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Defining obesity: An adventure in cardiovascular disease epidemiology

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While the association of overweight and health, as well as longevity, has been scrutinized in volumes of research, the association of overweight with cardiovascular disease is a dominant theme in the medical literature. This report will detail the arguments and present selected summaries of published reports that support the emerging consensus that overweight and obesity have the major causal role in the ongoing epidemic of cardiovascular disease in the United States. Examples will include relative risk and attributable risk estimates for several metabolic perturbations caused by overweight, including type 2 diabetes mellitus and hypertension. Results of the Nurses Health Study, which found a fivefold increased risk of type 2 diabetes among women with body mass index between 24.0 and 24.9 compared to the referent group with body mass index ≤22, will be highlighted. The presentation will also explicitly identify the position of excess adiposity in the causal chain that leads from overnutrition to the majority of cardiovascular disease. Based on the position in the causal sequence, a strategy for defining the threshold of "overweight" will be described. From the foregoing, it is concluded that the overweight threshold should be no higher than body mass index =25. Finally, it is concluded that the majority of men and women with a body mass index between 22 and 25 are overweight and should be identified and appropriately counseled to improve nutrition and increase physical activity. (J. Nutr. Biochem. 9:493–500, 1998) © *Elsevier Science Inc. 1998*

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Introduction

During the last several decades, the epidemiology of cardiovascular disease (CVD) has developed into a cohesive story that convincingly implicates several lifestyle attributes as causal factors of most of the many manifestations of the disease. The story has unfolded not without episodes of controversy and serious disagreement among the investigators who have undertaken this research endeavor. One issue that captured major attention over several decades was the role of obesity, or overweight resulting from adiposity, and whether it plays a primary or causal role in cardiovascular disease. For reasons that are becoming increasingly well understood, the case against overweight was not an easy one to make and a cogent, correct description of the role of obesity is still needed.

From the 1960s, when short term results of some of the first well designed prospective studies of coronary artery disease (CAD) became available, there seemed to be equivocal, sometimes contradictory and often enigmatic, results regarding the role of overweight in CAD.[1,2] A commonly held position throughout the 1970s was that obesity per se had nothing to do with, or did not cause, CAD. As recently as 1985, the data presented to the National Institutes of Health Consensus Development Panel on the Health Implications of Obesity was, at best, equivocal on this issue.[3]

However, after the mid-1980s, there began a rapid shift away from the view that overweight did not play a causal role in CAD. This shift appeared to be the result of research that used longer periods of observation,[4] made critical assessments of previously published studies,[5] and expanded, or better defined, the meaning of "overweight."[6,7]

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In addition, research on large, well designed prospective investigations in both women[8] and men[9–11] became available. Finally, evidence that weight changes induce corresponding changes in major atherogenic risk factors became available,[12,13] further implicating overweight as a cause of CVD.

Thus, there is an emerging consensus that obesity or overweight, however defined, has a causal role in cardiovascular disease. This article will detail the arguments and present selected summaries of published reports that support this view. It will also explicitly identify the position of excess adiposity in the causal chain that leads to the majority of cases of CVD. Finally, based on the position in the causal sequence, a strategy for defining the threshold of "overweight" will be outlined.

Cardiovascular disease defined: The big bad picture

CVD is the most pervasive health problem in the United States. The numerous manifestations or clinical expressions of the disease include myocardial infarction (MI), stable and unstable angina pectoris, sudden death, stroke and transient ischemic attack, congestive heart failure (CHF), and peripheral vascular disease. Most would agree that the majority, if not most, cases of end-stage renal disease (ESRD) also should be classified as cardiovascular disease.

These maladies caused over 962,000 deaths in the United States during 1995. As high as the death rates from CVD are, there are other important statistics that characterize the current epidemic of CVD in the United States. For example, it has been estimated that in 1995 nearly 58 million U.S. residents had CVD that resulted in approximately 5.8 million hospital admissions. A large proportion of these hospital admissions involved the application of new and expensive life-saving technologies. Such procedures, while undoubtedly saving thousands of lives each year, have contributed substantially to the enormous cost of the CVD epidemic. Cardiovascular accident (CVA) causes more disability, both long and short-term, than accidents and all other diseases combined. In addition, hospital stays are longer following stroke than any other acute illness. CHF and ESRD, organ failure of the heart and kidneys, respectively, can be characterized as outcomes with poor prognoses and very poor quality of life for the victims. Both outcomes often occur following the occurrence of other CVD events (such as CHF following MI) but they can and do occur in patients with only a history of diabetes, hypertension, or both. When the various manifestations are combined, the cardiovascular disease epidemic in the United States generates a burden of death, suffering, and medical utilization that dwarfs all other diseases.

Understanding the causes of cardiovascular disease

The big picture of cardiovascular disease epidemiology emerges from approximately 50 years of study that began in the late 1940s upon recognition of soaring deaths rates from MI. The strategy that proved most successful for identifying the causes of CVD was the prospective study in which large samples were observed over time for the development of specific CVD or CVD-related outcomes. The Framingham Study was one of the first and largest prospective or longitudinal cohort studies to report on the suspected causes of coronary heart disease (CHD).[14] The strategy of measuring an attribute such as cigarette smoking and following participants for fixed periods, such as 2-year increments, for the development of MI or CHD provided strong evidence that smoking is associated with CHD. Estimating the strength of the relationship, if it was detected, was also important. Usually the relationship between a risk factor and an outcome event such as MI was measured by the relative risk. The higher the relative risk (i.e., the ratio of incidence of new disease in the exposed [smokers] to the incidence of disease in the unexposed [nonsmokers]), the more likely the relationship might be deemed causal, given biologic plausibility.

Measures of the Association Between Lung Cancer and Cigarette Smoking

Lung Cancer Deaths in Smokers	191/100,000/Yr
Lung Cancer Deaths in Non-Smokers	8.7/100,000/Yr
Relative Risk of Lung Cancer for Smokers	22 (191/8.7 = 22)
Population Risk of Lung Cancer	72.5/100,000/Yr
Population Attributable Risk of Lung Cancer to Smoking	63.8/100,000/Yr (72.5 - 8.7 = 63.8)
Population Attributable Risk Percent	88% (63.8/72.5 x 100 = 88)

Figure 1 Measures of the association between lung cancer and cigarette smoking.

Once causality is established, one can estimate the population attributable risk percent (PAR), a different and more meaningful measure of association between a causal factor and disease. *Figure 1* shows the calculation of relative risk and PAR for lung cancer and its principle cause, cigarette smoking. The conclusion from the last line of *Figure 1* is that cigarette smoking causes 88% of all cases of lung cancer. Thus, while relative risk estimates the risk of disease for individuals, comparing the risk of those exposed to the causal factor to individuals who are not exposed, the PAR measures preventability of a disease. Specifically, PAR measures the percentage of the disease that results from the presence of the causal factor in the population. Therefore, the PAR is more useful in the context of summarizing the impact of a causal factor on the disease level of a population.

Identification of causal factors and the estimation of the strength of associations is the major work of CVD epidemiologists. The final step in understanding CVD and its numerous manifestations is to define a causal structure or logical paradigm that incorporates the knowledge about the

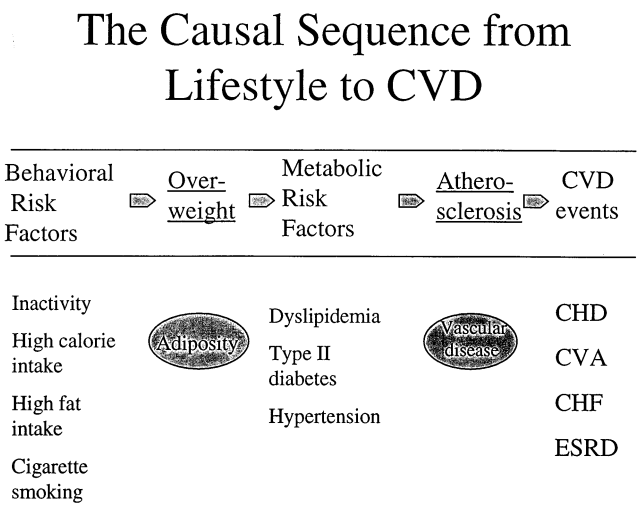

Figure 2 The causal sequence from lifestyle to cardiovascular disease (CVD). CHD, coronary heart disease; CVA, cerebrovascular accident; CHF, congestive heart failure; ESRD, end-stage renal disease.

precursors and causes of CVD that has accumulated in the literature. *Figure 2* displays a proposed causal structure for most CVD events. Beginning from the left, this paradigm assumes that lifestyle or behavioral factors are the primary initiating causes of a sequence of pathologic changes that include overweight, various metabolic perturbations, atherosclerosis, and finally overt, clinically apparent CVD.

The volumes of literature that support the detailed schema shown in *Figure 2* cannot be cited in this document but an overview of the historical perspective, logical support, and specific examples of data that support the paradigm will be presented. First, however, it is important to recognize that this paradigm is intended to summarize the general (epidemic) causal sequence involved in most, but not all, CVD. There are exceptions: individuals who exercise adequately, eat a healthy low fat diet, and never become overweight but still fall victim to CVD, are rare, but they do occur. Most such cases probably result from lipoprotein metabolism maladies, which often have an hereditary basis. Second, this paradigm cannot capture all of the complexities of the causal pathways from lifestyle to CVD. For example, even the segment from atherosclerosis to CVD events is the subject of a vast amount literature that documents a complex pathologic process from which CVD events evolve. Finally, the placement of cigarette smoking deserves special note. While smoking is clearly a behavior and a risk factor for CHD and CVA, the mechanism(s) by which it causes atherosclerosis (possibly through alteration in lipoprotein metabolism) or aggravates atherosclerotic status (possibly through clotting perturbations) have not been specifically delineated. Clearly smoking does not play a role in causing overweight, as most literature suggests smokers are likely to be underweight and, at least temporarily, to gain weight on cessation of smoking.[15] It is also important to acknowledge that smokers are a very special group in terms of risk for CVD because they can develop dyslipidemia, atherosclerosis, and CVD without being overweight.

An overview of the epidemiology of CVD from an historical perspective reveals a pattern of discovery that is not inconsistent with the logical framework of *Figure 2*. Long before there was suggestion of "risk factors" for CVD, the results of necropsy study of CVD victims revealed that atherosclerosis was usually present and appeared to be the common underlying cause of nearly all CHD and most CVA. In contrast, uncovering sedentary living as a risk factor for CHD and CVA was difficult and occurred much later.[16,17] This sequence of discovery was not so much an accident of science as it was the result of the actual causal sequence that determines CVD in the vast majority of victims, since a risk factor that is immediately proximal to disease *should* be the first to be identified, because of its strong, nearly singular relationship to the disease. A risk factor that is related to atherogenesis, that is, contributes to disease gradually and over a long period of time, varies with time during life and is difficult to measure, and if not immediately proximal to disease, is likely to elude detection. In addition, the case for exercise in protecting against CVD was slow in gaining acceptance because of studies that documented that vigorous exercise could trigger CVD events in the unfit individual. This apparent bi-directional association of exercise with CVD was finally fully explained and documented by Blair in 1995.[18]

Logical support for this paradigm comes from a vast amount of literature that describes the associations across the five distinguishable levels in the causal sequence depicted in *Figure 2*. In general, the literature documents that the factors that are close together in *Figure 2* have stronger associations than factors that are further apart. For example, inactivity is more strongly related to extravascular tissue adiposity than it is to hypertension, atherosclerosis, or CHD. In addition, the metabolic risk factors are more strongly related to CVD events than are the behavioral risk factors. Clearly, this logical framework is consistent with the view that the CVD epidemic is lifestyle driven, the major contributions being from overnutrition and cigarette smoking.

While the detailed evidence for each of the relationships depicted in *Figure 2* cannot be fully enumerated here, it is clear that some portions of the paradigm are more explicitly supported by the epidemiologic evidence than others. In general, however, the causal sequence from overnutrition (through obesity or overweight) to metabolic perturbations that cause atherosclerosis and ultimately various manifestations of CVD is plausible and supported by strong scientific evidence.

One example of this evidence is relatively new information from the Nurses Health Study regarding the close relationship between overweight and Type II (adult onset) diabetes mellitus. Colditz et al.[19] describe the relationship between body mass index (BMI) and the 14-year incidence of Type II diabetes. In this study, women with BMI of 22 or less at baseline had the minimum incidence of Type II diabetes. Risk rose rapidly as baseline BMI increased. For example, the relative risk of Type II diabetes was 5.0 (i.e., five times greater) when BMI was only moderately elevated at 24.0 to 24.9. When BMI reached 30, the relative risk soared to 27.6. This report also provides the information necessary to calculate the PAR for Type II diabetes, or the proportion of adult onset diabetes that is caused by elevations of BMI above 22. As shown in *Figure 3*, this

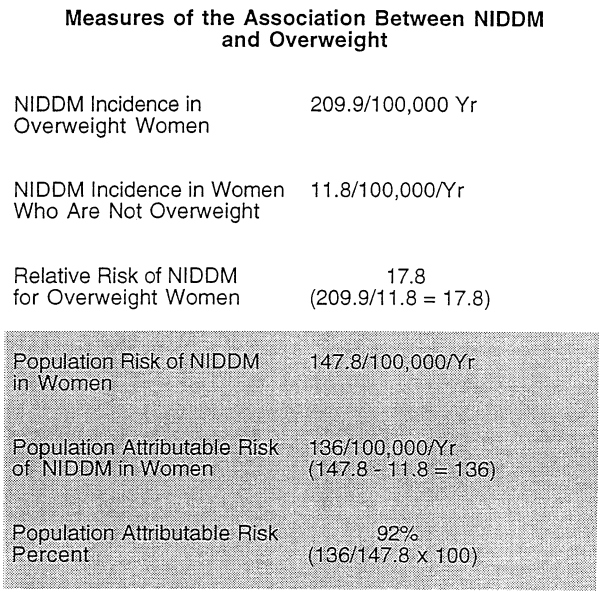

Figure 3 Measures of the association between non-insulin-dependent diabetes mellitus (NIDDM) and overweight.

calculation yields a PAR estimate of 92%. Thus, the causal linkage between overweight and adult onset diabetes appears to be even stronger than the linkage between smoking and lung cancer. Similarly, estimates for the impact of overweight on hypertension and dyslipidemia provide convincing evidence, if not slightly smaller PAR estimates, that overweight is the cause of most hypertension and dyslipidemia.[12,20]

Perspectives on the definition of obesity

Consensus on a definition of obesity, or excess adiposity, continues to elude medical science. This article will not attempt to itemize the suggestions for thresholds of overweight or obesity or enter the debate on the appropriateness of each. Continuing confusion on this issue does not allow even the astute and dedicated scientist to reach a quick conclusion on the population importance or attributable risk of obesity in the causation of CVD. If precise and valid measures of adipose tissue deposition (location, quantity, and quality) were available in the current large, well designed, and well executed epidemiologic studies of CVD, there would likely be little debate or confusion on this issue.

The current widely available measure of overweight is relative weight usually expressed as BMI (measured in kg/m^2). Thresholds for overweight or obesity in the recent literature vary from BMI of 22 to BMI of 30. Between these extremes are commonly used thresholds near BMI of 27[21] and BMI of 25,[5] as well as recommendations for age specific thresholds.[22] One of the reasons for confusion on this issue, as Manson et al.[5] point out, is that many studies fail to control for co-morbid factors that increase mortality but decrease weight. Despite the cogent and persuasive arguments made by Manson et al. in 1987, more recent publications continue to perpetuate the confusion.[23] Another reason for confusion is the diversity of outcome criteria that have emerged in the literature. No longer is total mortality the gold standard for determining "desirable," "healthy," or "ideal" weight for height. Clearly, this shift away from total mortality is appropriate in the era of modern medicine, in which previously fatal natural history of disease has been so drastically changed.

Depending which threshold is used to define obesity, the prevalence of obesity in adults in the United States varies between 22.5% (BMI threshold of 30) and 54.4% (BMI threshold of 25). Obviously, conclusions regarding the population attribution of CVD to obesity are heavily influenced by the threshold definition, with high BMI thresholds attributing little of CVD to obesity and low thresholds attributing potentially sizeable portions. Thus, the estimation of this threshold has a critical impact on quantification of where we will place overweight as a preventable contributor to disease. If the threshold is at low levels of BMI, the attributable risk will be estimated to be greater than if the threshold is determined to be at a higher level of BMI. While the determination of the threshold has important implications that are difficult to ignore, from the public health planning and medical utilization perspectives, they must be ignored. High quality scientific evidence should be used to objectively determine the threshold.

We propose that this threshold be determined by objective criteria using the logical framework described above. This paradigm suggests that the most appropriate indices of healthy weight are the metabolic risk factors that are most intimately connected with adiposity rather than the disease outcomes, such as CAD, that are more removed in the causal pathway. Because most of the variation in these metabolic factors is caused by variation in adiposity level, the nature of their relationship should be useful in determining an objective criterion for obesity. An example of how this can be accomplished is available from the Framingham Heart Study.

Toward objective criteria for optimal body weight

Between 1971 and 1975 a second Framingham cohort was enrolled for study. This cohort consists of the offspring (and their spouses) of the original cohort members, who were adults at the time of initiation of study. These study participants are often referred to as the Framingham offspring cohort. Offspring who had both parents in the original Framingham cohort were the first to be invited to the study. Spouses of these offspring were also enrolled whenever possible and the children of other members (without spouses) in the original cohort were also invited to participate. When recruitment was completed the offspring cohort consisted of 5,124 men and women aged 9 to 72 years. Most participants (92.1%) were aged from 20 to 54 years at the time of their initial examination between 1971 and 1975.

This initial examination was intended to screen participants for existing cardiovascular disease and obtain a medical history and baseline measurements of body weight, plasma lipoprotein levels, and blood pressure. Those who participated in this initial examination were invited to a

Table 1. Mean of cardiovascular risk factors and RSS and the relationship of each risk factor to RSS by gender

	Men		Women	
Risk factor	Mean	Beta	Mean	Beta
SBP (mmHg)	121.70	0.434	110.40	0.292
DBP (mmHg)	78.80	0.245	72.70	0.182
TC (mmol/L)	4.92	0.022	4.68	0.010
HDL (mmol/L)	1.16	−0.007	1.42	−0.008
LDL (mmol/L)	3.18	0.015	2.86	0.014
GL (mmol/L)	5.43	0.011	5.07	0.009
RSS (mm)	19.80		18.90	

RSS, right subscapular skinfold; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; GL, blood glucose level.

second, more extensive evaluation that began in 1979, approximately 8 years after the initial examination. Since 1979 the offspring cohort has been invited to participate in quadrennial evaluations. The offspring cohort members were asked to come to the Framingham clinic in the morning without having eaten breakfast. No remuneration was given to participants (including travel costs) but a light snack was provided to those who requested it after blood was drawn for testing. A 12-lead electrocardiogram was performed by a technician prior to an extensive physician-administered physical examination. The physician also performed two measurements of the systolic and diastolic blood pressure and completed the medical history interview, which included questions about medication use, cigarette smoking, and alcohol consumption. A nurse measured skinfold thickness at 1 inch below the right scapula, as well as stature and weight. The fasting blood specimen was used to measure the cholesterol content of high- (HDL) and low-density lipoprotein (LDL) fractions using Lipid Research Clinic methodology, and total cholesterol and plasma glucose were measured using standard laboratory methods.

Table 1 lists the mean values of right subscapular skinfold (RSS) thickness and the CVD risk factors as well as the age-adjusted regression coefficient for the regression of each risk factor on RSS for 20- to 30-year-old men and women. All CVD risk factors are statistically significantly related to RSS in both men and women in this group of young adults. With the exception of total plasma cholesterol, in which the regression coefficient for men is more than two times greater than for women, relationships appear to be very similar in women and men. This similarity holds despite consistently more adverse mean values of the CVD risk factors in men. Although the strength and shape of the relationships vary, all measures show an unfavorable association with adiposity. The decile of RSS that had the lowest average (highest HDL cholesterol) was determined and a summary threshold was determined based on the maximum decile for which any CVD risk factor had a minimum value. This resulted in a healthy adiposity threshold of RSS of less than 12 for men and less than 15 for women.

When men and women with RSS at or above these levels were excluded, there remained only 89 men and 380 women nonsmokers (ages 20–59 years) who could be considered to have healthy adiposity status. The mean BMIs for this group of men and women were 22.6 and 21.2, respectively. The comparison of these distributions with the BMI distribution of the entire sample allows an estimate of the probability of having an unhealthy adiposity level for each individual unit of BMI as shown in *Figure 4*. The body adiposity percentage (BAP) curve appears to rise more rapidly in men than in women as BMI increases but it reaches a plateau with probabilities of over 0.90 in both genders at a BMI of 25.

Thus, the BAP curves show that men and women with a BMI above 24.5 have a very high probability (above 0.90) of having adiposity in excess of that which is consistent with optimum cardiovascular health. Furthermore, individuals with a BMI greater than 22 have a high (above 0.50) probability of unhealthy adiposity levels. Individuals at these levels are strong candidates for careful evaluation to determine whether they have unhealthy adiposity levels. Even men with a BMI as low as 21 should be considered for more careful testing. Thus, these findings suggest that prevalence estimates of overweight using a BMI of 25 are too low and that a substantial percentage of men and women with a BMI of 22 or greater but less than 25 are, indeed, overweight.

Given the recent documentation that most attempts to lose weight are unsuccessful,[24] findings such as these might be taken as entirely unrealistic. However, arguments can be made that the large number of moderately obese middle-aged individuals might appropriately be targeted for weight loss because they make up a very large “at risk” group in which success in even a relatively small proportion of subjects would be expected to relieve a substantial burden of overt disease, suffering, and medical resources. There is also a possibility that such individuals have less ingrained obesity-promoting lifestyles and would be more amenable to changes to lower adiposity levels.

Because CVD is the major cause of morbidity, disability, and death, and is a dominant and growing focus of medical resources in North America, it seems most appropriate that the measures of health used in this report all are established “risk factors” for clinically recognizable CVD. Although the use of these risk factors to define “health” may seem arbitrary, the fact is that these attributes are the focus of most current health screening efforts in asymptomatic individuals. In the future, the availability of large samples for detailed biochemical studies and noninvasive testing should result in better definitions of health involving many different organ systems.

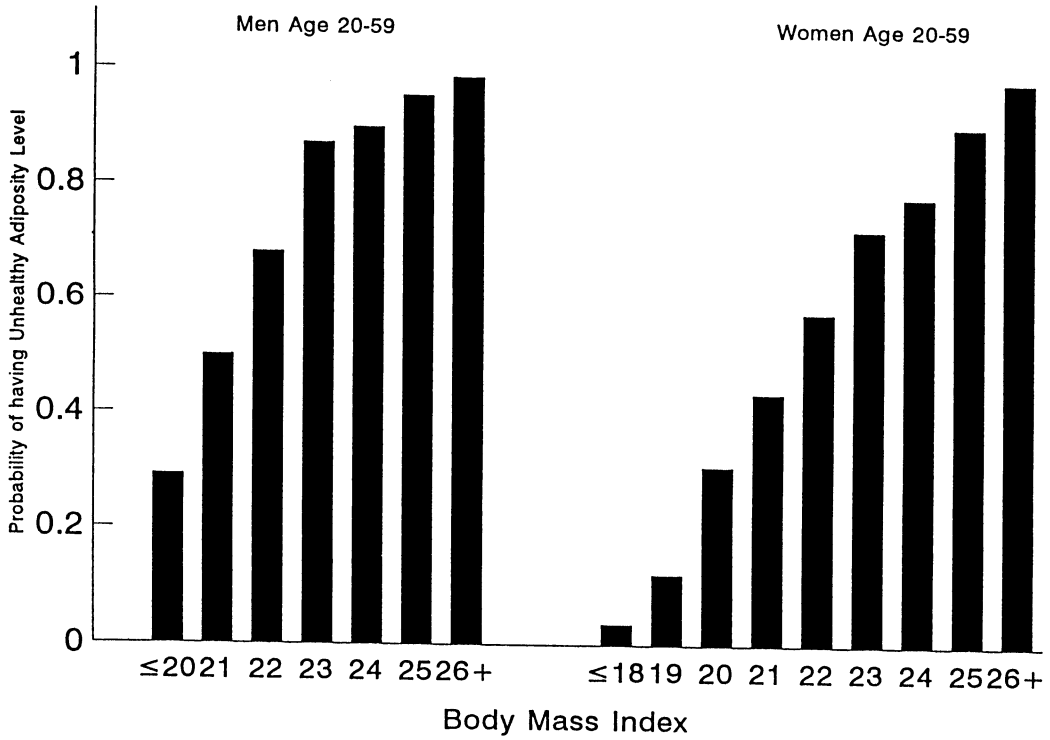

Figure 4 Body mass index adiposity probability curves for men and women, ages 20 to 59 years.

The partners of perplexity: Heterogeneity of response and homogeneity of exposure

The consequences of atherosclerosis seem to be very diverse, given how relatively homogeneous and complete the exposure of the population to the atherogenic lifestyle.[25] It is obvious that two individuals with equivalent adiposity exposures do not necessarily experience the same overt CVD consequences. The reasons for such disparities are not as well understood as the underlying causes of atherosclerosis, but there is evidence that implicates genetic causation of the heterogeneity of response. There are several well documented genetically determined causes of the diversity of response. For example, certain genotypes have easily discernible alterations in lipoprotein metabolism that have drastic impact on propensity for atherogenesis. Information about more subtle differences in lipoprotein structure and function is rapidly expanding and continues to contribute to the evidence that similar overnutrition in different individuals can have very diverse impacts on the pace and extent of atherosclerosis. In addition, the hypertensive response to overnutrition, characterized by adiposity and elevated salt intake, appears to have a strong genetic determination. Genetic differences are the most likely explanation for why some obese individuals never develop hypertension, while most do.

The proposition that, not only does overweight matter, but the location of adiposity is relevant to risk of CAD is an important example of heterogeneity of response to overnutrition. In addition to the large epidemiologic studies such as that of Rimm et al.,[26] which has shown the predictive value of waist/hip measurement in older men, studies by Prineas et al.[27] and Folsom et al.[28] have documented similar trends in women aged 55 to 69 years for CAD death and for CVD death, respectively. Recent reports add to the evidence by exploring the mechanisms that might explain the findings of the larger studies. Among them is a report by Katzel et al.[29] that used exercise electrocardiography and tomographic thallium scintigraphy to establish the presence of myocardial ischemia in volunteers who had no symptoms of CAD. When compared with the subjects who had no silent ischemia, those with disease had a significantly higher waist:hip ratio (WHR). These findings were further strengthened when they found similar elevations in WHR in a comparison group of patients with overt CAD.

An even more revealing study was reported by Walton et al.,[30] which measured adiposity distribution directly by dual energy X-ray absorptiometry (DEXA). In 103 men, serum total cholesterol, serum triglyceride, HDL, and LDL were found to have expected univariate associations with both adiposity and adiposity distribution. However, in multivariate analysis, only increasing android-to-gynoid ratio was found to be related to triglyceride and decreased HDL. Thus, this report identifies new details regarding the nature of the adiposity–CAD relationship but was not able to identify whether adipose tissue within the abdomen (visceral fat) was responsible. A study by Nakamura et al.[31] provides these details.

Nakamura et al.[31] studied the location of abdominal fat in men with CAD who were not overweight (BMI range 18.7–26.3), and compared it with men of the same age and BMI who did not have CAD. Computed tomography was used to measure visceral fat area (VFA) and subcutaneous

fat area at the level of the umbilicus in both groups. The mean VFA was significantly higher in the CAD patients and the percentage of CAD patients with elevated VFA was also higher. The patients with elevated VFA also were more likely to have abnormal glucose tolerance tests, a finding that confirms numerous other reports of such an association.[32,33] This study not only identifies visceral fat as an important source of risk factor perturbations that increase the risk of CAD, but it also suggests an explanation for the occurrence of CAD in the BMI 22 to 25 range.

Closing the book on obesity and CVD: The recent chapter

Finally, it must be noted that the recent reports from large prospective studies add validity to the logical framework presented in *Figure 2*. These studies show that when sample sizes are large enough to incorporate adequate numbers of low weight (BMI $\leq$ 25) nonsmokers, there is power to detect the benefit of low BMI levels. Two prospective studies have made major contributions to the understanding how much overweight is needed to elevate the risk of CAD. Willett et al.[34] present the results of a 14-year follow-up of 115,818 women who were between 30 and 55 years old at the beginning of their study in 1976. Baseline information, including weight and height was gathered with a self-administered questionnaire returned by mail. The investigators restricted their analysis to women who had no history of diagnosed CAD and who were not pregnant when the questionnaire was completed. CAD that occurred in the 14-year interval was ascertained by biennial follow-up questionnaires and documented, in most cases, by hospital records.

The relationship between BMI at baseline and CAD incidence during the 14-year follow-up was the focus of this report. However, because cigarette smoking was a strong risk factor for CAD and, as in many samples, there was tendency for the smoking women to weigh less than average, a multivariate analysis was required to estimate the true relationship between BMI and the incidence of CAD. The results of the multivariate analysis show a continuous gradient of increasing risk of CAD that begins at BMI levels that are well below average for adult women. When compared with women with a BMI of less than 21 (the leanest group), there was a nearly 50% increased risk of CAD in women with a BMI between 23 and 24.9 kg/m^2. Even women with very slightly elevated BMI, between 21 and 22.9 kg/m^2 showed some elevation in the risk of CAD (not statistically significant), and the authors conclude that body fat is a cause of CAD. More important is their conclusion that, from the healthy heart perspective, "excess" is defined as a rather small elevation in adiposity. For example, even a 5 to 7.9 kg weight gain resulted in a detectable increase in CAD incidence. It is more difficult to document that comparable weight loss in the overweight individual results in a similar reduction in CAD incidence.

A smaller study of men aged 40 to 75 years, which utilized a similar design, revealed similarly convincing indictment of moderate overweight.[26] After only 3 years of follow-up the men under age 65 years who had a BMI between 25 and 28.9 kg/m^2 had a 72% increase in their risk of CAD. Because average BMI for middle-aged men in the United States is in this range, it is clear that these findings suggest that, not only is "modest" overweight dangerous, but the majority of men are at risk because of overweight.

While the evidence continues to mount that excess adiposity, even at heretofore acceptable levels, is a major cause of CVD, the number one killer and source of morbidity for Americans, there are disturbing suggestions that the lifestyles that promote adiposity[35] are not improving. One recent publication,[36] which was intended to draw the attention of the medical community to the epidemic sedentary lifestyle, recommended daily moderate activity of at least 30 minutes duration. Despite the increasing recognition and understanding of excess adiposity as a cause of CVD, and calls to action[36] from public health and medical professionals, recent statistics from U.S. national surveys indicate movement of many Americans, adults[21] and youth[37] alike, to increased levels of adiposity. Given the major role of overnutrition in the burdensome and tragic epidemic of CVD, it is unlikely that major progress in the prevention of CVD can be made without fundamental and pervasive changes in exercise and eating behavior.

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