present in a variety of subgroups. In analyses controlling for the same variables, as well as BMI at age 18, women who gained weight after age 18 were at significantly increased risk of developing asthma during the 4-year follow-up period (P for trend < .001).

Conclusions: The BMI has a strong, independent, and positive association with risk of adult-onset asthma. The increasing prevalence of obesity in developed nations may help explain concomitant increases in asthma prevalence.

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STHMA AFFECTS at least 5% of the US population and its prevalence continues to rise. In 1990, the management of asthma already accounted for more than $6 billion in medical expenditures. Despite the enormity of the problem, there are relatively few large-scale epidemiological studies on the etiology of asthma, particularly adult-onset asthma. In recent years, investigators have begun to define genetic and environmental risk factors in the hope that timely interventions might prevent individuals from developing asthma.

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The prevalence of obesity in the United States has increased steadily during the past 30 years. In recent years, even lesser degrees of overweight have been linked to a variety of health problems, including premature mortality. Although patients with poorly controlled asthma might gain weight as a result of activity limitations, the relationship between obesity and risk of asthma is not known. We examined the relation of body mass index (BMI), which is calculated as weight in kilograms divided by the square of height in meters, and weight change to risk of adult-onset asthma during 4 years of follow-up in more than 85,000 women.

In 1991, at baseline, the mean weight of participants in the Nurses’ Health Study II cohort was 3.3 kg (7.3 lb) less than women of similar age in the general US population. The participants’ mean ± SD BMI was 24.5 ± 5.2. Table 1 shows the baseline characteristics according to BMI in 1991. Women with higher BMIs tended to be older, do less physical activity, and have a larger energy intake. Obese women in 1991 tended to weigh more at age 18 and have gained more weight during the ensuing years. Obese women also were less likely to have recently undergone a health screening examination or to use nutritional supplements.
Diagnosis of Asthma

All women who reported in the 1993 or 1995 follow-up questionnaires that a physician had first diagnosed them as having asthma during the preceding 2 years received supplementary questionnaires on the symptoms, diagnosis, and therapy of asthma. Follow-up from July 1991 to June 1995 was 95% complete. Each participant who reported asthma was categorized based on 3 case definitions of increasingly stricter criteria. Case definition 1 defines an incident case of asthma and was considered confirmed if the nurse did the following: (1) reiterated on the supplementary questionnaire that a physician had diagnosed her as having asthma, and (2) reported using an asthma medication since diagnosis. To meet case definition 2, participants had to fulfill both of the preceding criteria and report use of a prescribed long-term preventive medication (ie, inhaled corticosteroids, Cromolyn sodium, nedocromil, salmeterol) in the past year. Finally, to meet case definition 3, participants had to meet all the criteria from case definitions 1 and 2 plus report that their physician-diagnosed asthma was within 1 month of symptom onset. In 1998, we recontacted a random sample of 100 women who met the criteria of case definition 2 to determine their asthma status approximately 5 years after receiving the physician diagnosis of asthma (1991-1995). Further validation was not pursued because of the following: (1) these criteria are considerably stricter than those of most asthma epidemiology studies; (2) we found highly accurate reporting of other chronic diseases among registered US nurses; and (3) the cost of pulmonary function testing in this cohort would be prohibitive.

Statistical Analysis

Participants were grouped according to the BMI, based on height and weight reported in the 1991 questionnaire. Incident cases of asthma were assigned to the BMI category at baseline. Cumulative incidence rates were calculated by dividing the number of new asthma cases by the number of people at risk in a given BMI category. The relative risk (RR), computed as the cumulative incidence in a specific category of BMI divided by the corresponding value in the second category (BMI, 20.0-22.4), was used as a measure of the strength of the association. Multivariate logistic regression models controlled for multiple risk factors simultaneously. A test for linear trend was conducted by assigning a score of 1 through 6 for each available BMI value, and this score was then analyzed as a continuous variable. A similar approach was used for analyses involving weight change since age 18. The absolute excess risks (attributable risks) due to adiposity (using the cumulative incidence for women with a BMI of 20.0-22.4 as the reference) or weight change (using those with <2-kg weight change as the reference) were calculated using the multivariate RR. Group comparisons were made using the χ² test. All RRs are presented with 95% confidence intervals (CIs), and all reported P values are 2-sided.

During 4 years of observation, from 1991 to 1995, we identified 1596 case definition 1 incident cases of asthma. This yielded a cumulative incidence of approximately 0.5% per year. By definition, in all incident cases the participants reported a physician diagnosis of asthma on 2 separate questionnaires and use of at least 1 asthma medication since diagnosis. The median duration from symptom onset to physician diagnosis was 2 months (interquartile range, 0-19 months). Given the 2-year follow-up cycle, the supplementary asthma questionnaire...
was sent to participants with incident asthma a median of 21 months after they received their asthma diagnosis (interquartile range, 15-28 months). Thus, almost 2 years after first being told they had asthma, 90% of asthmatic participants reported use of an asthma medication in the past year. Use of inhaled corticosteroids was reported by 59%. Other medications used in the past year included oral or intravenous steroids for asthma (25%), cromolyn or nedocromil (12%), and salmeterol (5%). Parental history of asthma was reported by approximately 21% of incident cases of asthma. Common triggers of asthma exacerbations included respiratory infections (70%) and exposure to environmental allergens (67%), such as pets, house dust, mold, or pollen. Only 2% of nurses reported latex allergy as a precipitant of an asthma exacerbation. Smoking also was uncommon, with 66% never smokers, 23% past smokers, and 11% current smokers at baseline. Approximately 7% of incident cases of asthma reported at least 1 hospitalization for acute asthma since physician diagnosis of asthma.

The 1998 validation survey of 100 participants who met the criteria of case definition 2 raised issues in 1998 that might lead us to question their diagnosis (eg, asthma symptoms resolved when 1 woman stopped taking β-blockers; another woman received a diagnosis of asthma based on 1 visit to the emergency department and reported mild respiratory symptoms thereafter). Another 4% of cases had symptomatic asthma requiring regular medication use for more than 6 months but reported asthma “resolution” by the time of the 1998 survey. Even if we include these potential noncases, 89% of women who originally met case definition 2 raised issues in 1998 that might lead us to question their diagnosis (eg, asthma symptoms resolved when 1 woman stopped taking β-blockers; another woman received a diagnosis of asthma based on 1 visit to the emergency department and reported mild respiratory symptoms thereafter). 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stricting cases to participants who used a preventive medication in the past year \( (n = 1079) \) yielded almost identical results. Because some cases may have had activity limitations before diagnosis, we included only those with physician-diagnosed asthma within 1 month of symptom onset \( (n = 433) \). Again, BMI in 1991 remained a strong, independent risk factor for developing asthma during the 4-year follow-up. All these models were recalculated while controlling for additional factors (eg, diet, menopause, use of oral contraceptives or hormones) without any material change in the BMI-asthma association (data not shown).

Because obesity represents the complex interplay of both lifestyle and genetic factors, we also report the RR of developing asthma according to levels of physical activity and total energy intake; data on familial predisposition to obesity or asthma were not available. In the primary model (case definition 1 in Table 2), the multivariate RR of asthma for quintiles of increasing physical activity was 1.0 (reference), 1.0, 1.0, 0.9, and 1.0 \( (P \text{ for trend} = .31) \). Substituting frequency of vigorous physical activity, as opposed to quintiles of overall physical activity, yielded similar results (data not shown). By contrast, the multivariate RR of asthma for quintiles of increasing total energy intake was the following: 1.0 (reference), 1.0, 1.0, 0.9, and 1.0 \( (P \text{ for trend} < .001) \). Results from similar models that used stricter case definitions did not differ materially (data not shown).

Weight change since age 18 also had a strong, independent, and positive association with risk of adult-onset asthma (Table 3). Women who lost weight appeared to be at slightly decreased risk, whereas women who gained weight were at increased risk. As before, stronger associations were present for case definition 2 and case definition 3 \( (P \text{ for trend} < .001) \). For example, in the analysis using case definition 3, participants who gained more than 25 kg since age 18 had a multivariate RR of 4.7 \( (95\% \text{ CI, 3.1-7.0}) \), compared with those participants whose weight had remained stable.

To address potential concerns about detection bias, we reexamined the BMI-asthma association of the cohort according to 2 characteristics that might serve as markers of health-oriented behavior: (1) history of undergoing a recent health screening examination (72% of cohort), and (2) baseline use of nutritional supplements (56% of cohort). We also reexamined the BMI-asthma association according to smoking status in 1991. The Figure shows the strong dose-response association between BMI and RR of asthma among women who reported undergoing a recent health screening examination \( (n = 1061 \text{ cases}) \). Relative risks are adjusted for all 9 potential confounding factors listed in the first footnote of Table 2. The bars represent 95% confidence intervals. \( P \text{ for trend} < .001 \).

<table>
<thead>
<tr>
<th>Change in Weight, kg</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariate RR (95% CI)</th>
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<tbody>
<tr>
<td>≤ -5</td>
<td>1.0 (0.7-1.3)</td>
<td>0.8 (0.6-1.1)</td>
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<td>-5 to -2.1</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>-2 to 2</td>
<td>0.9 (0.8-1.2)</td>
<td>0.9 (0.8-1.2)</td>
</tr>
<tr>
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<td>1.1 (0.9-1.3)</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>5.1 to 10</td>
<td>1.4 (1.2-1.7)</td>
<td>1.4 (1.2-1.7)</td>
</tr>
<tr>
<td>10.1 to 20</td>
<td>2.1 (1.7-2.6)</td>
<td>2.0 (1.6-2.5)</td>
</tr>
<tr>
<td>20.1 to 25</td>
<td>2.7 (2.2-3.4)</td>
<td>2.5 (2.0-3.1)</td>
</tr>
<tr>
<td>&gt; 25</td>
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*Case definition 1 includes participants who reported a physician diagnosis of asthma on 2 separate questionnaires and the use of an asthma medication since diagnosis. Ellipses indicate not applicable; CI, confidence interval. Multivariate RRs are adjusted for age, race, US region, smoking status, physical activity, total energy intake, hysterectomy status, birth weight, duration of breastfeeding, and body mass index at age 18.

Relative risk of adult-onset asthma during 1991 to 1995, according to body mass index, among 61 324 women who reported undergoing a recent health screening examination \( (n = 1061 \text{ cases}) \). Relative risks are adjusted for all 9 potential confounding factors listed in the first footnote of Table 2. The bars represent 95% confidence intervals. \( P \text{ for trend} < .001 \).

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tion between WHR and asthma risk. However, when both adiposity measures were included in the multivariate model, BMI remained a significant risk factor (eg, RR, 2.8 for BMI $\geq 30.0$ vs 20.0-22.4; 95% CI, 2.2-3.6; $P$ for trend $<.001$), whereas WHR was not associated with asthma risk (RR, 0.9-1.2; all $P$ values $>.30$). Substituting waist circumference for WHR yielded similar results (data not shown).

Of the overall incidence of asthma in the cohort, 38% was accounted for by excessive body weight, defined as a baseline BMI of 22.5 or higher. For women with a BMI of 25.0 or higher, 50% of their increased risk could be accounted for by their excess weight. For women who were obese (BMI $\geq 30.0$), 62% of their increased risk could be accounted for by their excess weight. Alternatively, 26% of the overall incidence of asthma could be accounted for by weight gains of 2 kg or more since age 18. Likewise, 60% of the risk among those gaining more than 25 kg could be attributed to their weight gain after age 18.

Finally, we characterized the incident asthma of thin (BMI $<22.5$) vs obese (BMI $\geq 30.0$) women. Compared with thin women with asthma ($n = 503$), obese women with asthma ($n = 398$) were equally likely to report the use of an asthma medication in the past year (88% vs 90%, respectively; $P = .50$), the use of inhaled corticosteroids (56% vs 59%; $P = .49$), and a parental history of asthma (20% vs 22%; $P = .55$). Thin women with asthma were equally likely to report an environmental allergen as an acute asthma trigger (66% vs 63%; $P = .29$), but they were less likely to report respiratory infections as a past trigger (68% vs 77%; $P = .003$). In addition, thin women with asthma were less likely than obese women with asthma to report at least 1 hospitalization for asthma since physician diagnosis of asthma (5% vs 12%; $P = .001$). Overall, the clinical characteristics of incident asthma among thin vs obese women appeared similar.

**COMMENT**

In this large, prospective cohort study of female nurses, BMI had a strong, independent, and positive association with the risk of developing adult-onset asthma. This association was present using several definitions of asthma. Indeed, the use of stricter definitions led to even stronger associations between BMI and asthma risk. Weight gain since age 18 also was strongly associated with increased risk of asthma.

Prior epidemiological data on the relationship between adiposity and asthma are sparse. A few cross-sectional studies have reported that individuals with asthma tend to weigh more than those without asthma and that adiposity is associated with an increased prevalence of wheezing and asthma. Furthermore, cross-sectional studies of adiposity and pulmonary function show that obese individuals tend to have decreased forced vital capacity or forced expiratory volume in 1 second. Results from one small study showed that reduction in expiratory reserve volume due to obesity also showed a tendency of closure of small peripheral airways (<2 mm) in dependent lung zones. However, across a “normal” range of body weights these relatively weak associations may not be apparent, perhaps because of confounding by smoking or the presence of a nonlinear association between body weight and pulmonary function. Regardless, the use of the cross-sectional study design in the studies mentioned herein makes it difficult to determine if obesity preceded or followed asthma onset. Because individuals with poorly controlled asthma may gain weight as a result of activity limitations, the temporal nature of the relationship is critical.

The only relevant prospective studies examined the relation of adiposity to level of pulmonary function, not incidence of asthma. Higher baseline weight or BMI predicted subsequent declines in pulmonary function in some, but not all, participants in these studies. Weight gain during follow-up was significantly associated with a decline in pulmonary function, particularly among men. However, because weight gain did not clearly precede the observed decrease in pulmonary function, these results may have simply reflected antecedent declines in pulmonary function followed by activity limitation and weight gain. Marked weight loss among subjects who are morbidly obese led to improved pulmonary function in most but not all, subjects in these studies. We believe the information from the studies above show sufficient evidence to support the plausibility of the observed BMI-asthma association.

Although mechanistic research is understandably limited, there are several explanations for how adiposity might increase asthma risk. Animal models suggest that obesity leads to a variety of histological changes in the rat lung, but the relevance of this work to humans, particularly across the spectrum of BMI, is uncertain. Of greater relevance, weight gain leads to progressive reductions in airway caliber as a result of chest wall restriction. Since airway conductance is a function of the fourth power of airway radius, other asthma risk factors would only need to have a small effect on airway size to have relatively large effects on air flow. By analogy, differences in relative airway size might explain sex differences in asthma prevalence across the age spectrum. Cross-sectional studies also suggest that obese children without asthma and obese patients with mild chronic obstructive pulmonary disease have more bronchial hyperreactivity than their lean counterparts. The mechanism for this hyperreactivity is unclear but may relate to a reduction in airway caliber, which is associated with hyperreactivity, or to alterations in lipid metabolism. The BMI also may be representative of sedentary lifestyles associated with infrequent deep inspirations, which have been shown to increase bronchial hyperreactivity, however, controlling for a variety of physical activity measures in our study did not alter the results. Alternatively, obese individuals may be at higher risk because they tend to spend more time indoors, thereby leading to more sustained exposure to the indoor allergens associated with asthma. Obese individuals are at increased risk for gastroesophageal reflux disease, an important risk factor for adult-onset asthma. Another possible explanation is that obese and lean women might have different diets, and a preliminary study has linked intake of specific nutrients with pulmonary disease. We examined the possibility of dietary differences in detail (data not shown).
not shown) and conclude that nutrient intake did not account for the strong association between BMI and asthma.

Obesity also is known to influence estrogen and progesterone levels.31-33 and these sex hormones have been loosely linked to risk of asthma and other atopic disorders. For example, asthma prevalence is higher among women than men during the reproductive years, but not earlier.34 Postmenopausal estrogen use appears to increase asthma risk,35 although postmenopausal estrogens were not implicated as a confounding factor in the present study given the age range of participants. However, the relation of obesity to estrogen is complex, with increased plasma levels found in obese postmenopausal women,31 compared with their lean counterparts, but decreased plasma levels found in obese premenopausal women.32 Interpretation of the relation of obesity to estrogen concentration is further complicated by evidence that obese women may have higher levels of free, biologically active, plasma estradiol because of concomitant decreases in sex hormone–binding globulin.37 More research is needed to clarify the interrelations between obesity, sex hormones, and asthma.

Regardless of the exact mechanism of how adiposity might increase asthma risk, the public health implications of our findings are potentially large. Nationally representative surveys indicate that one third of US adults are “overweight” (BMI $\geq 27.3$).38 If one applies the 2-fold to 3-fold increased asthma risk of comparable women in the present study to the general population, the population attributable risk would be approximately 23% to 40%.39 The rising prevalence of overweight individuals in the United States (25% in 1971-1974 to 33% in 1988-1991)40 may help explain concomitant increases in asthma prevalence. Furthermore, we observed that the unusual sociodemographic distribution of obesity closely resembles that of asthma: both disorders are more common in developed nations, but, paradoxically, the highest prevalences are among the most disadvantaged members of these same societies.41-42 Thus, public health campaigns to encourage weight loss may have an additional benefit in that they may prevent onset or expression of asthma.

One potential limitation of our findings involves the select nature of the cohort. Because the age range of participants was 26 to 46 years at baseline, the results from this study may not apply to individuals with asthma that begins in childhood or after age 50. Furthermore, in the early phases of any long-term study, participants tend to be healthier than nonparticipants because individuals who are severely ill and chronically disabled are less likely to volunteer for enrollment. Women enrolled in the Nurses’ Health Study II were a subgroup of a source population of nurses that differs in many ways from the general population. The registered nurses’ level of education, ready access to medical care, and above-average standard of living are all differences that might limit generalizability. All these factors probably contributed to the cohort’s high number of health screening examinations and the popularity of nutritional supplement use. The factors also may explain the cohort’s lower mean adiposity level compared with that of the general US population. Nonetheless, there is little biological basis for suspecting that the observed relationship between BMI and asthma would be materially different in other groups of women. Furthermore, the group’s relative homogeneity and good baseline health help minimize confounding by socioeconomic factors that are associated with asthma.

Other potential limitations of our study included use of self-reported adiposity factors, self-reported asthma, and the possibility of detection bias. However, BMI and weight change since age 18 were found to be highly correlated with measured values in prior validation studies.40,41 With regard to asthma diagnosis, this remains a formidable challenge.42 Although we believe that asthma was accurately reported by this select group of registered US nurses, we note that chronic obstructive pulmonary disease would be rare in this age group and that the BMI-asthma association was present in nonsmokers. Furthermore, we used multiple case definitions to address possible misclassification. The strictest definition, case definition 3, required the participant to report the following: (1) physician diagnosis of asthma on 2 separate questionnaires; (2) use of a prescribed long-term preventive asthma medication, such as an inhaled corticosteroid, in the past year; and (3) physician diagnosis of asthma within 1 month of symptom onset. These criteria are considerably stricter than those generally reported in the asthma epidemiology literature.43 The strong association between BMI and asthma became even stronger when using the case definition 3 case group. We considered that the results may have resulted from bias, particularly detection bias. However, we found strong evidence for an obesity-asthma association in a variety of subgroups, and no evidence that the asthma severity of obese women with asthma was less than that of their thin counterparts. Moreover, we observed that the risk for asthma was elevated even at a BMI of 22.5 to 24.9. This level is below standard clinical criteria for obesity and, therefore, is unlikely to have led to any detection bias. Even women with a weight that is considered “normal” or average were at slightly increased risk.

In summary, this large, prospective cohort study demonstrated that high BMI and weight gain since age 18 are associated with increased risk of developing adult-onset asthma. Confirmation of this finding in other populations, particularly among the young and minority groups, is warranted. Nonetheless, the present results are consistent with cross-sectional reports that individuals with asthma tend to weigh more than those without asthma and that obesity may have an adverse effect on pulmonary function. The magnitude of the RR is larger than that of many putative asthma risk factors and, when combined with the high prevalence of obesity in the United States, suggests that obesity may explain much of the current asthma epidemic. These data add to existing evidence that excess body fat is a major cause of human disease and suggest a new avenue for asthma management and prevention.

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