A PROSPECTIVE STUDY OF OBESITY AND RISK OF CORONARY HEART DISEASE IN WOMEN

JoAnn E. Manson, M.D., Graham A. Colditz, M.B., B.S., Meir J. Stampfer, M.D., Walter C. Willett, M.D., Bernard Rosner, Ph.D., Richard R. Monson, M.D., Frank E. Speizer, M.D., and Charles H. Hennekens, M.D.

Abstract We examined the incidence of nonfatal and fatal coronary heart disease in relation to obesity in a prospective cohort study of 115,886 U.S. women who were 30 to 55 years of age in 1976 and free of diagnosed coronary disease, stroke, and cancer. During eight years of follow-up (775,430 person-years), we identified 605 first coronary events, including 306 nonfatal myocardial infarctions, 83 deaths due to coronary heart disease, and 216 cases of confirmed angina pectoris.

A higher Quetelet index (weight in kilograms divided by the square of the height in meters) was positively associated with the occurrence of each category of coronary heart disease. For increasing levels of current Quetelet index (<21, 21 to <23, 23 to <25, 25 to <29, and ≥29), the relative risks of nonfatal myocardial infarction and fatal coronary heart disease combined, as adjusted for age and cigarette smoking, were 1.0, 1.3, 1.3, 1.8, and 3.3 (Mantel-extension χ for trend = 7.29; $P<0.00001$). As expected, control for a history of hypertension, diabetes mellitus, and hypercholesterolemia — conditions known to be biologic effects of obesity — attenuated the strength of the association. The current Quetelet index was a more important determinant of coronary risk than that at the age of 18; an intervening weight gain increased risk substantially.

These prospective data emphasize the importance of obesity as a determinant of coronary heart disease in women. After control for cigarette smoking, which is essential to assess the true effect of obesity, even mild-to-moderate overweight increased the risk of coronary disease in middle-aged women. (N Engl J Med 1990; 322:882-9.)

THE influence of obesity on the risk of coronary heart disease remains controversial despite a well-established association between adiposity and unfavorable coronary risk-factor status. Obesity is a cause of diabetes mellitus, hypertension, and lipid abnormalities.[1-3] Despite the biologic plausibility of a strong link between obesity and atherogenesis, epidemiologic studies have not consistently corroborated an association. Several investigators have proposed undefined protective factors associated with adiposity to explain this apparent paradox.[4-6]

The proportion of overweight adults in the United States has been steadily increasing in the past several decades,[7,8] especially among women.[9] At present, approximately one in five adult Americans, or 34 million people, are obese as defined by a weight that is 20 percent or more above the desirable level.[10] Thus, an improved understanding of whether obesity affects the risk of coronary heart disease has major implications for public health.

There are limited data about the influence of obesity on cardiovascular risk in women. Although coronary heart disease remains the leading cause of death in both sexes in the United States, most prospective studies of obesity and coronary disease have included only men. In addition, most previous studies have failed to control for cigarette smoking or weight loss due to preexisting disease or have equated the true effect of obesity with its residual influence after control for the biologic effects of obesity, such as hypertension and hyperglycemia.[11-23]

We examined the influence of current obesity, relative weight at the age of 18, and intervening weight gain on the subsequent risk of fatal and nonfatal coronary heart disease in a large prospective cohort of women. We also explored the importance of controlling for cigarette smoking in the assessment of the effect of obesity, as well as possible interrelations of obesity with diet and physical activity.

From the Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital (J.E.M., G.A.C., M.J.S., W.C.W., B.R., F.E.S., C.H.H.); the Department of Preventive Medicine, Harvard Medical School (J.E.M., B.R., C.H.H.); and the Departments of Epidemiology (M.J.S., W.C.W., R.R.M.) and Nutrition (W.C.W.), Harvard School of Public Health, Boston. Address reprint requests to Dr. Manson at 180 Longwood Ave., Boston, MA 02115.

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Methods

The Nurses' Health Study cohort was established in 1976, when 121,700 female registered nurses 30 to 55 years of age living in a total of 11 states responded to questionnaires requesting information about their medical histories and lifestyles. Further details have been published elsewhere.[24,25] The subjects of this investigation were 115,886 women who were free of diagnosed coronary heart disease, stroke, and cancer in 1976 and who provided data on their height and weight. From a subgroup of 249 participants, we estimated that 98 percent of the cohort was white.

Risk Factors

Our 1976 questionnaire requested information about age, current weight and height, current and past cigarette smoking, parental history of myocardial infarction, reproductive history, use of oral contraceptives or postmenopausal hormones, and personal history of coronary heart disease (myocardial infarction or angina pectoris), stroke, hypertension, diabetes, elevated serum cholesterol level, and cancer. Follow-up questionnaires in 1978, 1980, 1982, and 1984 elicited updated information on these variables and ascertained the history of other major illnesses. In 1980 the participants were asked to record their weights at the age of 18, and a dietary questionnaire was included.

End Points

The disease end points in the analyses were nonfatal myocardial infarction, fatal coronary heart disease, and angina pectoris occurring after the 1976 questionnaire was returned but before June 1, 1984. Permission to review the medical records was sought from the

participants who reported having nonfatal myocardial infarctions or angina on follow-up questionnaires. Systematic reviews of the records were conducted by physicians who were unaware of the risk-factor status reported by the subjects. The follow-up rate for nonfatal events through 1984 was 96.7 percent of the total potential person-years of follow-up.

Myocardial infarctions were classified as confirmed if they met the criteria of the World Health Organization: symptoms and either diagnostic electrocardiographic changes or elevated cardiac-enzyme levels.[26] Thus, silent infarctions and those occurring at an indeterminate time and discovered on routine examination were excluded. Myocardial infarctions that required hospitalization and were corroborated by letter or telephone interview but for which hospital records were unavailable were classified as probable. We combined 238 confirmed and 68 probable cases of nonfatal myocardial infarction in one category because the results in the probable cases considered separately were nearly identical to those in the confirmed cases.

In the case of angina pectoris, medical records were obtained only from 1978 onward. The criteria for confirmed angina (incident cases between the return of the 1978 questionnaire and June 1, 1984) required the presence of at least one of the following: coronary angiography demonstrating more than 70 percent obstruction of any coronary artery, coronary-artery bypass grafting or angioplasty, or ST-segment depression of at least 1 mm on exercise testing in conjunction with a positive response to a mailed Rose questionnaire.[27] A woman could contribute only one coronary disease end point in these analyses; when more than one event (e.g., angina and nonfatal myocardial infarction) occurred during a two-year follow-up interval, only the most serious event was counted.

The mortality surveillance included systematic searches of the vital records of the states and the National Death Index to discover deaths among nonrespondents. In addition, deaths were reported by next of kin and postal authorities. We estimate that 98 percent of the deaths in the cohort were ascertained.[28] Fatal coronary heart disease was defined as fatal myocardial infarction confirmed by hospital records or autopsy or the listing of coronary heart disease as the cause of death on the death certificate if it was the underlying and only plausible cause and evidence of previous coronary heart disease was available. The statement of the cause of death on the death certificate was never relied on as providing sufficient confirmation by itself of a coronary death.

Validation Studies

In a validation substudy of self-reported weights, 184 participants living in the greater Boston area were weighed on a digital bathroom scale 6 to 12 months after completing the questionnaire. The weights reported by this sample of subjects were highly correlated with actual measurements (Spearman $r = 0.96$), although the self-reported weights averaged 1.5 kg less.[29] This difference is compatible with that between a random casual weight measured with clothing and a morning weight measured in the nude, after urination.

The participants in the Nurses' Health Study cohort weighed, on average, 3 kg less than a national sample of U.S. women.[30,31] The Quetelet index (the weight in kilograms divided by the square of the height in meters) was used as a measure of obesity. This index is independent of height ($r = -0.03$) and strongly related to weight ($r = 0.86$).[32] The Quetelet-index categories in our analyses were <21, 21 to <23, 23 to <25, 25 to <29, and ≥ 29. These categories correspond approximately to the percentiles 0 to 19, 20 to 34, 35 to 54, 55 to 74, and 75 to 100 of the Quetelet index among middle-aged U.S. women.[31] Expressed as percentages of the desirable weight according to the Metropolitan Life Insurance Company tables of 1983 (based on a minimum of mortality in the actuarial data), these Quetelet categories correspond approximately to the following percentages of the recommended weights: less than 95, 95 to 104, 105 to 114, 115 to 129, and 130 or above.[33]

Among a sample of participants in this cohort who reported risk factors, 100 percent of the self-reports of hypertension and 85.7 percent of the self-reports of hypercholesterolemia were confirmed by a review of medical records; for the purposes of the review, hypertension was defined as a blood pressure $\geq 140/90$ mm Hg, and hypercholesterolemia was defined as a cholesterol level ≥ 6.21 mmol per liter (≥ 240 mg per deciliter).[34] Dietary data were obtained in 1980 by a semiquantitative food-frequency questionnaire. A detailed description of the dietary questionnaire and documentation of its validity and reproducibility have been reported elsewhere.[35]

Statistical Analysis

The study subjects were classified in five groups according to Quetelet index on the basis of the height and weight reported on the 1976 and subsequent questionnaires. Incident cases of coronary heart disease were assigned to the Quetelet-index category and other categories of exposure status as defined in the most recent previous questionnaire, with the follow-up period dating from the return of the forms to the date of occurrence of disease or June 1, 1984, whichever came first. Women who reported myocardial infarction, angina, stroke, or cancer on one questionnaire were excluded from the subsequent analyses, so that the base population was free of cardiovascular disease and cancer at the beginning of each two-year period. Also, women who did not report their updated weight at the beginning of a two-year interval were excluded from the analyses for that period. Incidence rates were calculated by dividing the number of events by the accumulated person-time of follow-up for the women in a given Quetelet category. To estimate the incidence of fatal events and of fatal events combined with nonfatal myocardial infarction, we used the accumulated person-years (775,430) of the entire cohort. For the nonfatal end points, the total person-years of observation were fewer (749,882), because the end points were ascertained only among respondents. Since the diagnosis of angina pectoris was not confirmed before 1978, the person-time between the return of the 1978 questionnaire and June 1, 1984, was used to calculate the incidence rates for this outcome. In the analyses of alcohol consumption, person-time dated from the return of the 1980 questionnaire, when this information was first requested.

The relative risk, computed as the incidence rate of end points in women assigned to a specific category according to their Quetelet index divided by the corresponding rate in the Quetelet-index category that included the leanest women (and yielding the rate ratio), was used as a measure of the strength of the association between obesity and the risk of coronary events. The attributable-risk percentage (the difference between these two incidence rates divided by the absolute risk in each Quetelet-index category [$\times 100$ percent]) and the percentage of risk attributable to the population (the difference between the incidence rate in the total study population and that in the unexposed population divided by the incidence rate in the former [$\times 100$ percent]) indicated the proportion of cases in each category and in the total study population, respectively, that were attributable to adiposity.[36] All analyses were adjusted for age according to five-year categories. The Mantel-extension test[37] was used to assess the overall trend of increasing Quetelet index (on a scale from 1 to 5) in data stratified by age, as well as by both age and one additional variable. Proportional-hazards models were used to control for multiple risk factors simultaneously. We calculated the 95 percent confidence intervals for each relative risk[38] and two-tailed P values for the Mantel-extension test for linear trend.

Results

The distribution of the traditional indicators of coronary risk varied according to the category of Quetelet index (Table 1). Adiposity increased with age. After adjustment for age, relative weight had a strong inverse relation to smoking status; current smokers constituted 40 percent of the leanest group but only 25 percent of the heaviest. Obesity also correlated inversely with alcohol intake. Reported hypertension, diabetes, and elevated serum cholesterol levels were

two to five times more prevalent among women in the heavier Quetelet-index categories. The dietary intake of total fat and of types of fat, as well as dietary cholesterol, varied minimally in relation to the Quetelet-index category.

During the eight years of observation, 605 incident cases of coronary heart disease, including 306 nonfatal myocardial infarctions, 83 confirmed coronary deaths, and 216 cases of confirmed angina pectoris, occurred in 775,430 person-years among women previously free of cardiovascular disease and cancer.

The age-adjusted relative risks for nonfatal myocardial infarction, fatal coronary heart disease, and angina pectoris rose progressively with each category of increasing relative weight (Table 2). The age-adjusted relative risk for nonfatal myocardial infarction combined with fatal coronary heart disease in the heaviest women (Quetelet index, ≥29) as compared with the leanest (Quetelet index, <21) was 2.6 (95 percent confidence interval, 1.8 to 3.6). The effect of adjustment for cigarette smoking is shown in Figure 1. Smoking, which correlates inversely with the Quetelet index (Table 1) and has an independent positive association with the risk of coronary disease,[39] confounded the relation of obesity with coronary heart disease. After adjustment for age and smoking, the relative risks increased monotonically through the first four categories, then rose sharply with the fifth: 1.0, 1.3, 1.3, 1.8, and 3.3 (Mantel-extension χ for linear trend, 7.29; $P<0.00001$) (Table 2 and Fig. 1). This association persisted when we analyzed nonfatal myocardial infarction and fatal coronary disease separately; the relative risks for angina pectoris also increased stepwise according to the degree of adiposity (Table 2).

Table 1. Distribution of Potential Risk Factors, According to Quetelet-Index Category, in a Cohort of U.S. Women 30 to 55 Years of Age in 1976.*

Characteristic	Quetelet Index				
	<21	21–<23	23–<25	25–<29	≥29
No. of women†	30,164	30,512	22,709	20,107	12,394
Mean age (yr)	40.1±7.1	41.7±7.1	43.1±7.1	43.8±7.0	43.8±6.9
Mean weight (kg)	53.7±4.7	59.3±4.8	64.0±4.8	71.7±6.3	87.3±11.9
Mean height (cm)	164.4±6.2	163.9±6.1	163.3±5.9	163.8±6.4	163.1±6.2
Cigarette smoking status (%)‡					
Current smokers	39.9	33.0	31.0	29.2	25.1
Former smokers	21.5	23.7	23.8	23.1	24.5
Never smoked	38.0	42.4	44.6	46.6	49.9
Mean alcohol intake (g/day)§	7.9	7.6	6.8	5.7	4.0
Hypertension (%)	6.4	7.9	9.4	13.8	26.5
Diabetes mellitus (%)	1.0	1.0	1.2	1.7	5.1
High cholesterol (%)	2.3	2.5	3.1	3.5	4.8
Premenopausal (%)	71.0	72.4	71.9	71.9	72.6
Parent with infarction (%)¶	13.6	14.2	15.4	15.0	16.0
Mean fat intake (g/day)§					
Total	75.5	75.6	75.8	75.8	75.9
Saturated	30.0	30.0	30.1	30.2	30.2
Polyunsaturated	11.4	11.4	11.4	11.4	11.5
Monounsaturated	31.2	31.3	31.4	31.4	31.4
Mean cholesterol intake (mg/day)§	314.2	323.8	323.3	322.4	322.6

*Percentages and means shown (except ages, weights, and heights) are adjusted to the age distribution of the entire cohort according to five-year categories. Plus–minus values are means ±SD. The Quetelet index is the weight in kilograms divided by the square of the height in meters.

†Numbers shown are the numbers of women in each category at the beginning of follow-up in 1976.

‡Totals for each category are less than 100 percent because of rounding and missing values for smoking in 0.3 percent of participants.

§Data are from a 1980 food-frequency questionnaire. Values are adjusted for age and total caloric intake, except those for alcohol, which are adjusted only for age.

¶Denotes a parent with a myocardial infarction that occurred at ≤60 years of age.

After adjustment for age and smoking, the rate of nonfatal myocardial infarction and fatal coronary disease combined was 32 per 100,000 person-years in the leanest weight category and 106 per 100,000 person-years in the heaviest group. The attributable-risk estimate (difference in rates) related to adiposity was 74 excess cases per 100,000 person-years in the heaviest Quetelet-index category (≥29); thus, 70 percent of the coronary events in this group could be attributed to adiposity. Although it was most pronounced in the heaviest category, an elevated risk was apparent at all Quetelet-index levels as compared with the leanest. Women mildly to moderately overweight (Quetelet index, 25 to 28.9) had a risk of coronary disease 80 percent higher than their lean counterparts.

We also examined the effects of coronary risk factors in modifying the association between relative weight and coronary heart disease (Fig. 2). Obesity conferred an elevated coronary risk in both the presence and the absence of other risk factors, such as smoking, hypertension, a high serum cholesterol level, and diabetes. For all risk-factor strata, the relative risk in the heaviest Quetelet-index category was at least double that in the leanest category, and there was no suggestion of a U or J shape to the curves. The excess risk associated with obesity was particularly high among current smokers and diabetic women. These data, based on an extended follow-up period, expand on the information previously reported about the adverse interaction between smoking and obesity in this cohort.[39]

We performed a proportional-hazards analysis to adjust simultaneously for a number of potential risk factors (Table 3). These analyses permit an assessment of the independent effect of obesity on the risk of coronary disease after the elimination of potential confounding factors, as well as the residual effect after the removal of the known biologic mechanisms

Table 2. Relative Risks of Nonfatal Myocardial Infarction, Fatal Coronary Heart Disease, and Angina Pectoris, According to Quetelet-Index Category, in the Cohort of U.S. Women 30 to 55 Years of Age.*

Characteristic	Quetelet Index					Mantel-Extension χ	P Value
	<21	21–<23	23–<25	25–<29	≥29		
No. of person-years	177,356	194,243	155,717	148,541	99,573		
Nonfatal myocardial infarction							
No. of cases	41	57	56	67	85		
Relative risk							
Adjusted for age	1.0	1.1	1.2	1.4	2.6	5.25	<0.00001
Adjusted for age and smoking	1.0	1.2	1.3	1.6	3.2	6.57	<0.00001
Fatal coronary heart disease							
No. of cases	10	18	13	22	20		
Relative risk							
Adjusted for age	1.0	1.4	1.2	2.0	2.6	2.58	0.01
Adjusted for age and smoking	1.0	1.6	1.4	2.4	3.5	3.17	0.002
Nonfatal myocardial infarction and fatal coronary heart disease							
No. of cases	51	75	69	89	105		
Relative risk (95% CI)							
Adjusted for age	1.0	1.1 (0.8–1.6)	1.2 (0.8–1.7)	1.5 (1.1–2.1)	2.6 (1.8–3.6)	5.85	<0.00001
Adjusted for age and smoking	1.0	1.3 (0.9–1.8)	1.3 (0.9–1.9)	1.8 (1.2–2.5)	3.3 (2.3–4.5)	7.29	<0.00001
Angina pectoris							
No. of cases	28	40	53	58	37		
Relative risk							
Adjusted for age	1.0	1.1	1.5	1.6	1.5	2.24	0.025
Adjusted for age and smoking	1.0	1.2	1.7	1.7	1.8	2.75	0.006

*Adjusted for age with five-year age categories and adjusted for cigarette smoking with eight categories (never, former only, and six categories for number of cigarettes currently smoked daily: 1 to 4, 5 to 14, 15 to 24, 25 to 34, 35 to 44, and 45 or more). The reference category is the group with a Quetelet index of less than 21. CI denotes confidence interval.

through which obesity acts, such as hypertension, diabetes, and hyperlipidemia. The latter are not confounding variables but rather intermediate steps in the causal pathway. After we controlled in one model for true confounders (Table 3, model 1), the relative risks of nonfatal myocardial infarction and fatal coronary disease combined remained essentially unchanged from those in the analyses adjusted for age and smoking alone. Control for hypertension attenuated this association, as expected; control for diabetes and high cholesterol levels also weakened the relation. In a multivariate model with simultaneous adjustment for all the variables, including a parental history of myocardial infarction before the age of 60, the relative risks were attenuated but remained significantly elevated in the heaviest relative-weight stratum (relative risk, 1.9; 95 percent confidence interval, 1.3 to 2.6; Table 3). Control for alcohol intake slightly weakened the association (Table 3).

We explored the effect of early obesity and found that the Quetelet index at the age of 18 was positively correlated with the risk of coronary heart disease in middle age (Table 4). For nonfatal myocardial infarction combined with fatal coronary heart disease, the age-adjusted relative risk for the heaviest quintile at the age of 18 (≥25) as compared with the leanest (<20) was 2.0 (95 percent confidence interval, 1.4 to 2.8). This effect was weaker than that observed with the current Quetelet index. After we controlled for both age and the current Quetelet index, only a very modest effect of early obesity persisted. The influence of weight gain after the age of 18 is presented in Table 5. The age-adjusted risk for women who had gained more than 10 kg since the age of 18 was higher than that for women with stable weights (defined as a change of less than 3 kg). A weight gain of more than 20 kg in the preceding four years also conferred an increased risk (data not shown). After adjustment for base-line Quetelet index, these risks remained elevated approximately twofold as compared with those for women with stable weight. The number of women with sustained weight loss in our study was insufficient to assess the influence of weight reduction on the risk of coronary events.

Discussion

These prospective data demonstrate a strong positive association between obesity and the risk of coronary heart disease in women. Adjustment for cigarette smoking, which correlates inversely with relative weight and directly with coronary risk, increased the magnitude of the association. After adjustment for age and smoking, the risk of both nonfatal myocardial infarction and fatal coronary disease among women in the heaviest Quetelet-index category (≥29) was more than three times higher than that in the leanest group. The highest Quetelet-index category corresponds to a weight 30 percent or more above the desirable weight in the 1983 Metropolitan Life Insurance Company tables[33] and includes approximately 25 percent of the U.S. women 35 to 64 years of age.[31]

A significantly increased rate of coronary heart disease was also found for mildly to moderately overweight women (Quetelet index, 25 to 28.9), among whom the rate was increased by 80 percent. This category represents an additional 20 percent of middle-aged U.S. women.[31] The leanest group of women (corresponding to less than 95 percent of the desirable weight) had the lowest rates of coronary disease; women of average weight had coronary risks approximately 30 percent higher than those of lean women.

Among the heaviest women (Quetelet index, ≥29), 70 percent of the coronary heart disease events were

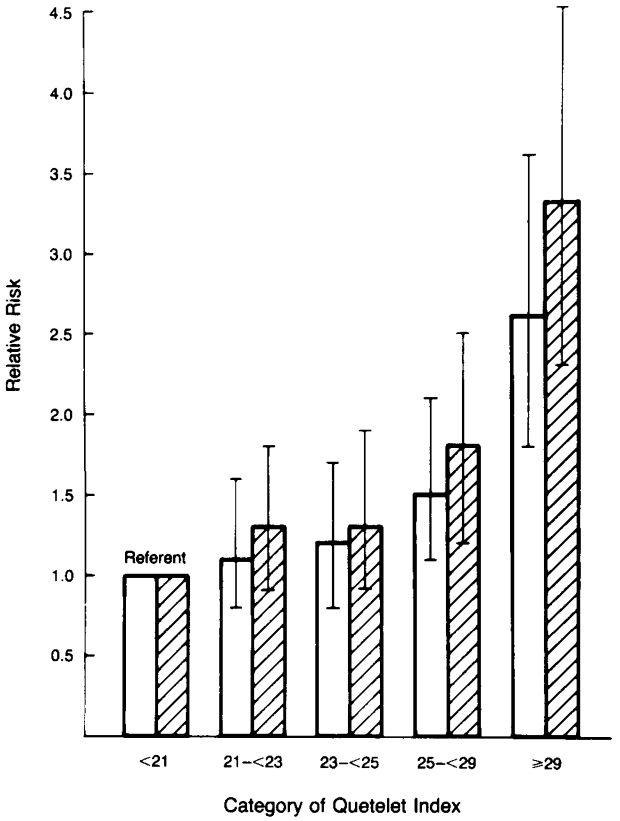

Figure 1. Relative Risks of Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease (Combined), According to Category of Quetelet Index in a Cohort of U.S. Women 30 to 55 Years of Age in 1976.

The reference category was that with an index under 21. For the other categories, open bars show the relative risks as adjusted for age, and hatched bars show the relative risks as adjusted for both age and smoking. The vertical lines represent 95 percent confidence intervals.

attributable to obesity. In the overall study population, 40 percent of the coronary events were attributable to adiposity.

In a multivariate model, control for hypertension, diabetes, and high serum cholesterol levels reduced substantially the magnitude of the association between obesity and coronary disease. In longitudinal studies these conditions have been shown to increase after weight gain and to decline after weight reduction.[2,3] Instead of being confounders, these variables are at least in part the biologic consequences of obesity and associated insulin resistance,[2] and represent mechanisms through which obesity mediates its effects on coronary risk. In our data, obesity retained a moderate residual effect after we controlled for these variables, as well as for true potential confounders, in a proportional-hazards model (Table 3). This residual elevation in risk may be due to imperfect measurement of, and thus incomplete control for, hypertension, glucose tolerance, or lipid levels in our cohort, but it may also reflect the presence of additional mechanisms by which obesity increases coronary risk. Among such postulated mechanisms are increased intravascular volume and cardiac workload[40] and altered fibrinogen levels and fibrinolytic activity.[41]

The current level of obesity was a more important determinant of present risk than obesity in early adulthood, as measured by the Quetelet index at the age of 18. A weight gain during adulthood, however, approximately doubled the coronary risk after control for the initial relative weight level.

The prospective design of this study had the advantage of greatly reducing the likelihood of biased reporting of premorbid weight. Furthermore, since women with previously diagnosed coronary disease were excluded, weight changes were unlikely to have been motivated or induced by previous disease. The follow-up rate in this cohort was extremely high (more than 96 percent through 1984) and uniform across relative weight categories; thus, the study results were unlikely to be biased by incomplete follow-up. Although the current heights and weights were self-reported, these

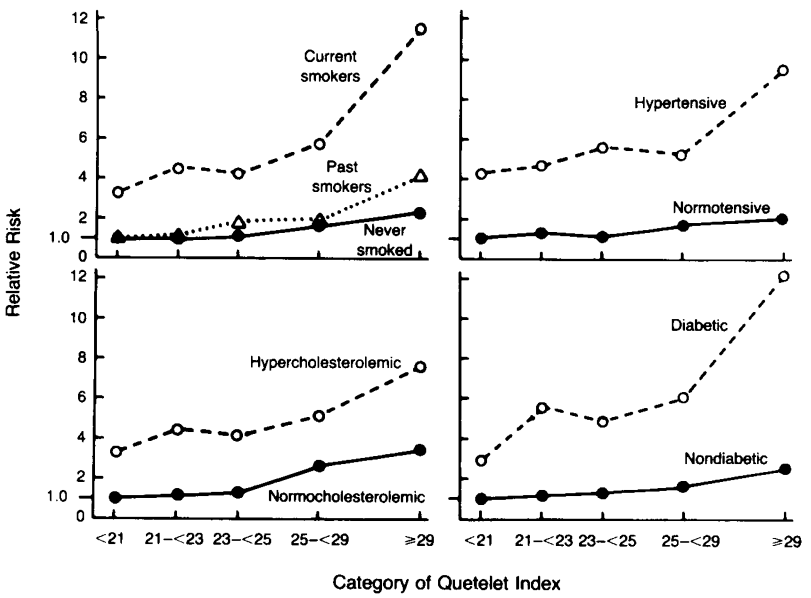

Figure 2. Relative Risks of Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease (Combined), According to Quetelet Index and Coronary Risk-Factor Status, after Adjustment for Age and Smoking.

The reference group in each panel comprised the women in the leanest Quetelet-index category who did not have the specified coronary risk factor. The diabetic group included women who received their diagnoses at ≥30 years of age. In all strata, the relative risk in the heaviest Quetelet category was at least twice that in the leanest.

Table 3. Relative Risks of Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease (Combined), According to Quetelet-Index Category, after Simultaneous Adjustment for Potential Risk Factors in a Proportional-Hazards Model.

VARIABLE	QUETELET INDEX				
	<21	21–<23	23–<25	25–<29	≥29
			relative risk (95% confidence interval)		
Model 1*					
Alone	1.0	1.3 (0.9–1.8)	1.3 (0.9–1.9)	1.7 (1.2–2.4)	3.4 (2.4–4.7)
With hypertension	1.0	1.2 (0.9–1.8)	1.2 (0.8–1.7)	1.4 (1.0–2.0)	2.2 (1.6–3.1)
With diabetes	1.0	1.3 (0.9–1.8)	1.3 (0.9–1.9)	1.6 (1.2–2.3)	2.8 (2.0–3.9)
With high serum cholesterol	1.0	1.3 (0.9–1.8)	1.3 (0.9–1.9)	1.6 (1.2–2.3)	3.1 (2.2–4.4)
With parent with infarction†	1.0	1.3 (0.9–1.8)	1.3 (0.9–1.9)	1.7 (1.2–2.4)	3.3 (2.4–4.6)
With all above variables	1.0	1.2 (0.9–1.8)	1.2 (0.8–1.7)	1.3 (0.9–1.9)	1.9 (1.3–2.6)
Model 2‡					
Alone	1.0	1.4 (0.8–2.4)	1.4 (0.8–2.4)	1.8 (1.1–3.0)	4.2 (2.6–6.8)
With alcohol	1.0	1.4 (0.8–2.4)	1.4 (0.8–2.3)	1.7 (1.0–2.8)	3.7 (2.3–6.0)

*Model 1 includes simultaneous control for age in five-year intervals, cigarette smoking (never, former only, and currently smoking 1 to 14, 15 to 24, or 25 or more cigarettes per day), follow-up period (1976 to 1978, 1978 to 1980, 1980 to 1982, and 1982 to 1984), menopausal status, and postmenopausal use of hormones (never, former only, and current). The reference category is the group with a Quetelet index of less than 21.

†Denotes a parent with a myocardial infarction that occurred at ≤60 years of age.

‡Model 2 includes the same variables as model 1, but follow-up was limited to the period from 1980 through 1984, when data on alcohol consumption were available.

data were found to be highly reliable in an internal validation study, as well as in other studies.[42,43] The reported weights at the age of 18 could not be validated in our cohort because of inadequate availability of records, but weight at the age of 25 self-reported by middle-aged men has previously been found to be quite accurate.[44] Coronary end points were documented by a review of the medical records according to standardized and uniform criteria.

Since the Quetelet index is an imperfect surrogate for body-fat composition (r = 0.6 to 0.8 with more direct measures of adiposity[45,46]), the resultant random misclassification will underestimate any true relation between adiposity and coronary heart disease. Consequently, the true magnitude of the effect of adiposity is likely to be greater than that observed in this cohort.

Dietary fat content and level of physical activity have been proposed as major determinants of adiposity.[47-49] The extent to which they may explain the association between obesity and coronary disease remains speculative. In our cohort, the dietary intake of saturated fat, polyunsaturated fat, monounsaturated fat, and cholesterol bore little relation to the Quetelet-index category; the mean intake of these nutrients after adjustment for age and total caloric intake was nearly identical across weight strata (Table 1). Thus, these variables could not materially affect the associations observed between adiposity and coronary disease. Physical activity was assessed in a random sample of 194 Boston-area participants, with a questionnaire developed by Paffenbarger et al.[50] An inverse correlation was observed between the Quetelet index and an activity index based on the number of blocks walked, stairs climbed, and sports participated in during the previous week (r = −0.31). If we assume that the relative risk of cardiovascular disease associated with a sedentary, as compared with a more active, lifestyle is 2.0 — as high an estimate as the literature generally supports[51,52] — physical inactivity could explain only a modest portion of the effect of obesity on coronary disease in this cohort. Recent evidence

Table 4. Influence of Quetelet Index at the Age of 18 on the Relative Risk of Coronary Heart Disease during Middle Adulthood in the Cohort.

VARIABLE	QUETELET INDEX*					MANTEL-EXTENSION χ	P VALUE
	<20	20–<21	21–<23	23–<25	≥25		
No. of person-years†	133,141	178,602	184,909	120,131	106,788		
Nonfatal myocardial infarction and fatal coronary heart disease‡							
No. of cases	50	74	73	58	81		
Relative risk (95% CI)§							
Adjusted for age	1.0	1.1 (0.8–1.6)	1.1 (0.8–1.5)	1.3 (0.9–1.9)	2.0 (1.4–2.8)	3.92	<0.0001
Adjusted for age and current Quetelet index¶	1.0	1.0 (0.7–1.5)	0.9 (0.6–1.4)	1.0 (0.7–1.6)	1.5 (1.0–2.3)	1.48	0.14

*The ranges of the Quetelet-index categories at the age of 18 are lower than those for current weight because of differences in the distribution of weights in the cohort at the younger age. The reference category is the group with a Quetelet index of less than 20.

†Values for weight at the age of 18 were missing in 19.2 percent of the cohort.

‡Denotes the combined end point of nonfatal myocardial infarction and fatal coronary heart disease.

§CI denotes confidence interval.

¶Adjusted for the current Quetelet index according to the most recent weight reported in the period from 1976 through 1984. The correlation of the current Quetelet index and that at age 18 was 0.52.

Table 5. Relative Risk of Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease (Combined) in Relation to Weight Gain since the Age of 18.*

Weight Gain (kg)	No. of Cases	No. of Person-Years†	Relative Risk (95% CI)	
			Adjusted for Age	Adjusted for Age and Initial Quetelet Index‡
<3	44	150,288	1.0	1.0
3–4.9	16	84,794	0.6 (0.3–1.1)	0.6 (0.4–1.1)
5–9.9	52	154,572	1.0 (0.6–1.4)	1.0 (0.6–1.5)
10–19.9	97	151,419	1.6 (1.1–2.3)	1.7 (1.2–2.5)
20–34.9	59	63,508	2.2 (1.5–3.2)	2.5 (1.7–3.7)

*Adjusted for age according to five-year categories. The group with a weight change (gain or loss) of <3 kg served as the reference category. The follow-up period was from 1976 through 1984. CI denotes confidence interval.

†Values for weight at the age of 18 were missing in 19.2 percent of the cohort.

‡The Quetelet index at the age of 18 was used in the adjustment for initial Quetelet index.

suggests that weight loss induced by either dieting or increased exercise produces comparable beneficial changes in plasma levels of high-density lipoprotein cholesterol and triglycerides.[53] Furthermore, the interrelations of physical activity and adiposity are extremely complex, because a sedentary lifestyle is both a cause and a consequence of obesity.

There have been few prospective studies of obesity and coronary heart disease in women. Noppa et al.[18] followed 1462 middle-aged women in Göteborg, Sweden, for 10 years, using skinfold thicknesses and an index of weight divided by height as a measure of adiposity. They found only a weak, nonsignificant association between obesity and coronary disease, but there were only 15 cases of myocardial infarction and 55 of angina, and the analyses were not controlled for cigarette smoking. In the Framingham Study,[54] Hubert et al. followed 2818 women 28 to 62 years of age for a 26-year period and found a strong positive association between relative weight and the incidence of coronary heart disease. In a large-scale study by the American Cancer Society, self-reported weight was associated positively with mortality from coronary heart disease, approximately doubling the risk in persons more than 40 percent above the average weight.[55] Control for cigarette smoking increased these mortality ratios further. Nonfatal coronary events were not included in the analyses, however. Tuomilehto et al.[56] studied 4120 women 30 to 59 years of age in eastern Finland, among whom 52 had myocardial infarctions during seven years of follow-up. These investigators found no statistically significant association between the Quetelet index and the rate of myocardial infarctions, but the small number of events may have precluded the detection of even a moderate association. None of these studies evaluated the potential contribution of dietary factors or physical activity to the association between obesity and coronary risk.

Studies of relative weight and coronary heart disease in men have also yielded apparently conflicting results.[11-17,19-23,54,55] Apparent discrepancies among these studies can be explained at least in part by the effect of a small sample, differences in the surrogate measures of adiposity, failure to control for cigarette smoking or weight changes due to previous disease, or a tendency to equate the true effect of obesity with its residual influence after control for the effects of adiposity, such as hypertension, glucose intolerance, and dyslipoproteinemia.[57]

Several studies have suggested that besides the overall quantity of excess fat, the pattern of body-fat distribution or somatotype may have important effects on the risk of coronary heart disease.[58,59] The deposition of fat predominantly in the abdomen and upper body has frequently been associated with abnormalities of blood pressure, glucose tolerance, and serum lipid levels.[58] We do not have data from our cohort to address this issue. If any one aspect of obesity is related more specifically to coronary disease, our results would provide underestimates of the magnitude of the association.

In conclusion, obesity is a strong risk factor for coronary heart disease in middle-aged women. Even mild-to-moderate overweight is associated with a substantial elevation in coronary risk. Weight gain during adulthood further increases the risk. As much as 70 percent of the coronary disease observed among obese women and 40 percent of that among women overall is attributable to overweight and is therefore potentially preventable. Multivariate analyses indicate that although a major portion of the excess coronary risk is attributable to the influence of adiposity on blood pressure, glucose tolerance, and lipid levels, a moderate residual effect persists that may be due to other mechanisms. Differences in dietary fat intake or physical activity do not appear to explain these findings. These data indicate that obesity is a major cause of excess morbidity and mortality from coronary heart disease among women in the United States.

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