OBESITY AND THE RISK OF HEART FAILURE

SATISH KENCHAIAH, M.D., JANE C. EVANS, D.SC., DANIEL LEVY, M.D., PETER W.F. WILSON, M.D.,
EMELIA J. BENJAMIN, M.D., MARTIN G. LARSON, S.D., WILLIAM B. KANNEL, M.D., M.P.H.,
AND RAMACHANDRAN S. VASAN, M.D.

ABSTRACT

Background   Extreme obesity is recognized to be a risk factor for heart failure. It is unclear whether overweight and lesser degrees of obesity also pose a risk.

Methods   We investigated the relation between the body-mass index (the weight in kilograms divided by the square of the height in meters) and the incidence of heart failure among 5881 participants in the Framingham Heart Study (mean age, 55 years; 54 percent women). With the use of Cox proportional-hazards models, the body-mass index was evaluated both as a continuous variable and as a categorical variable (normal, 18.5 to 24.9; overweight, 25.0 to 29.9; and obese, 30.0 or more).

Results   During follow-up (mean, 14 years), heart failure developed in 496 subjects (258 women and 238 men). After adjustment for established risk factors, there was an increase in the risk of heart failure of 5 percent for men and 7 percent for women for each increment of 1 in body-mass index. As compared with subjects with a normal body-mass index, obese subjects had a doubling of the risk of heart failure. For women, the hazard ratio was 2.12 (95 percent confidence interval, 1.51 to 2.97); for men, the hazard ratio was 1.90 (95 percent confidence interval, 1.30 to 2.79). A graded increase in the risk of heart failure was observed across categories of body-mass index. The hazard ratios per increase in category were 1.46 in women (95 percent confidence interval, 1.23 to 1.72) and 1.37 in men (95 percent confidence interval, 1.13 to 1.67).

Conclusions   In our large, community-based sample, increased body-mass index was associated with an increased risk of heart failure. Given the high prevalence of obesity in the United States, strategies to promote optimal body weight may reduce the population burden of heart failure. (N Engl J Med 2002; 347:305-13.)

Copyright © 2002 Massachusetts Medical Society.

HEART failure is a major health problem that is increasing in scope.[1] Despite recent therapeutic advances, morbidity and mortality after the onset of heart failure remain substantial.[1] Consequently, prevention of heart failure through identification and management of risk factors and preclinical phases of the disease is a priority.[2] In this context, several studies have evaluated body-mass index (the weight in kilograms divided by the square of the height in meters) as a risk factor for left ventricular remodeling and overt heart failure. In these investigations, obesity has been consistently associated with left ventricular hypertrophy and dilatation,[3-6] which are known precursors of heart failure.[7,8] Whereas extreme obesity has been associated with heart failure,[9] data are limited regarding the influence of overweight and lesser degrees of obesity on the risk of heart failure.[10-12] Accordingly, we investigated the relation of body-mass index with the risk of heart failure in a community-based sample.

METHODS

Participants

The design and selection criteria of the Framingham Heart Study have been described previously.[13,14] Participants in the 15th biennial examination of the original cohort (1976 through 1979, 2632 subjects) and the second offspring study examination (1979 through 1983, 3863 subjects) were eligible for the present investigation. We excluded 614 attendees (9.5 percent) for the following reasons: age under 30 years (271 subjects), underweight (body-mass index less than 18.5 [85 subjects]),[15,16] heart failure at base-line examination

From the Framingham Heart Study, Framingham, Mass. (S.K., J.C.E., D.L., P.W.F.W., E.J.B., M.G.L., W.B.K., R.S.V.); the Section of Preventive Medicine (D.L., E.J.B., M.G.L., W.B.K., R.S.V.) and the Cardiology Section (E.J.B., R.S.V.), Boston University School of Medicine, Boston; the Cardiology Division, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston (D.L.); and the National Heart, Lung, and Blood Institute, Bethesda, Md. (D.L.). Address reprint requests to Dr. Vasan at the Framingham Heart Study, 73 Mt. Wayte Ave., Suite 2, Framingham, MA 01702, or at vasan@fram.nhlbi.nih.gov.

(84 subjects), missing information on covariates (172 subjects), and lack of follow-up data (2 subjects). After these exclusions, 5881 subjects (3177 women and 2704 men) remained eligible. Written informed consent was obtained from the study participants, and the research protocol was reviewed and approved by the institutional review board of the Boston University School of Medicine.

Estimation of Adiposity and Covariates

At each examination, a medical history was taken, a physical examination (including anthropometric measurements and measurement of blood pressure) was performed, a 12-lead electrocardiogram was obtained, and risk factors for cardiovascular disease were assessed. Height and weight were measured according to a standardized protocol. The body-mass index was calculated and was used as an estimate of overweight and obesity.[16] The criteria and methods of measurement of all covariates have been described previously.[17]

Outcome

Surveillance for the development of cardiovascular events was continuous for all participants. A panel of three experienced physicians reviewed suspected cardiovascular events by examining hospital records and information from outside physicians.[17] In this investigation, the primary outcome of interest was the occurrence of a first episode of heart failure, as defined by the Framingham Heart Study criteria.[18] The simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria was required to establish a diagnosis of heart failure. Major criteria included paroxysmal nocturnal dyspnea or orthopnea, jugular venous distention, pulmonary rales, radiographic cardiomegaly, acute pulmonary edema, a third heart sound, central venous pressure above 16 cm of water, hepatojugular reflux, and weight loss of at least 4.5 kg in five days in response to treatment for heart failure. Minor criteria included bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, and a heart rate of at least 120 beats per minute. Minor criteria were acceptable only if they could not be attributed to another medical condition (such as chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome).

Statistical Analysis

We used Cox proportional-hazards regression models,[19] stratified according to cohort (original or offspring), to examine the relation of body-mass index to the incidence of heart failure. We performed both sex-specific and sex-stratified analyses. Body-mass index was evaluated as both a continuous variable (with increases in risk calculated per increment of 1) and a categorical variable. Subjects with values of 18.5 to 24.9 were classified as normal (the reference group), those with values of 25.0 to 29.9 as overweight, and those with values of 30.0 or more as obese.[15,16] We adjusted for the following base-line covariates: age, smoking status, alcohol consumption, total serum cholesterol level, and presence or absence of valve disease, hypertension, diabetes mellitus, electrocardiographic left ventricular hypertrophy, and myocardial infarction (all defined at base line). We constructed trend models to determine whether there was a continuous gradient of heart-failure risk across categories of body-mass index. To evaluate the risk of heart failure associated with varying degrees of obesity, we performed analyses that categorized the obese group into three classes with body-mass indexes of 30.0 to 34.9 (group 1), 35.0 to 39.9 (group 2), and 40.0 or more (group 3).[15,16] We also evaluated models with body-mass index and all covariates treated as time-dependent variables (updated every four years, including adjustment for the occurrence of interim myocardial infarction).

Elevated body-mass index could predispose persons to heart failure by promoting atherogenic traits such as hypertension, diabetes mellitus, and dyslipidemia, which, in turn, could result in myocardial infarction. Therefore, we constructed hierarchical statistical models using covariates defined at base line, with adjustment for potential confounders (age, cigarette smoking, alcohol consumption, and valve disease) and for all these variables plus covariates that are known to be along the causal pathway from excess weight to heart failure (e.g., hypertension, electrocardiographic left ventricular hypertrophy, diabetes mellitus, high total serum cholesterol level, and myocardial infarction). We also evaluated stepwise models with body-mass index, systolic blood pressure, alcohol intake, and total serum cholesterol as continuous measures (other covariates were dichotomous).

We examined models incorporating interaction terms to evaluate variation in the effect of body-mass index on the risk of heart failure according to age, sex, smoking status, alcohol consumption, and the presence or absence of valve disease, hypertension, diabetes mellitus, and myocardial infarction (all defined at base line).

We estimated the category-specific population attributable risk (PAR), expressed as a percentage, as a function of the proportion of cases occurring in a given category of body-mass index (pd) and the multivariable-adjusted relative risk (RR, equivalent to hazard ratios from models with covariates defined at base line) with the following equation:[20]

$$PAR = pd \left(\frac{RR-1}{RR} \right) \times 100.$$

To obtain insight into the type of heart failure (systolic vs. diastolic) associated with increasing body-mass index, we reviewed echocardiographic reports for a subgroup of participants who underwent evaluation of left ventricular systolic function within 30 days after their first hospitalization for heart failure between 1989 and 1998. Heart failure was presumed to be due to systolic dysfunction (systolic heart failure) if the estimated left ventricular ejection fraction was less than 50 percent, whereas a left ventricular ejection fraction of 50 percent or more was considered to be consistent with diastolic heart failure.[21] The proportion of patients with heart failure who had a left ventricular ejection fraction under 40 percent, indicating moderate or severe left ventricular systolic dysfunction, was also examined.

Although underweight subjects were excluded from the primary analyses, we performed supplementary analyses comparing the risk of heart failure in these subjects with that in subjects with a normal body-mass index.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with SAS software (version 6.12).[22]

RESULTS

Clinical Characteristics

A third of the women and half the men in our sample were overweight. The prevalence of obesity was similar in the two sexes (about 16 percent). The prevalence of hypertension and diabetes mellitus increased with increasing body-mass index (Table 1).

Body-Mass Index and the Risk of Heart Failure

During a mean follow-up of 14 years (maximum, 21.8), heart failure developed in 496 participants (258 women and 238 men). The crude cumulative incidence (Fig. 1) and the age-adjusted incidence rates (Table 2) of heart failure increased across categories of body-mass index for both men and women.

After adjustment for known risk factors, there was an increase in the risk of heart failure of 5 percent for men and 7 percent for women for each increment of

TABLE 1. BASE-LINE CHARACTERISTICS ACCORDING TO THE CATEGORY OF BODY-MASS INDEX.*

CHARACTERISTIC†	WOMEN			MEN		
	NORMAL (N=1729)	OVERWEIGHT (N=955)	OBESE (N=493)	NORMAL (N=869)	OVERWEIGHT (N=1378)	OBESE (N=457)
Age (yr)	53±15	60±13	59±13	54±14	55±13	53±12
Body-mass index	22.3±1.7	27.1±1.4	34.1±4.0	23.2±1.4	27.2±1.4	32.7±2.6
Current cigarette smoking (%)	33.5	26.8	22.5	35.9	26.9	28.7
Alcohol consumption (%)						
Mild to moderate	42.5	40.0	39.0	47.4	49.1	47.5
Heavy	25.6	18.2	12.0	30.0	29.5	30.4
Blood pressure (mm Hg)						
Systolic	123±19	131±20	136±18	128±18	131±17	135±16
Diastolic	74±9	76±9	80±9	77±10	80±9	84±9
Hypertension (%)	26.2	45.0	57.0	30.3	39.6	53.0
Diabetes mellitus (%)	7.7	14.4	17.7	10.2	14.2	15.5
Total cholesterol (mg/dl)	212±42	231±45	227±44	205±37	214±38	214±35
Electrocardiographic evidence of left ventricular hypertrophy (%)	0.9	0.8	0.4	1.2	0.8	2.2
Valve disease (%)	4.2	6.0	6.5	4.7	3.8	3.5
Myocardial infarction (%)	0.9	0.5	1.2	4.7	4.1	5.5

*The body-mass index was 18.5 to 24.9 in normal subjects, 25.0 to 29.9 in overweight subjects, and 30.0 or more in obese subjects. Values for continuous variables are given as means ±SD.

†Hypertension was defined by a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or pharmacologic treatment of previously elevated blood pressure. Diabetes mellitus was defined by a fasting plasma glucose level of at least 7.0 mmol per liter (126 mg per deciliter), a random nonfasting level of at least 11.11 mmol per liter (200 mg per deciliter), or the use of insulin or oral hypoglycemic agents. Mild-to-moderate alcohol consumption was defined as up to one drink per day in women and up to two drinks per day in men; heavy consumption was defined as more than one drink per day in women and more than two drinks per day in men. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

1 in body-mass index (Table 3, model IA). As compared with women who have a normal body-mass index, overweight women had a 50 percent greater risk of heart failure, and obese women had a doubling of the risk of heart failure (Table 3, model IB). Whereas overweight men had a nonsignificant 20 percent increase in heart-failure risk over men with a normal body-mass index, obese men had a statistically significant 90 percent increase in the risk of heart failure. In sex-stratified analyses, an increased risk of heart failure was evident for both overweight subjects (a 34 percent increase) and obese subjects (a 104 percent increase) and there was a 43 percent greater risk of heart failure per category increase in body-mass index. Among obese subjects, the risk of heart failure increased in a graded fashion with increasing severity of obesity (Fig. 2). Men with class 3 obesity were excluded from this analysis because of the small sample (eight subjects). The association of body-mass index with the risk of heart failure remained robust in models incorporating body-mass index and other risk factors as time-dependent variables (Table 3, models IIA and IIB).

In models adjusted only for age, smoking status, alcohol consumption, and valve disease, the hazard ratios for heart failure per increase of 1 in the body-mass index were 1.08 (95 percent confidence interval, 1.06 to 1.11) in women and 1.07 (95 percent confidence interval, 1.04 to 1.11) in men. In these models, in comparison with subjects with a normal body-mass index, the hazard ratios for heart failure were 1.53 (95 percent confidence interval, 1.15 to 2.04) for overweight women, 2.24 (95 percent confidence interval, 1.62 to 3.11) for obese women, 1.35 (95 percent confidence interval, 0.99 to 1.85) for overweight men, and 2.34 (95 percent confidence interval, 1.60 to 3.41) for obese men. Additional adjustment for hypertension, diabetes mellitus, high total serum cholesterol level, electrocardiographic left ventricular hypertrophy, and myocardial infarction (variables along the causal pathway) led to a slight attenuation of the hazard ratios in men but not in women (Table 3, models IA and IB). In models with stepwise selection of covariates (at an alpha level of <0.05), age, myocardial infarction, valve disease, and systolic blood pressure entered ahead of body-mass index. The hazard ratio for heart failure associated with body-mass index was nearly identical to that shown in model IA in Table 3.
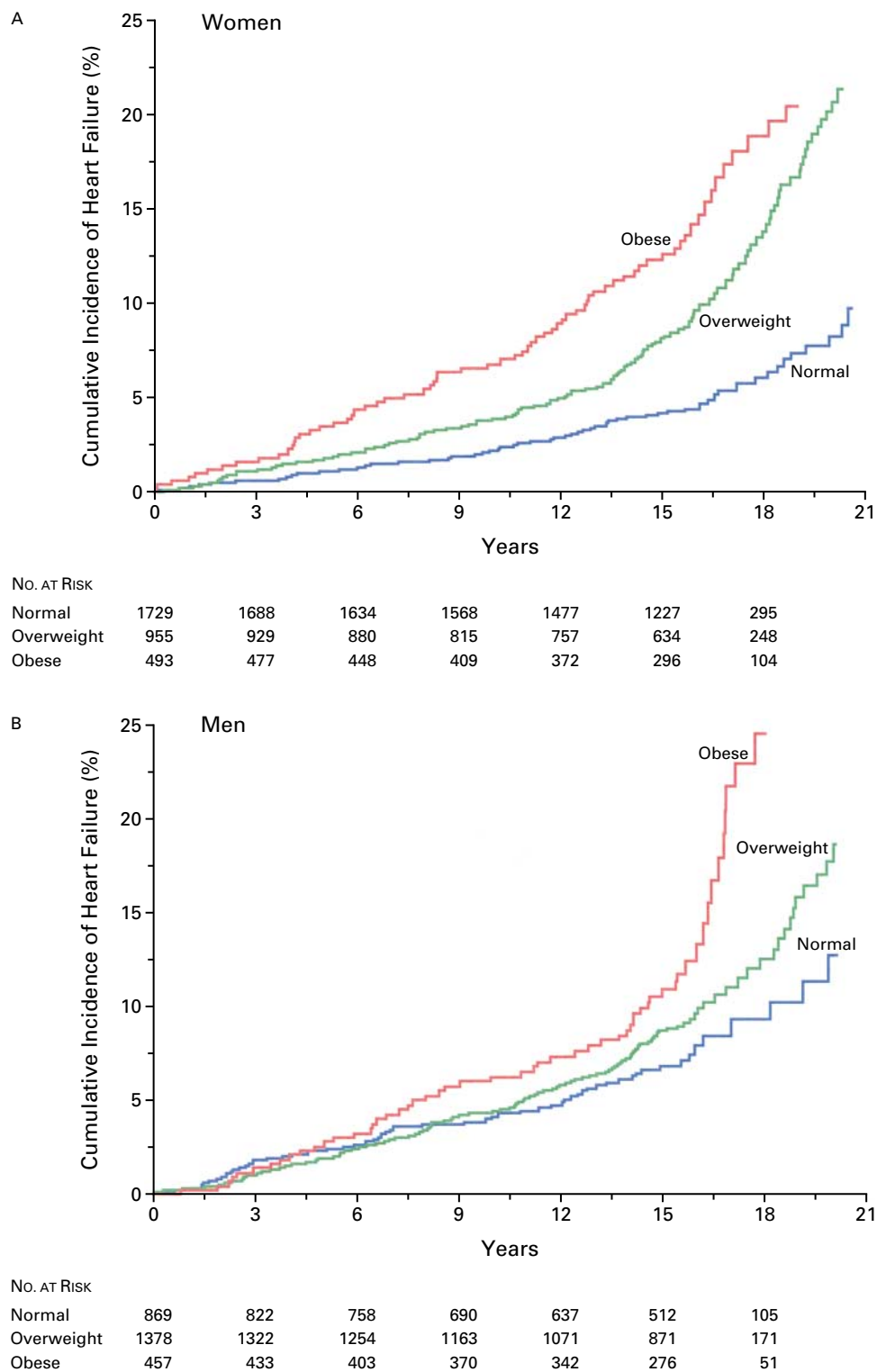
Figure 1. Cumulative Incidence of Heart Failure According to Category of Body-Mass Index at the Base-Line Examination.
The body-mass index was 18.5 to 24.9 in normal subjects, 25.0 to 29.9 in overweight subjects, and 30.0 or more in obese subjects.

TABLE 2. CUMULATIVE INCIDENCE OF HEART FAILURE AMONG STUDY PARTICIPANTS ACCORDING TO THE CATEGORY OF BODY-MASS INDEX AT BASE LINE.

BODY-MASS INDEX	WOMEN		MEN	
	NO. OF EVENTS/ NO. OF PERSON-YR OF FOLLOW-UP	AGE-ADJUSTED 10-YR CUMULATIVE INCIDENCE	NO. OF EVENTS/ NO. OF PERSON-YR OF FOLLOW-UP	AGE-ADJUSTED 10-YR CUMULATIVE INCIDENCE
		% (95% CI)*		% (95% CI)*
Normal (18.5–24.9)	82/26,005	3.4 (2.4–4.3)	58/11,744	4.9 (3.3–6.5)
Overweight (25.0–29.9)	108/14,232	3.7 (2.6–4.8)	125/19,358	6.1 (4.6–7.5)
Obese (≥30.0)	68/7004	6.8 (4.7–8.9)	55/6219	10.0 (6.2–13.8)

*The values have been adjusted by direct standardization to the overall age distribution of the participants in the study sample in five age groups: under 40 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 years or more. CI denotes confidence interval.

TABLE 3. RESULTS OF MULTIVARIABLE COX PROPORTIONAL-HAZARDS MODELS EXAMINING THE RELATION OF BODY-MASS INDEX TO THE RISK OF HEART FAILURE.*

MODEL AND CATEGORY OF BODY-MASS INDEX	SEX-SPECIFIC ANALYSES				SEX-STRATIFIED ANALYSES	
	WOMEN (N=3177)		MEN (N=2704)		TOTAL (N=5881)	
	hazard ratio (95% CI)	P value	hazard ratio (95% CI)	P value	hazard ratio (95% CI)	P value
I. Models with body-mass index and all covariates defined at base line†						
A. Body-mass index as a continuous variable (per increment of 1)	1.07 (1.04–1.10)	<0.001	1.05 (1.02–1.09)	0.005	1.06 (1.04–1.09)	<0.001
B. Body-mass index as a categorical variable						
Normal (18.5–24.9)	1.00		1.00		1.00	
Overweight (25.0–29.9)	1.50 (1.12–2.02)	0.007	1.20 (0.87–1.64)	0.27	1.34 (1.08–1.67)	0.007
Obese (≥30.0)	2.12 (1.51–2.97)	<0.001	1.90 (1.30–2.79)	0.001	2.04 (1.59–2.63)	<0.001
Trend across categories	1.46 (1.23–1.72)	<0.001	1.37 (1.13–1.67)	0.002	1.43 (1.26–1.62)	<0.001
II. Models with body-mass index and all covariates defined as time-dependent variables‡						
A. Body-mass index as a continuous variable (per increment of 1)	1.07 (1.04–1.10)	<0.001	1.04 (1.00–1.07)	0.03	1.06 (1.04–1.08)	<0.001
B. Body-mass index as a categorical variable						
Normal (18.5–24.9)	1.00		1.00		1.00	
Overweight (25.0–29.9)	1.68 (1.25–2.27)	<0.001	1.17 (0.86–1.61)	0.32	1.39 (1.12–1.72)	0.003
Obese (≥30.0)	2.17 (1.54–3.05)	<0.001	1.80 (1.22–2.64)	0.003	1.98 (1.54–2.56)	<0.001
Trend across categories	1.48 (1.25–1.75)	<0.001	1.33 (1.09–1.63)	0.005	1.41 (1.24–1.60)	<0.001

*The normal body-mass index category was the reference category. CI denotes confidence interval.

†Models were stratified according to cohort status and adjusted for age, alcohol consumption (none; up to one drink per day in women and up to two drinks per day in men; and more than one drink per day in women and more than two drinks per day in men), total serum cholesterol level, and presence or absence of current cigarette smoking, valve disease, hypertension, diabetes mellitus, electrocardiographic left ventricular hypertrophy, and myocardial infarction.

‡Models were stratified according to cohort status and adjusted for base-line age and the following time-dependent covariates: alcohol consumption (as defined above), total serum cholesterol level, and presence or absence of current cigarette smoking, valve disease, hypertension, diabetes mellitus, electrocardiographic left ventricular hypertrophy, and myocardial infarction.

Effect Modification

The effect of body-mass index on the risk of heart failure did not vary with age, sex, smoking status, alcohol consumption, or the presence or absence of valve disease or diabetes mellitus (P>0.10). However, we noted effect modification with hypertension (P=0.03) and myocardial-infarction status (P=0.02). The hazard ratio for the trend in the risk of heart failure across body-mass index categories was lower in subjects with hypertension (1.30; 95 percent confidence interval, 1.11 to 1.52) than in subjects without hypertension (1.66; 95 percent confidence interval, 1.33 to 2.07). Increased body-mass index was not associated with an increased risk of heart failure in those with
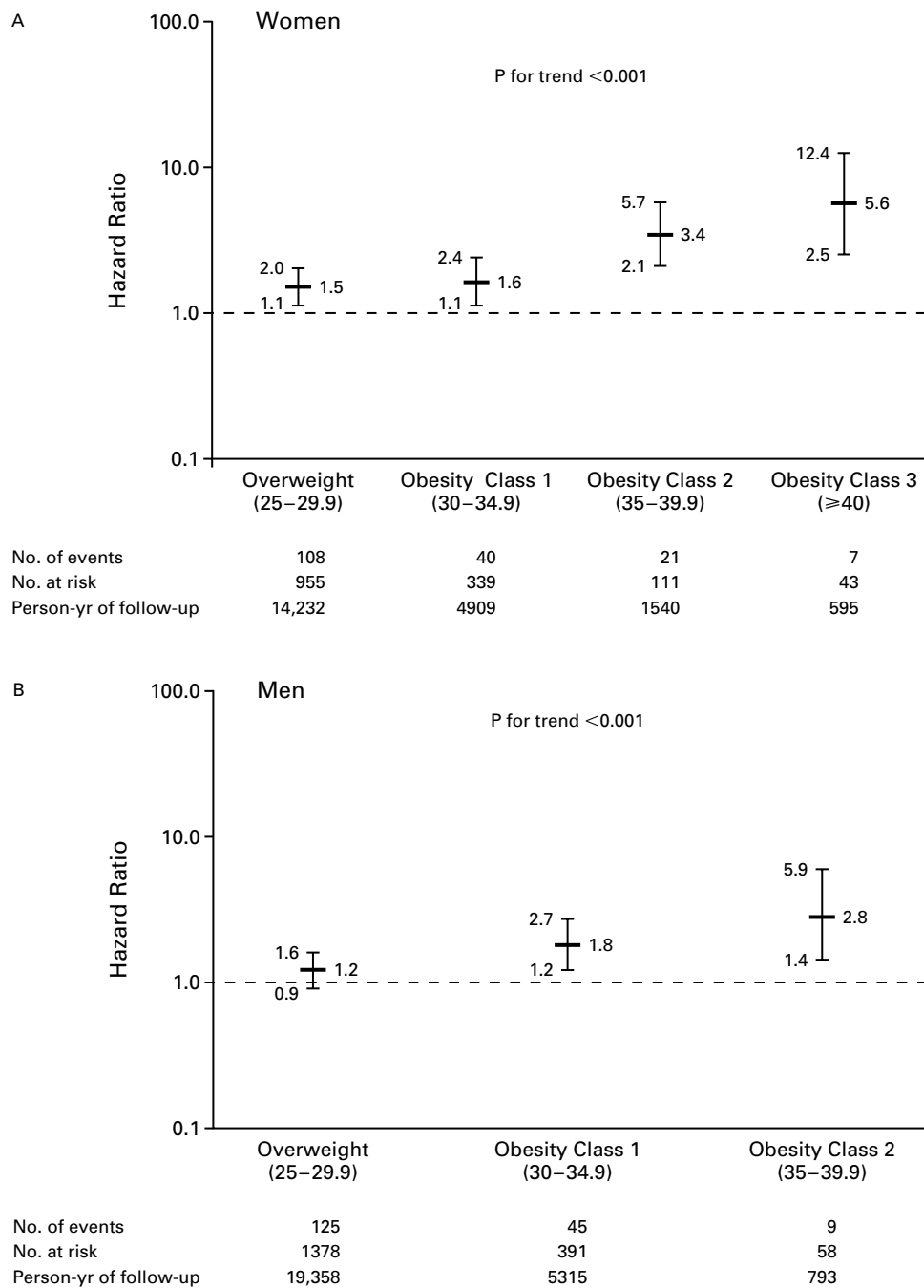
A

Women

P for trend <0.001

Hazard Ratio

	Overweight (25–29.9)	Obesity Class 1 (30–34.9)	Obesity Class 2 (35–39.9)	Obesity Class 3 (≥40)
No. of events	108	40	21	7
No. at risk	955	339	111	43
Person-yr of follow-up	14,232	4909	1540	595

B

Men

P for trend <0.001

Hazard Ratio

	Overweight (25–29.9)	Obesity Class 1 (30–34.9)	Obesity Class 2 (35–39.9)
No. of events	125	45	9
No. at risk	1378	391	58
Person-yr of follow-up	19,358	5315	793

Figure 2. Risk of Heart Failure in Obese Subjects, According to Category of Body-Mass Index at the Base-Line Examination.

I bars represent the 95 percent confidence intervals for the hazard ratios. Hazard ratios were adjusted for age, total serum choles-terol level, cigarette smoking, alcohol consumption, and presence or absence of valve disease, hypertension, diabetes mellitus, elec-trocardiographic evidence of left ventricular hypertrophy, and myocardial infarction at base line. Normal weight (body-mass index, 18.5 to 24.9) was the reference category. Hazard ratios on the y axis are shown on a logarithmic scale. Data for men in obesity class 3 are not provided because of the small sample (eight subjects).

myocardial infarction at base line (148 subjects; hazard ratio for trend across categories, 0.80; 95 percent confidence interval, 0.50 to 1.30) as compared with those without myocardial infarction (5733 subjects; hazard ratio, 1.50; 95 percent confidence interval, 1.31 to 1.71). The statistical power to detect hazard ratios of 1.5, 2.0, and 2.5 for heart failure (for trend across body-mass index categories at an alpha level of <0.05) in subjects with myocardial infarction at base line was 0.38, 0.81, and 0.96, respectively.

Population Attributable Risk

The population attributable risk of heart failure due to overweight was 14.0 percent in women and 8.8 percent in men. The corresponding population attributable risks due to obesity were 13.9 percent in women and 10.9 percent in men.

Echocardiographic Evaluation

Of the 120 participants who underwent echocardiographic evaluation within 30 days of their first hospitalization for heart failure (24 percent of those with heart failure), 75 percent (21 of 28) of those with a normal body-mass index, 65 percent (37 of 57) of overweight subjects, and 66 percent (23 of 35) of obese subjects had a left ventricular ejection fraction of less than 50 percent (indicative of systolic heart failure). The proportions of subjects with heart failure who had a left ventricular ejection fraction of less than 40 percent in the normal, overweight, and obese groups were 53.6 percent, 52.6 percent, and 42.9 percent, respectively.

Risk of Heart Failure in Underweight Subjects

Only 3 of the 76 underweight subjects (64 women and 12 men) had heart failure on follow-up. In sex-stratified models, underweight subjects had a multivariable-adjusted hazard ratio of 0.95 (95 percent confidence interval, 0.37 to 2.45) as compared with those with a normal body-mass index.

DISCUSSION

Elevated body-mass index was associated with an increased risk of heart failure, without evidence of a threshold. This increased risk was evident in both sexes and was not limited to persons with extreme obesity. Although the hazard ratio for heart failure in overweight men did not achieve statistical significance, analyses evaluating body-mass index as a continuous variable and findings of trend models support the existence of a continuous gradient of heart-failure risk with increasing body-mass index in both sexes. The finding of an increased risk of heart failure associated with elevated body-mass index remained robust in analyses incorporating body-mass index and other covariates as time-dependent variables. It is important to note that statistical models in which adjustment is made for all risk factors underestimate the effects of adiposity on the risk of heart failure.

The smaller effect of body-mass index on the risk of heart failure in subjects with hypertension probably indicates a decreased contribution of obesity to the risk of heart failure in the presence of this major risk factor. The lack of effect of body-mass index on the risk of heart failure in subjects with myocardial infarction, however, must be interpreted with caution because of the small sample. In a subgroup of subjects who underwent echocardiographic evaluation within 30 days after their first hospitalization for heart failure, obesity was associated with both systolic and diastolic heart failure.

Three prior community-based studies reported an association of increased body-mass index with an increased risk of heart failure.[10-12] However, they did not use the contemporary body-mass index classification,[15,16] and ascertainment of heart failure was based primarily on hospital-discharge codes or death certificates. Furthermore, none of these studies assessed the entire range of body-mass index values or modeled covariates as time-dependent variables. Only one study[10] adjusted for the occurrence of an interim myocardial infarction.

Other investigators have reported that a low body-mass index is associated with increased mortality among patients with heart failure.[23,24] Our study had limited power to evaluate the risk of heart failure in underweight subjects. In this context, it is important to draw a distinction between the role of elevated body-mass index as a risk factor for heart failure and its effect on survival after the onset of heart failure.

The strength of the association, the stepwise increase in the risk of heart failure across increasing categories of body-mass index, the demonstration of a temporal sequence (with increased body-mass index preceding the development of heart failure), and the consistency of results in multiple analyses suggest a causal relation between increased body-mass index and heart failure. There are several plausible mechanisms for such an association. Increased body-mass index is a risk factor for hypertension,[25] diabetes mellitus,[26,27] and dyslipidemia,[16] all of which augment the risk of myocardial infarction,[28,29] an important antecedent of heart failure.[10-12,30] In addition, hypertension and diabetes mellitus independently increase the risk of heart failure.[10-12,30,31] Elevated body-mass index is associated with altered left ventricular remodeling,[3-6,8] possibly owing to increased hemodynamic load,[32,33] neurohormonal activation,[34] and increased oxidative stress.[35] Recently, Zhou et al. raised the possibility of a direct effect of obesity on the myocardium by demonstrating cardiac steatosis and lipoapoptosis in an animal model of obesity.[36]

The strengths of our investigation include the large community-based sample, standardized assessment of body-mass index, consistent use of the same diagnostic criteria for heart failure, and the long period of follow-up. Nonetheless, it is important to acknowledge several limitations. Although a diagnosis of heart failure was made only after a careful review of the records by a panel of three physicians, it is still possible that symptoms (such as dyspnea) and signs (such as ankle edema) may be misconstrued as indicating heart failure more often in obese persons.[37] Pedal edema was more common among obese subjects with heart failure, but the distributions of major and all other minor heart-failure criteria were similar among subjects with heart failure in the three categories of body-mass index (data not shown). Exclusion of pedal edema as a minor criterion in the obese subjects did not alter the diagnosis of heart failure by the Framingham Heart Study adjudication panel in any instance. Other evidence against misclassification of subjects with heart failure as the explanation for the observed association includes the substantial increase in the risk of heart failure among those who were overweight and those with lesser degrees of obesity, and the finding in a subgroup analysis that 43 percent of obese subjects with heart failure had moderately or severely impaired left ventricular systolic function. Finally, because our sample was predominantly white, we avoided confounding by race but at the same time, we reduced the generalizability of our findings to other races and ethnic groups.

Our findings suggest that obesity is an important risk factor for heart failure in both women and men. Approximately 11 percent of cases of heart failure among men and 14 percent among women in the community are attributable to obesity alone. The contribution of obesity to the risk of heart failure has not been adequately recognized, and our observational data suggest that efforts to promote optimal body weight may reduce the risk of heart failure. Our results are particularly relevant given the alarming trend toward increasing obesity in the United States.[16]

REFERENCES

1. American Heart Association. 2002 Heart and stroke statistical update. Dallas: American Heart Association, 2001.
2. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101-13.
3. Messerli FH, Sundgaard-Riise K, Reisin ED, et al. Dimorphic cardiac adaptation to obesity and arterial hypertension. Ann Intern Med 1983;99:757-61.
4. Hammond IW, Devereux RB, Alderman MH, Laragh JH. Relation of blood pressure and body build to left ventricular mass in normotensive and hypertensive employed adults. J Am Coll Cardiol 1988;12:996-1004.
5. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry: the Framingham Heart Study. JAMA 1991;266:231-6.
6. Alpert MA, Lambert CR, Terry BE, et al. Influence of left ventricular mass on left ventricular diastolic filling in normotensive morbid obesity. Am Heart J 1995;130:1068-73.
7. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. N Engl J Med 1997;336:1350-5.
8. Gardin JM, McClelland R, Kitzman D, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). Am J Cardiol 2001;87:1051-7.
9. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci 2001;321:225-36.
10. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. Am J Med 1999;106:605-12.
11. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.
12. Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men — morbidity, risk factors, and prognosis. J Intern Med 2001;249:253-61.
13. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health 1951;41:279-86.
14. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. Am J Epidemiol 1979;110:281-90.
15. Obesity: preventing and managing the global epidemic: report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:1-253.
16. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, Md.: National Heart, Lung, and Blood Institute, 1998. (NIH publication no. 98-4083.)
17. Kannel WB, Wolf PA, Garrison RJ, eds. The Framingham Study: an epidemiological investigation of cardiovascular disease. Section 34. Some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements: Framingham Heart Study, 30-year follow-up. Bethesda, Md.: National Heart, Lung, and Blood Institute, 1987. (NIH publication no. 87-2703.)
18. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971;285:1441-6.
19. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
20. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15-9.
21. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000;101:2118-21.
22. SAS/STAT software: PHREG procedure: changes and enhancements through release 6.12. Cary, N.C.: SAS Institute, 1997:871-948.
23. Anker SD, Rauchhaus M. Insights into the pathogenesis of chronic heart failure: immune activation and cachexia. Curr Opin Cardiol 1999;14:211-6.
24. Mosterd A, Cost B, Hoes AW, et al. The prognosis of heart failure in the general population: the Rotterdam Study. Eur Heart J 2001;22:1318-27.
25. Stamler J. Epidemiologic findings on body mass and blood pressure in adults. Ann Epidemiol 1991;1:347-62.
26. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961-9.
27. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481-6.
28. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. Diabetes Care 1979;2:120-6.
29. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 1990;322:882-9.

30. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for estimating risk of heart failure. Arch Intern Med 1999; 159:1197-204.

31. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557-62.

32. Alexander JK, Dennis EW, Smith WG, Amad KH, Duncan WC, Austin RC. Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. Cardiovasc Res Cent Bull 1963;1:39-44.

33. Messerli FH, Sundgaard-Riise K, Reisin E, Dreslinski G, Dunn FG, Frohlich E. Disparate cardiovascular effects of obesity and arterial hypertension. Am J Med 1983;74:808-12.

34. Engeli S, Sharma AM. The renin-angiotensin system and natriuretic peptides in obesity-associated hypertension. J Mol Med 2001;79:21-9.

35. Vincent HK, Powers SK, Stewart DJ, Shanely RA, Demirel H, Naito H. Obesity is associated with increased myocardial oxidative stress. Int J Obes Relat Metab Disord 1999;23:67-74.

36. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A 2000;97: 1784-9.

37. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000;321:215-8.

Copyright © 2002 Massachusetts Medical Society.