Relation of Body Weight to Development of Coronary Heart Disease

The Framingham Study

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SUMMARY

Interrelationships between weight change, serum cholesterol, blood pressure levels, and the risk of developing coronary heart disease have been explored in 5,127 men and women who have been followed over 12 years for signs of initial development of coronary heart disease. Antecedent relative weight and weight gain after age 25 years proved to be strongly related to risk of angina pectoris and sudden death but were unassociated with development of myocardial infarction. An excess risk of angina pectoris and sudden death appeared to exist in obese men both with and without elevations of blood pressure and serum cholesterol, indicating an independent contribution of obesity to the rate of development of these manifestations of coronary heart disease. Unless accompanied by an increase in blood pressure and serum cholesterol level, obesity appeared to play a negligible role in women. Subjects with both these predisposing factors and obesity had a pronounced increase in risk, greater than that associated with either factor alone. The data suggest that overweight may be instrumental in bringing out symptoms of angina pectoris or in precipitating sudden death by imposing an increased workload on a heart with an already compromised coronary circulation.

ADDITIONAL INDEXING WORDS:
Obesity Cholesterol Hypertension Sudden death Myocardial infarction Atherosclerosis

The results of many studies of the relationship of body weight and obesity to coronary heart disease (CHD) in the past several decades have, in general, tended to show an excess of the disease in the obese.1-4 Other investigations of the problem have, however, failed to show any clear-cut relationship.5-9 This has resulted in uncertainty concerning the role of obesity in the development of atherosclerosis and CHD. In general, studies of large population groups have tended to show a relationship of weight to CHD, while investigations of smaller groups, particularly those confined to men, and comparing cases and controls, have not.7,8

Even prospective longitudinal studies, which are more free of possible selective sampling bias, while tending to show an excess risk in the grossly obese, have not demonstrated a consistent relationship between body weight and the rate of development of CHD.10-12 This prompted a detailed study of the relationship of body weight to CHD in the Framingham Study, which has been following a sample of the adult population of the town of Framingham, Massachusetts, for the past 12 years. In this study, a modest relationship between gross obesity and CHD had been noted previously.13,14 Since the grossly obese had, on the average, higher blood pressures and serum cholesterol levels, even this relationship to development of disease seemed secondary. Now that a sufficient number of

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persons in the population under surveillance have developed CHD, it has been possible to explore in more detail the independent contribution of body weight and weight change to the development of each manifestation of CHD.

Methods

In an effort to delineate the factors related to the development of CHD, the Heart Disease Epidemiology Study of the National Heart Institute at Framingham, Massachusetts, has been studying 5,127 men and women aged 30 to 62 years. This study group was derived from the respondents of a random sampling of 6,507 adult men and women residents of Framingham. An additional 740 volunteers were added after separate analysis, up to the time of the fourth biennial examination, revealed a morbidity and mortality experience and distribution of personal characteristics almost identical to the respondents of the original sample.15

This study group of 5,127 men and women has been followed since 1949, providing 12 years of follow-up. At the time of the seventh biennial examination only 1.2% of the study group was completely lost to follow-up for myocardial infarction and fatal episodes of coronary heart disease.

Details of the sampling procedure, type of cardiovascular examination, criteria for diagnosis of CHD, and general methodology have been reported previously.10, 15–17

By means of an investigation of the subsequent rate of development of initial events of CHD in the population sample classified on the initial examination according to their habits and personal attributes, various factors of risk have been identified and highly susceptible individuals delineated.10, 13, 14, 16 Effort is being made to assess the independent contribution of each of the various interrelated factors so identified. The present report focuses on body weight.

Subjects were grouped on the basis of relative weights determined on the initial examination, and the rate of development of manifestations of CHD was compared in the several groups. The relative risk of developing CHD was expressed as a “morbidity ratio,” comparing the number of observed cases to the number expected for each particular subgroup of the population. This fraction was multiplied by 100 to produce whole numbers. The expected number of cases was calculated by applying, in each sex, the age-specific incidence rates (in 5-year groups) for the whole population to the subjects in the particular subgroup of the population under consideration. If relative weights were entirely un-

related to the subsequent incidence of disease, the number of cases observed would approach that expected and would produce a morbidity ratio close to 100.

Examination of the relation of body weight to development of CHD requires consideration of the proper method for expressing this variable. Rather than expressing weight in absolute terms, a relative expression of weight, taking the size of the individual into account, seemed more appropriate. Examination of the problem in terms of the presence or absence of obesity seemed arbitrary, except as a convenience for tabulation, since it is not known in any absolute physiological sense, what is a normal or obese weight. Adiposity may be confused with muscularity. Since the major interest in this investigation was to relate adiposity to morbidity and mortality from CHD, a relative expression of weight was adopted. In addition, risk of developing disease was determined in relation to weight gain after completion of musculoskeletal growth (that is, from age 25 which is also particularly apt to reflect adipose tissue accumulation).

The relative weight indicates the deviation of each individual’s weight from the median of the population to which the subject belongs with respect to height and sex. Thus for example, a person who was just at the median weight for his height was assigned a “Framingham Relative Weight” (“FRW”) of 100, and a person 20% above the median was assigned an FRW of 120. The relation of weight to the later development of disease was examined in various subgroups of the distribution of the FRW on the initial examination. This relation was also studied using weight gain after age 25, and on occasion, using an arbitrary designation of obesity (FRW, 120 or greater).

Figure 1

New coronary heart disease according to clinical manifestation; 12 year follow-up, Framingham heart study.
Because of the possible effect of higher than average blood pressure and serum cholesterol levels, the relationship of relative weight to development of manifestations of CHD was examined at specified levels of blood pressure and serum cholesterol. Since such a cross-classification requires large numbers of subjects, it was possible to do this only within certain limits. Persons with either an elevated blood pressure (that is, at least 160 systolic or 95 diastolic) or an elevated cholesterol level (greater than 250 mg%), or both, were contrasted with respect to obesity with those having neither of these. In this way it was possible to determine the effect of both obesity and elevation of blood pressure or cholesterol level on the development of each manifestation of CHD in both sexes, each independent (within limits) of the other.

Overt CHD is manifested by a number of clinical syndromes: angina pectoris, myocardial infarction, coronary insufficiency, and sudden, unexpected death. The criteria for these diagnoses have been defined elsewhere. Less certain manifestations including congestive heart failure in the elderly without other apparent cause, cardiac arrhythmias such as atrial fibrillation, and certain electrocardiographic abnormalities such as intraventricular block were excluded from consideration.

**Results**

**Sex Differences**

In 12 years of observation, 252 men and 128 women developed CHD. Examination revealed a difference in the clinical manifestations of this disease in the two sexes (fig. 1). The predominant manifestation in women was uncomplicated angina pectoris, while the men mainly developed the more serious and lethal forms of the disease.

There was a gradient of risk of developing CHD according to initial relative weight in both men and women (fig. 2). When the association between body weight and the rate of the development of each clinical manifestation of CHD was examined, certain interesting differences in this relationship became apparent. No striking or statistically significant association between relative weight on the initial examination and the rate of development of myocardial infarction could be demonstrated in either men or women (fig. 3). However, a striking relationship between the risk of developing angina pectoris and relative weight on initial examination was demonstrated in both men and women. The
Figure 3

Risk of myocardial infarction in 12 years according to obesity status at specified levels of systolic blood pressure and serum cholesterol. Men and women, 30 to 59 years of age at entry to Framingham heart study.

Figure 4

Risk of developing angina pectoris in 12 years according to Framingham relative weight. Men and women, 30 to 59 years of age at entry to Framingham heart study.
risk appeared to be related to the relative weight per se, and not to the presence of gross obesity alone (fig. 4). The gradient of risk, with increasing relative weight, was steeper in men than in women.

Sudden Death

Another manifestation of CHD which proved to be strongly related to overweight was the occurrence of sudden unexpected death. Because of the small number of sudden deaths in women, the relationship could be examined only in men. Those with relative weights of more than 20% above the median had a marked excess risk of sudden death due to CHD (fig. 5).

The demonstrated relationship of relative weight to risk of developing disease could reflect some other parameter of body build than adiposity. Weight increase subsequent to completion of musculoskeletal growth is most apt to reflect adipose tissue accumulation. The possible effect of adiposity on risk of angina pectoris was therefore further evaluated by an examination of the relation of weight gain after age 25 years in persons who were not already obese to the rate of development of disease. Increased risk of angina pectoris, proportional to weight gain, was observed (fig. 6).

Cholesterol Levels and Blood Pressure

While the accumulation of adipose tissue evidently is related in some way to the development of CHD, the mechanism remains obscure. Since changes in body weight are believed to affect blood pressure and cholesterol levels, and the latter are known to be related to risk of developing coronary disease, it is possible that the contribution of excess weight to increased risk of the disease is due to its association with the level of blood pressure and cholesterol.

In order to explore the interrelationship of

Figure 5

Risk of developing sudden death in 12 years according to Framingham relative weight. Men, 30 to 59 years of age at entry to Framingham heart study.
these variables further, assessment of the contribution of adiposity to risk of CHD independent of associated effect of blood pressure and serum cholesterol was sought by an examination of the risk of the various manifestations of CHD according to "obesity status" at specified levels of blood pressure and serum cholesterol. Persons with either elevated blood pressure or cholesterol level, or both, were contrasted with those having neither of these after being subdivided as obese and non-obese. It is of interest to note that even among those men who had neither an elevated blood pressure nor cholesterol level, the obese appeared to develop an excess of angina pectoris or sudden death (fig. 7). Those presumably predisposed to atherosclerosis, by an elevation of either the blood pressure or serum cholesterol, or both, were demonstrated to exhibit a definite increase in risk of sudden death or angina pectoris if, in addition, they were also obese. This would not be expected if adiposity was only acting through an association with elevation of blood pressure and cholesterol level. Conversely, independent effects of blood pressure and cholesterol level, quite distinct from the effects of adiposity, are also operative. As previously indicated, another evidence of a unique effect of adiposity was the absence of its relationship to risk of developing myocardial infarction, a manifestation of CHD strongly related to antecedent blood pressure and cholesterol level. Again, no relationship of obesity status could be demonstrated to the rate of development of myocardial infarction, either in those with or without elevated serum cholesterol and blood pressure levels, while a distinct
excess development of myocardial infarction was evident in any weight category in those with elevated blood pressure and cholesterol levels (fig. 3).

The augmentation of risk of angina pectoris by the occurrence of excess weight in hypertensive men was not simply the result of higher blood pressures in subjects with both these abnormalities since the blood pressures were only slightly higher (180 mm Hg versus 186 mm Hg average systolic blood pressure) in the obese. This small difference could not account for the degree of excess risk noted on comparing the obese with the nonobese.

Analysis of the independent contribution of adiposity to risk of angina pectoris in women in a similar manner, with the small numbers of cases available, revealed that adiposity in the absence of an elevated blood pressure or cholesterol level had no effect. Only in those women presumably predisposed by elevation of blood pressure or cholesterol level was there a possible excess risk among the obese (fig. 8).

Discussion

The evidence relating obesity and relative weight to the development of CHD has, in the past, been inconsistent. An excess of obesity, variously defined, has been reported in subjects with CHD, as compared to controls in some studies while no correlation has been found in other investigations. In some reports, only extreme obesity was noted to be associated with an increased rate of development of CHD. For a long time insurance statistics have associated obesity with excess mortality, largely from cardiovascular disease. In addition, it has been claimed that reduced mortality was noted in subjects re-rated for insurance following reduction of weight.

The data presented in this report suggest...
that the failure of controlled clinical and epidemiological studies to show consistent results concerning the relationship of body weight to development of CHD may well be the result of a failure to relate body weight to each specific overt manifestation of CHD. It is conceivable that conflicting reports result from the differences in the proportion of angina pectoris, myocardial infarction, and sudden deaths included in the series of cases being reported.

While the belief that obesity and cardiovascular morbidity and mortality are related is widely held, the exact nature of this relationship requires further clarification. Weight is only one parameter of body form, and it is possible that body build is more closely related to development of CHD than is adiposity. It could be lean body mass, muscularity, or adiposity that is important. Indeed, some investigators have claimed that while they could demonstrate no association between relative weight and CHD, they could show a relationship to body fat, as assessed by skinfold measurements. CHD has also been found to be related to body build, but not to body weight by other observers.

There are several possible mechanisms, physiological and metabolic in nature, by which obesity could produce an excess of CHD: (1) increased cardiac work load and blood pressure resulting from excess weight; (2) increase in the amount of coronary atherosclerosis resulting from higher caloric intake and increased lipid levels and blood pressure accompanying gain in weight; (3) decrease in physical activity associated with obesity, which may result in deficient development of collateral circulation in subjects with atherosclerotic involvement of the coronary arteries; and (4) combinations of 1 to 3 above. All of the factors enumerated could produce excess occurrence of myocardial infarction as well as angina pectoris and sudden death.

An increased cardiac work load in the obese appears necessary in order to maintain the increased oxygen supply demanded by the body. During exertion, an obese individual
may require as much as twice the oxygen consumed by the normal weight individual under the same circumstances. Although no direct measurements of blood flow to adipose tissue are available, by measuring splanchnic, renal, and cerebral blood flow it has been inferred by exclusion that the increased cardiac output associated with obesity is secondary to increased blood flow to adipose tissue. This increased cardiac work load must be accompanied by an increased oxygen supply to the myocardium. The coronary circulation is unique in that 75% of the oxygen presented to the myocardium is extracted. Because of the rather limited capacity of the myocardium to incur an oxygen debt and a concomitant high rate of oxygen extraction, the coronary blood flow must be capable of adjusting rapidly to the rate of oxygen consumption by the heart. Increased oxygen demands imposed by obesity, and the associated increased cardiac work load, require a supple coronary vascular bed capable of dilating to increase the coronary blood flow. The atherosclerotic individual, with a narrowed vessel lumen, does not appear to be able to do this adequately. If he is obese, myocardial ischemia and pain may occur when any additional burden is placed on the heart. The limited ability of the atherosclerotic coronary arteries to dilate was demonstrated by Gorlin and associates who measured coronary blood flow and vascular resistance before and after inducing vasodilation with nitroglycerin.

In addition to effects on circulatory dynamics and possible metabolic alterations associated with obesity, some mechanical disturbances which occur in the obese appear to contribute indirectly to impairment of cardiac function. In the obese, displacement of the heart by an elevated diaphragm, decreased respiratory excursion, and increased work required for breathing and moving about may cause a lowered vital capacity, ventilatory deficiency, carbon dioxide retention, increased oxygen debt, and increased hematocrit values.

In view of the evidence suggesting an increased cardiac work load in association with obesity, and less striking evidence of metabolic alteration definitely enhancing atheromatous formation, it is reasonable to assume that the association of relative body weight with the rate of development of angina pectoris and sudden death is based more on alteration of cardiac work load than on a metabolic derangement. Subjects with comparable amounts of coronary atherosclerosis who are not over-weight might tolerate an equal amount of physical exertion without developing angina pectoris since they lack the additional cardiac work load imposed by obesity.

Factors which precipitate clinical events and affect survival once an attack occurs are not necessarily the same ones as those predisposing to accelerated atherogenesis. While it is quite likely that adiposity makes some contribution to the atherosclerotic process by virtue of its association with higher than average blood pressure and lipid levels, it seems clear that it is primarily a precipitating factor. In subjects predisposed to atherosclerosis, with an already compromised coronary circulation, the development of adiposity appears to precipitate attacks of angina pectoris or a fatal ischemia-induced arrhythmia leading to sudden death. Why it does not also precipitate myocardial infarction is uncertain.

The data suggest that the usual mechanism producing angina pectoris and sudden death differ from that resulting in myocardial infarction. There is good evidence that the symptom of angina pectoris is related to the work load imposed on the heart. Also, it is reasonable to expect that some sudden deaths may result from an increased cardiac work load provoking a fatal ischemia-induced arrhythmia. Evidence of a direct relationship between actual myocardial infarction and an increased load on the heart is less certain.

While some myocardial infarctions appear to occur in the absence of actual occlusion, some evidence supports the contention that coronary artery occlusion is responsible for most actual infarctions. In instances in which occlusions are not found, the evidence suggests that postmortem lysis of a fresh unorganized thrombus may have taken place in...
subjects dying soon after a thrombotic occlusion. Spain and Bradess have shown that the proportion of actual occlusions demonstrated at necropsy increased with the time interval between onset of symptoms and death. Hence, angina pectoris and sudden death may be acute ischemic phenomena, not necessarily dependent on actual occlusion, while myocardial infarction usually requires actual occlusion, and this is not precipitated by ischemia alone.

Obesity is as much a product of sloth as of gluttony. At the very least, it tends to promote sedentary living. Lack of physical exercise, in the presence of a compromised coronary circulation, fails to promote collateral circulation. Once an occlusion occurs, such individuals are less likely to survive an attack. Obesity also increases the cardiac work load in such individuals and is apt to bring on angina pectoris. Neither of these mechanisms appears to contribute to the development of myocardial infarction, since their contribution to the underlying atherosclerotic process is modest.

Avoidance of obesity because of its association with higher blood pressure and cholesterol level would appear desirable in a preventive program designed to delay the onset of all manifestations of CHD. In subjects already predisposed to atherosclerosis by virtue of elevated blood pressure and cholesterol levels, a program of weight reduction would presumably achieve a decrease in the level of these risk factors, and, at the same time, decrease the cardiac work load and increase exercise tolerance. Risk of sudden death, which is considerable in such subjects, would be expected to decrease. Obese subjects with myocardial infarction would very likely have improved exercise tolerance following weight reduction and might be expected to develop less angina pectoris or an improvement in an already established anginal syndrome. Subjects with established angina pectoris induced to lose weight should exhibit improved exercise tolerance and a lower risk of sudden death.

References


S. Weir Mitchell on The Physician, 1887

There are those of my profession who have a credulity about the action of drugs, a belief in their supreme control and exactness of effect which amounts to superstition, and fills many of us with amazement. This form of idolatry is at times the dull-witted child of laziness, or it is a queer form of self-esteem, which sets the idol of self-made opinion on too firm a base to be easily shaken by the rudeness of facts. But, if you watched these men, you would find them changing their idols. Such too profound belief in mere drugs is apt, especially in the lazy thinker, to give rise to neglect of more natural aids, and these tendencies are strengthened and helped by the dislike of most patients to follow a schedule of life, and by the comfort they seem to find in substituting three pills a day for a troublesome obedience to strict rules of diet, of exercise, and of work.—S. Weir Mitchell: Doctor and Patient, ed. 4. Philadelphia and London, J. B. Lippincott Company, 1904, p. 27.
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