

ORIGINAL ARTICLE

Body-Mass Index and Symptoms of Gastroesophageal Reflux in Women

Brian C. Jacobson, M.D., M.P.H., Samuel C. Somers, M.D.,
Charles S. Fuchs, M.D., M.P.H., Ciarán P. Kelly, M.D.,
and Carlos A. Camargo, Jr., M.D., Dr.P.H.

ABSTRACT

BACKGROUND

From Boston University School of Medicine and Boston Medical Center (B.C.J.), Beth Israel Deaconess Medical Center (S.C.S., C.P.K.), Dana-Farber Cancer Institute (C.S.F.), Massachusetts General Hospital (C.A.C.), and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (C.S.F., C.A.C.) — all in Boston. Address reprint requests to Dr. Jacobson at Boston University Medical Center, 85 E. Concord St., Rm. 7721, Boston, MA 02118, or at brian.jacobson@bmc.org.

Overweight and obese persons are at increased risk for gastroesophageal reflux disease. An association between body-mass index (BMI) — the weight in kilograms divided by the square of the height in meters — and symptoms of gastroesophageal reflux disease in persons of normal weight has not been demonstrated.

METHODS

In 2000, we used a supplemental questionnaire to determine the frequency, severity, and duration of symptoms of gastroesophageal reflux disease among randomly selected participants in the Nurses' Health Study. After categorizing women according to BMI as measured in 1998, we used logistic-regression models to study the association between BMI and symptoms of gastroesophageal reflux disease.

RESULTS

Of 10,545 women who completed the questionnaire (response rate, 86 percent), 2310 (22 percent) reported having symptoms at least once a week, and 3419 (55 percent of those who had any symptoms) described their symptoms as moderate in severity. We observed a dose-dependent relationship between increasing BMI and frequent reflux symptoms (multivariate *P* for trend <0.001). As compared with women who had a BMI of 20.0 to 22.4, the multivariate odds ratios for frequent symptoms were 0.67 (95 percent confidence interval, 0.48 to 0.93) for a BMI of less than 20.0, 1.38 (95 percent confidence interval, 1.13 to 1.67) for a BMI of 22.5 to 24.9, 2.20 (95 percent confidence interval, 1.81 to 2.66) for a BMI of 25.0 to 27.4, 2.43 (95 percent confidence interval, 1.96 to 3.01) for a BMI of 27.5 to 29.9, 2.92 (95 percent confidence interval, 2.35 to 3.62) for a BMI of 30.0 to 34.9, and 2.93 (95 percent confidence interval, 2.24 to 3.85) for a BMI of 35.0 or more. Even in women with a normal baseline BMI, an increase in BMI of more than 3.5, as compared with no weight changes, was associated with an increased risk of frequent symptoms of reflux (odds ratio, 2.80; 95 percent confidence interval, 1.63 to 4.82).

CONCLUSIONS

BMI is associated with symptoms of gastroesophageal reflux disease in both normal-weight and overweight women. Even moderate weight gain among persons of normal weight may cause or exacerbate symptoms of reflux.

N Engl J Med 2006;354:2340-8.

Copyright © 2006 Massachusetts Medical Society.

GASTROESOPHAGEAL REFLUX DISEASE, with hallmark symptoms of heartburn and acid regurgitation,¹ is a common disorder, affecting up to 60 percent of persons at some time during the course of a year and 20 to 30 percent of persons at least weekly.^{2,3} Gastroesophageal reflux disease accounts for at least 9 million office visits to physicians in the United States each year and costs approximately \$10 billion annually.⁴ Frequent or severe symptoms of gastroesophageal reflux disease are associated with time lost from work,⁵ impaired health-related quality of life,⁶ and esophageal adenocarcinoma,⁷ further emphasizing the clinical significance of this entity.

Several cross-sectional studies and one meta-analysis have demonstrated a positive association between elevated body-mass index (BMI) — the weight in kilograms divided by the square of the height in meters — and symptoms of gastroesophageal reflux disease.⁸⁻¹⁶ However, in these previous studies, analyses were restricted to overweight and obese subjects, with those who had a BMI of less than 24 or less than 25 serving as a reference group. We sought to explore more fully the association between BMI and symptoms of gastroesophageal reflux disease by determining the relative risks among a broader range of categories of BMI and among persons with various degrees of frequency, severity, and duration of symptoms.

METHODS

The cohort of the Nurses' Health Study was established in 1976, when 121,700 female registered nurses, 30 to 55 years of age, completed a mailed questionnaire about risk factors for cancer and cardiovascular disease. Participants have subsequently received follow-up questionnaires every two years. In 2000, a supplemental questionnaire about gastroesophageal reflux disease was sent to 11,080 participants with asthma and chronic obstructive pulmonary disease (COPD) and 11,080 randomly selected controls. For this analysis of BMI, the study population consisted of 11,080 control participants without asthma or COPD plus 1112 randomly selected women with airway disease (to represent the percentage of the entire Nurses' Health Study cohort with these conditions), for a total population of 12,192 women.

The supplemental questionnaire inquired about

the frequency, severity, and duration of heartburn and acid regurgitation. We defined symptoms of gastroesophageal reflux disease as the presence of heartburn, acid regurgitation, or both. Heartburn was defined as "a burning pain or discomfort behind the breast bone in your chest," and acid regurgitation as "a bitter or sour-tasting fluid coming into your throat or mouth," definitions that have been validated previously.¹⁷ The frequency of symptoms was reported as none in the past year, less than once a month, about once a month, about once a week, several times a week, and daily. We considered symptoms occurring once a week or more as frequent. Severity of symptoms was reported as mild ("can be ignored if I don't think about it"), moderate ("cannot be ignored but does not affect my lifestyle"), severe ("affects my lifestyle"), and very severe ("markedly affects my lifestyle"). Participants were also asked for the year when their symptoms began, whether they were awakened at night by symptoms, and whether they were taking antacid, antisecretory, or gastric-motility agents.

We determined BMI from measurements of height provided by participants in the 1976 Nurses' Health Study questionnaire and from measurements of weight in the 1998 questionnaire. A 1980 questionnaire was used to obtain participants' weight at the age of 18 years. Waist and hip measurements were self-reported in 1986. The smoking status and history of diabetes mellitus were obtained in 1976 and updated every two years thereafter. Use of antihypertensive and asthma medication was assessed with the 1998 questionnaire. Menopausal status and use of postmenopausal hormones were determined in 1976 and updated every two years thereafter. Dietary information, including intake of coffee, tea, and alcohol, and information about physical activity were obtained in 1998. Each activity reported was measured in metabolic-equivalent (MET) hours per week. One MET represents the energy expended during one hour of rest. Self-reported BMI, waist and hip measurements, age at menopause, dietary information, and physical activity have been validated previously.^{18,19}

Women were categorized according to BMI (<20.0, 20.0 to 22.4, 22.5 to 24.9, 25.0 to 27.4, 27.5 to 29.9, 30.0 to 34.9, and ≥ 35.0). We used age- and multivariate-adjusted unconditional logistic regression to obtain odds ratios and 95 percent confidence intervals for the risk of re-

porting frequent symptoms of gastroesophageal reflux disease. For these analyses, women with a BMI of 20.0 to 22.4 served as the reference population. A test for trend across the categories of interest (e.g., BMI) was calculated by treating each category as an ordinal variable in the multivariate model. Potentially confounding variables included age; cigarette smoking (never smoked, former smoker, or current smoker); total daily activity in MET per week; total daily caloric intake; the number of drinks of alcohol, coffee, and tea per day; servings of chocolate per day; use of postmenopausal hormone therapy (premenopausal use, never any use, former use, current use of estrogen only, or current use of estrogen plus progesterone); use of antihypertensive or asthma medication; and presence or absence of a history of diabetes.

To maximize the specificity of symptoms of gastroesophageal reflux disease for our primary analyses, we considered only participants with frequent symptoms and excluded women with symptoms less frequent than weekly. We analyzed the association between BMI and symptoms of gastroesophageal reflux disease on the basis of severity and duration. We performed two analyses specifically to detect the presence of reverse causality between BMI and symptoms of gastroesophageal reflux disease (i.e., that reflux symptoms result in increased BMI). In one, we limited the analysis to women reporting symptoms for less than five years according to their BMI in 1994 (six years before the assessment of symptoms). In the second analysis, we studied women reporting at least 10 years of symptoms and used their 1984 BMI (16 years before the assessment of symptoms). Further analyses examined the associations between BMI and nocturnal symptoms of gastroesophageal reflux disease and between the waist-to-hip ratio and such symptoms. The attributable risks of symptoms of gastroesophageal reflux disease due to adiposity were calculated with multivariate relative risks (in this case, odds ratios) with the use of the formula $(RR-1) \div RR$, where RR is the relative risk, and with a BMI of 20.0 to 22.4 as the referent.

We evaluated the effect of weight change on symptoms by calculating the change in BMI between 1984 and 1998 and between age 18 and 1998. Women with missing BMI data were excluded from the analyses. We conducted all analyses with the use of SAS software (version 8.2);

two-sided P values of less than 0.05 were considered to indicate statistical significance. The study was approved by the institutional review board of Brigham and Women's Hospital.

RESULTS

A total of 10,545 participants returned the questionnaire about gastroesophageal reflux disease (response rate, 86 percent). Of these, 2497 (24 percent) reported having symptoms of gastroesophageal reflux disease less than once a month, 1302 (12 percent) once a month, 986 (9 percent) once a week, 1027 (10 percent) several times a week, and 297 (3 percent) daily. Frequency was missing for 106 women (2 percent). Therefore, 6215 women (59 percent) had symptoms and 2310 (22 percent) reported having symptoms at least once a week and were considered to have frequent episodes of gastroesophageal reflux disease. Of the women with symptoms, 3394 (55 percent) reported having both heartburn and acid regurgitation. No heartburn or acid regurgitation was reported in the previous year by 4330 women (41 percent), but 414 of these asymptomatic women reported taking medications often used for symptoms of gastroesophageal reflux disease, such as proton-pump inhibitors. To avoid potential misclassification, these women were excluded from the analysis, leaving 3916 women who were categorized as noncases.

Of the women with symptoms of gastroesophageal reflux disease, 3419 (55 percent) described their symptoms as moderate in severity, 2396 (39 percent) as mild, 273 (4 percent) as severe, and 30 (<1 percent) as very severe. Data about severity were missing for 97 women (2 percent). Information about the year of onset of symptoms was available for only 2765 (44 percent) of the women. Among those who provided information about duration, 1180 (43 percent) had had symptoms of gastroesophageal reflux disease for less than 5 years, 400 (14 percent) had had symptoms for 5 to 9 years, and 1185 (43 percent) had had symptoms for at least 10 years.

Characteristics of participants with frequent symptoms of gastroesophageal reflux disease and of those without symptoms are presented in Table 1. Women with frequent symptoms were more likely than women without symptoms to have a higher BMI, to have used hormone therapy or asthma or antihypertensive medications,

to have a greater daily caloric intake, and to be less active. At the time of the survey, women with gastroesophageal reflux disease were less likely to be current smokers but more likely to be former smokers than those without symptoms. Dietary factors such as the consumption of alcohol were similar between the two groups.

A dose-dependent relationship was observed between increasing BMI and frequent reflux symptoms in both univariate and multivariate analyses (Fig. 1). This relationship continued across all categories of BMI, including those less than 25.0. Women with a BMI of 22.5 to 24.9 were approximately 40 percent more likely to report frequent symptoms of gastroesophageal reflux disease than women with a BMI of 20.0 to 22.4, whereas overweight and obese women (BMI, 25.0 to 30.0 and

≥30.0, respectively) were two to three times as likely to report frequent symptoms. Women in the lowest category of BMI (<20.0) had a lower risk of frequent symptoms of gastroesophageal reflux disease than did those with a BMI of 20.0 to 22.4 (multivariate odds ratio, 0.67; 95 percent confidence interval, 0.48 to 0.93).

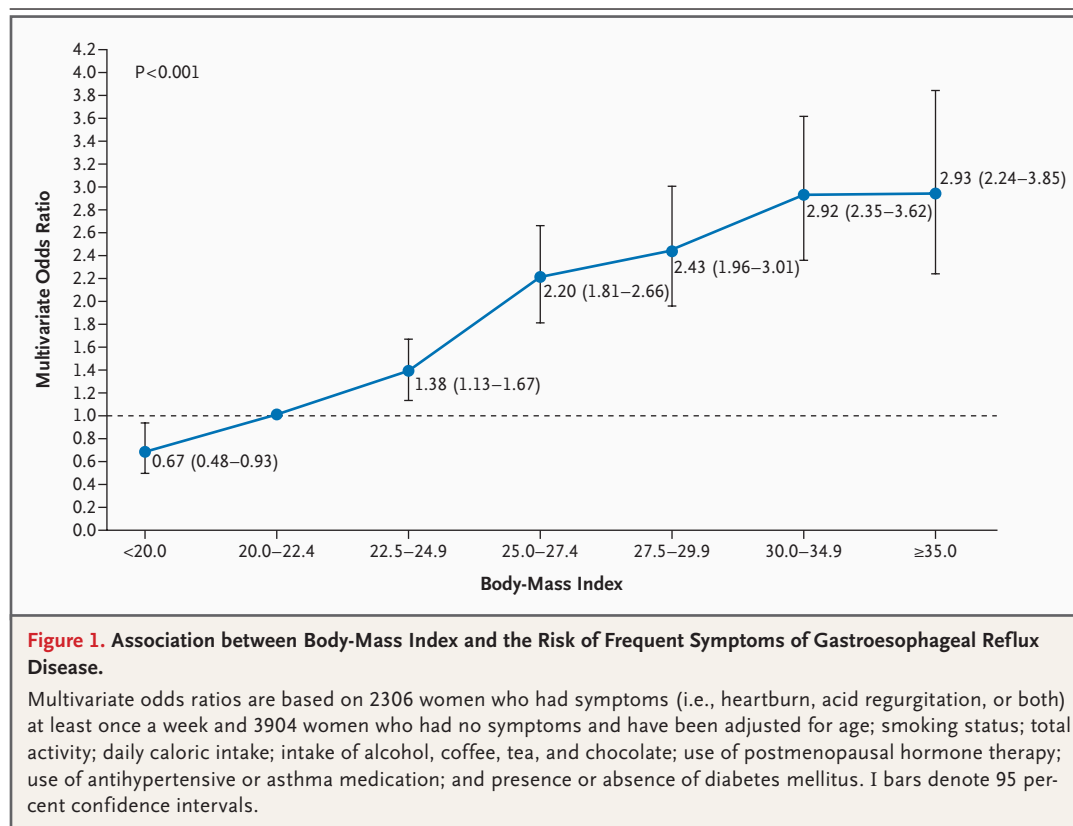
This same trend was observed among the entire population of women who had had symptoms of gastroesophageal reflux disease at least once in the past year, among women who had had moderate-to-very-severe symptoms several times a week or daily, among women who had had only heartburn or only acid regurgitation, and among women who had had nocturnal symptoms (P for trend <0.001 for all models; data not shown). Fifty-one percent of the increased risk of frequent

Table 1. Characteristics of Women with and Women without Symptoms of Gastroesophageal Reflux Disease.*

Characteristic	Symptoms of GERD at Least Weekly (N=2310)	No Symptoms of GERD in the Past Year (N=3916)
Age (yr)	66±7	66±7
Body-mass index	27.8±5.3	25.6±5.0
Smoking status (%)		
Never smoked	44	47
Former smoker	47	40
Current smoker	6	9
Data missing	3	4
Total activity (MET/wk)	16±19	19±22
Total caloric intake (kcal/day)	1763±534	1695±523
Alcohol intake (drinks/day) †	0.3±0.7	0.4±0.8
Coffee intake (cups/day)	1.7±1.4	1.7±1.5
Tea intake (cups/day)	0.7±1.2	0.7±1.1
Chocolate (servings/day)	0.1±0.2	0.1±0.2
Hormone therapy (%)		
Premenopausal use	2	3
Never any use	20	26
Former use	22	19
Current use of estrogen only	20	15
Current use of estrogen and progesterone	12	14
Missing data	24	23
Use of antihypertensive medication (%)	37	28
Use of asthma medication (%)	11	6
History of diabetes (%)	7	8

* Symptoms of gastroesophageal reflux disease were defined as heartburn, acid regurgitation, or both. GERD denotes gastroesophageal reflux disease, and MET metabolic equivalents. Plus-minus values are means ±SD.

† A drink was defined as one drink or shot of liquor; one glass, bottle, or can of beer; or one 4-oz (118-ml) glass of wine.



symptoms of reflux among the entire cohort with a BMI of at least 20.0 was accounted for by excessive body weight, defined as a BMI of at least 22.5. For women with a BMI of 22.5 to 24.9, 25 percent of the increased risk could be accounted for by their excess weight. For women with a BMI of at least 25, 60 percent of the increased risk could be accounted for by their excess weight.

We also examined the waist-to-hip ratio as an alternative measure of adiposity. We observed a dose-response relationship between the risk of reflux symptoms and increasing waist-to-hip ratios (P for trend <0.001 for all models; data not shown) that was similar to that between symptoms of reflux and increasing BMI. For example, women in the highest quintile as compared with the lowest quintile of waist-to-hip ratios had a multivariate odds ratio of 1.88 (95 percent confidence interval, 1.45 to 2.45) for reporting frequent symptoms of gastroesophageal reflux disease. When BMI and the waist-to-hip ratio were introduced simultaneously in our model, the contribution of the waist-to-hip ratio was blunted (odds ratio for the highest quintile as compared

with the lowest quintile, 1.34; 95 percent confidence interval, 1.02 to 1.76), whereas that for BMI did not change. In general, our findings from all analyses were similar between age-adjusted univariate and multivariate models, suggesting minimal confounding by the other covariates tested. Furthermore, our findings did not vary significantly when dietary factors such as the intake of citrus, onions, tomatoes, other fruits and vegetables, and total fat was included in our model (data not shown).

The relationship between BMI and symptoms of gastroesophageal reflux disease persisted when the severity of symptoms was evaluated (P for trend <0.001 for all models) (Table 2). As compared with women with a BMI of 20.0 to 22.4, women with a BMI of 22.5 to 24.9 had a 36 to 50 percent increase in the risk of having mild or moderate symptoms on multivariate analysis. In contrast, the risk of severe or very severe symptoms was elevated only among overweight and obese women (BMI, ≥ 25.0), although the small number of women reporting this degree of symptoms (256 women) may have prevented us from detecting an elevated risk among women with a

Table 2. Association between Body-Mass Index and Frequent Symptoms of Gastroesophageal Reflux Disease.*

Variable	No. of Women	Body-Mass Index					P for Trend		
		<20.0	20.0–22.4†	22.5–24.9	25.0–27.4	27.5–29.9		30.0–34.9	≥35.0
Mild symptoms									
No. of women with symptoms of GERD	473	13	63	99	115	64	85	34	
No. of controls	3829	314	812	917	740	439	412	195	
Univariate odds ratio (95% CI)		0.55 (0.30–1.02)	1.00	1.38 (0.99–1.92)	2.00 (1.45–2.77)	1.88 (1.30–2.72)	2.62 (1.85–3.71)	2.20 (1.41–3.43)	<0.001
Multivariate odds ratio (95% CI)		0.61 (0.33–1.14)	1.00	1.36 (0.96–1.92)	2.04 (1.45–2.88)	1.75 (1.17–2.61)	2.33 (1.59–3.43)	2.05 (1.24–3.39)	<0.001
Moderate symptoms									
No. of women with symptoms of GERD	1678	47	170	303	400	285	319	154	
No. of controls	3899	317	815	939	757	448	425	198	
Univariate odds ratio (95% CI)		0.72 (0.51–1.02)	1.00	1.54 (1.25–1.91)	2.53 (2.06–3.11)	3.05 (2.44–3.80)	3.57 (2.87–4.45)	3.68 (2.81–4.81)	<0.001
Multivariate odds ratio (95% CI)		0.70 (0.48–1.02)	1.00	1.50 (1.20–1.87)	2.36 (1.89–2.94)	2.71 (2.13–3.45)	3.18 (2.50–4.06)	3.15 (2.33–4.26)	<0.001
Severe-to-very-severe symptoms									
No. of women with symptoms of GERD	256	6	37	38	50	45	54	26	
No. of controls	3874	317	811	931	751	445	421	198	
Univariate odds ratio (95% CI)		0.43 (0.18–1.04)	1.00	0.89 (0.56–1.41)	1.46 (0.94–2.26)	2.22 (1.41–3.48)	2.76 (1.79–4.27)	2.81 (1.66–4.75)	<0.001
Multivariate odds ratio (95% CI)		0.55 (0.22–1.33)	1.00	0.94 (0.57–1.53)	1.37 (0.85–2.21)	1.92 (1.16–3.19)	2.40 (1.46–3.96)	2.36 (1.28–4.37)	<0.001

* Frequent symptoms of gastroesophageal reflux disease were defined as heartburn, acid regurgitation, or both occurring at least weekly. Severity of symptoms was defined as mild ("can be ignored if I don't think about it"), moderate ("cannot be ignored but does not affect my lifestyle"), severe ("affects my lifestyle"), and very severe ("markedly affects my lifestyle"). GERD denotes gastroesophageal reflux disease, and CI confidence interval. Multivariate odds ratios have been adjusted for age; smoking status; total activity; daily caloric intake; intake of alcohol, coffee, tea, and chocolate; use of postmenopausal hormone therapy; use of antihypertensive medication or asthma medication; and presence or absence of diabetes mellitus.

† Women with a body-mass index of 20.0 to 22.4 served as the reference population.

normal BMI. Women with a BMI of less than 20.0 appeared to have some protection against symptoms of any severity, with multivariate odds ratios ranging from 0.55 to 0.70 (Table 2).

We found the same dose–response relationships for symptoms across all categories of BMI regardless of the duration of symptoms (data not shown). When we used BMI records from 1994 to analyze women who had had symptoms for less than 5 years and BMI records from 1984 for those who had had symptoms for at least 10 years, we found a similar dose–response relationship between BMI and the risk of symptoms of gastroesophageal reflux disease. As compared with women with a BMI of 20.0 to 22.4, women with a BMI of less than 20.0 had a multivariate odds ratio of 0.29 (95 percent confidence interval, 0.11 to 0.73) for reporting a recent onset of frequent symptoms of gastroesophageal reflux disease (duration, <5 years), whereas those with a BMI of 22.5 to 24.9 had a multivariate odds ratio of 1.46 (95 percent confidence interval, 1.07 to 1.99) for reporting chronic frequent symptoms (duration, at least 10 years).

To further assess the relationship between BMI and reflux, we analyzed the effect of weight change on the risk of symptoms of gastroesophageal reflux disease. Among women who gained weight during the previous 14 years, a dose-dependent increase in the risk of symptoms was observed (Table 3). Women with an increase in BMI of more than 3.5 increased their risk of having frequent symptoms of gastroesophageal reflux disease by more than a factor of two. Risks were significantly decreased among women who lost weight during the same period. There was a reduction of nearly 40 percent in the risk of frequent symptoms among women with a decrease in BMI of more than 3.5 as compared with women without a change in BMI (odds ratio, 0.64; 95 percent confidence interval, 0.42 to 0.97). A similar trend was also observed when the change in BMI was evaluated over a longer duration — namely, between the reported weight of the participants at the age of 18 years and in 1998 and when the analysis was restricted to women whose BMI in 1984 was less than 25.0 (Table 3). The odds ratio for frequent reflux in women whose BMI was less than 25.0 in 1984 but subsequently increased by more than 3.5 was 2.80 (95 percent confidence interval, 1.63 to 4.82).

Table 3. Association between Weight Change (between 1984 and 1998) and Frequent Symptoms of Gastroesophageal Reflux Disease.*

Variable	No. of Women	Decrease in BMI >3.5	Decrease in BMI >1.5 to 3.5	0.5 to 1.5	No Weight Change†	Increase in BMI >1.5 to 3.5	Increase in BMI >3.5	P for Trend
No. of women with symptoms of GERD	1886	42	113	132	202	548	564	
No. of controls	3176	122	278	299	534	825	557	
Multivariate odds ratio (95% CI)		0.64 (0.42–0.97)	0.90 (0.67–1.20)	1.13 (0.86–1.49)	1.00	1.23 (0.98–1.54)	2.29 (1.84–2.86)	<0.001
Multivariate odds ratio for women with a BMI <25.0 in 1984 (95% CI)‡		0.76 (0.4–1.45)	0.88 (0.59–1.31)	1.08 (0.75–1.54)	1.00	1.26 (0.94–1.70)	2.80 (1.63–4.82)	0.002

* Symptoms of gastroesophageal reflux disease were defined as heartburn, acid regurgitation, or both. Frequent symptoms were those occurring at least weekly. GERD denotes gastroesophageal reflux disease, and CI confidence interval. Multivariate odds ratios have been adjusted for age; BMI in 1984; smoking status; total activity; daily caloric intake; intake of alcohol, coffee, tea, and chocolate; use of postmenopausal hormone therapy; use of antihypertensive and asthma medication; and presence or absence of diabetes mellitus.

† Women with no weight change served as the reference population.

‡ Analysis restricted to women with a BMI of less than 25.0 in 1984 included 613 women with symptoms of gastroesophageal reflux disease and 1704 controls.

DISCUSSION

We found a strong positive association between BMI and symptoms of gastroesophageal reflux disease in a large cohort of women. This association extended across all categories of BMI, suggesting that the risk of symptoms rises with BMI in both normal-weight and overweight persons. The association was not altered significantly after controlling for multiple potential confounding variables, including smoking, the consumption of alcohol, the use of medications that decrease the pressure at the lower esophageal sphincter, diabetes, and dietary habits. A similar dose-response relationship was observed for both frequent and infrequent symptoms, nocturnal symptoms, and for all degrees of the severity and duration of symptoms that we studied. Moreover, weight gain was associated with an increased risk of symptoms of gastroesophageal reflux disease, and weight loss was associated with a decrease in risk.

Our findings augment a growing body of literature addressing the association between BMI and gastroesophageal reflux disease.⁸⁻¹⁶ A recent large meta-analysis of previous studies demonstrated a dose-response relationship between BMI and the risk of reporting symptoms of gastroesophageal reflux disease among both men and women.¹⁵ However, the reference groups in these studies included participants with a BMI of less than 24 or less than 25 and, therefore, were unable to define the risk of symptoms of gastroesophageal reflux disease among normal-weight persons. It should be noted that three previous studies have found no significant relationship between BMI and symptoms of gastroesophageal reflux disease, although these studies were small.^{14,20,21} A large telephone survey limited to people with symptoms of gastroesophageal reflux disease revealed a dose-response relationship between quartiles of BMI and a daily frequency of symptoms; however, that study lacked asymptomatic controls.²²

Taken together, these previous studies have led to the assertion that overweight and obesity are risk factors for symptoms of gastroesophageal reflux disease. Our study extends those findings by showing that the risk of symptoms appears to be directly linked to BMI regardless of whether a person is of normal weight or is overweight. This suggests that moderate amounts of weight gain, even among normal-weight persons, may

result in the development or exacerbation of symptoms of gastroesophageal reflux disease. This is of particular concern given recent trends of rising BMI in the United States among both adults and children.^{23,24}

A causative mechanism for the association between BMI and reflux symptoms is not evident from our data. Adjustment for dietary factors had a minimal effect on our results, suggesting that either mechanical or hormonal factors are more likely to be responsible. We found that both BMI and the waist-to-hip ratio were associated with frequent symptoms of gastroesophageal reflux disease, but when both factors were analyzed simultaneously, BMI appeared to have a greater role in this association. The risk of symptoms therefore rises more with the percentage of body fat of a person (of which BMI is a marker) than with the distribution of that fat (i.e., the waist-to-hip ratio). This may suggest that a hormonal factor related to adiposity is more important in the pathogenesis of symptoms of gastroesophageal reflux disease than are mechanical factors, although probably multiple factors are responsible.

A limitation of our study is its cross-sectional design, which allows the possibility of reverse causality as an explanation of our findings. This seems unlikely, given that we controlled for physical activity and diet. In addition, we found similar findings in several subgroup analyses that examined the effect of BMI reported in the years before the onset of symptoms.

Another limitation is our use of a questionnaire to define symptoms of gastroesophageal reflux disease. However, several studies have been published that demonstrate the validity and reliability of these questions in identifying cases of gastroesophageal reflux disease.^{2,3,8-10,17} Also, symptoms assessed by questionnaire have been correlated with objective complications of gastroesophageal reflux disease, such as esophagitis and esophageal adenocarcinoma.^{7,25} Furthermore, to improve our specificity for gastroesophageal reflux disease, we restricted our primary analysis to women who reported at least weekly symptoms. Our study was limited to women; therefore, we are unable to comment on the association between BMI and symptoms of gastroesophageal reflux disease among men.

In summary, our findings suggest that the risk of symptoms of gastroesophageal reflux disease rises progressively with increasing BMI, even

among normal-weight persons. This seems true for all degrees of severity and duration of symptoms, as well as for nocturnal symptoms. Notably, weight loss was associated with a decreased risk of symptoms. Our findings have important implications for future studies, since even moderate weight gain may cause or exacerbate symptoms of gastroesophageal reflux disease.

Supported by grants from the National Institutes of Health (K08 DK070706, to Dr. Jacobson; and R21 AI-52338, to Dr. Camargo) and by an unrestricted, investigator-initiated grant to Drs. Camargo and Somers from Janssen-Eisai.

Dr. Camargo reports having served as a consultant to AstraZeneca and having received lecture fees from GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

REFERENCES

- Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. *Lancet* 1990;335:205-8.
- Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology* 1997;112:1448-56.
- El-Serag HB, Petersen NJ, Carter J, et al. Gastroesophageal reflux among different racial groups in the United States. *Gastroenterology* 2004;126:1692-9.
- Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002;122:1500-11.
- Henke CJ, Levin TR, Henning JM, Potter LP. Work loss costs due to peptic ulcer disease and gastroesophageal reflux disease in a health maintenance organization. *Am J Gastroenterol* 2000;95:788-92.
- Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. *Am J Med* 1998;104:252-8.
- Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340:825-31.
- El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. *Am J Gastroenterol* 2005;100:1243-50.
- Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA* 2003;290:66-72.
- Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Risk factors associated with symptoms of gastroesophageal reflux. *Am J Med* 1999;106:642-9.
- Kulig M, Nocon M, Vieth M, et al. Risk factors of gastroesophageal reflux disease: methodology and first epidemiological results of the ProGERD study. *J Clin Epidemiol* 2004;57:580-9.
- Murray L, Johnston B, Lane A, et al. Relationship between body mass and gastro-oesophageal reflux symptoms: the Bristol Helicobacter Project. *Int J Epidemiol* 2003;32:645-50.
- Stanghellini V. Three-month prevalence rates of gastrointestinal symptoms and the influence of demographic factors: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterol Suppl* 1999;231:20-8.
- Wu AH, Tseng C-C, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer* 2003;98:940-8.
- Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;143:199-211.
- Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E, Locke GR III, Rodriguez-Artalejo F. Symptoms of gastro-oesophageal reflux: prevalence, severity, duration and associated factors in a Spanish population. *Aliment Pharmacol Ther* 2004;19:95-105.
- Locke GR, Talley NJ, Weaver AL, Zinsmeister AR. A new questionnaire for gastroesophageal reflux disease. *Mayo Clin Proc* 1994;69:539-47.
- Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1990;1:466-73.
- Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol* 1994;23:991-9.
- Andersen LI, Jensen G. Risk factors for benign oesophageal disease in a random population sample. *J Intern Med* 1991;230:5-10.
- Lagergren J, Bergström R, Nyrén O. No relation between body mass and gastroesophageal reflux symptoms in a Swedish population based study. *Gut* 2000;47:26-9.
- Oliveria SA, Christos PJ, Talley NJ, Dannenberg AJ. Heartburn risk factors, knowledge, and prevention strategies: a population-based survey of individuals with heartburn. *Arch Intern Med* 1999;159:1592-8.
- Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* 2004;291:2847-50.
- Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 2002;288:1723-7.
- Johnson DA, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastroesophageal reflux disease. *Gastroenterology* 2004;126:660-4.

Copyright © 2006 Massachusetts Medical Society.

CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see *N Engl J Med* 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.