

Relationship of Metabolic Risk Factors and Development of Cardiovascular Disease and Diabetes

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Abstract

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The prevalence of obesity and diabetes has reached pandemic proportions. Obesity, particularly in association with high waist circumference and high BMI, is an independent risk factor for coronary heart disease (CHD) and diabetes. Several large studies have shown that marginal (5 lb) to moderate (11 to 22 lb) weight gain in adulthood (age 20 to 50 years) increases the risk of chronic disease and negatively affects CHD risk status. The metabolic syndrome, a clustering of cardiovascular and metabolic risk factors that includes abdominal obesity, is increasing among adults and children and is strongly associated with the development of diabetes and CHD. Recent evidence suggests that elevated liver enzymes, an indicator of non-alcoholic fatty liver disease, may comprise an additional component of the metabolic syndrome and may serve as a surrogate marker for type 2 diabetes, particularly if used in conjunction with C-reactive protein.

Key words: coronary heart disease, diabetes, non-alcoholic fatty liver disease, metabolic syndrome, C-reactive protein

Introduction

Since 1990, the United States has been in the grips of a twin epidemic of obesity and diabetes (Figure 1) (1–3). Presently, the majority of U.S. adults (>56%) are overweight (BMI ≥ 25 kg/m²), ~20% are obese (BMI

≥ 30 kg/m²), and 7.3% have diabetes. The latter figure is conservative and would probably rise to 10% if estimates included individuals with undiagnosed diabetes (1). Weight gain and high BMI, both of which comprise major risk factors for diabetes, are modifiable. In terms of contributing lifestyle factors, 27% of U.S. adults do not engage in any physical activity, whereas another 28.2% are not active on a regular basis (1). Yet, disturbingly, although both diabetes and obesity are proliferating and preventable, only 43% of obese persons are advised to lose weight during routine checkups (1).

The rates of overweight and obesity are currently approaching pandemic proportions, rapidly increasing in both industrialized and developing nations. According to the World Health Organization (WHO),¹ more than one billion adults worldwide were categorized as overweight (BMI > 25 kg/m²) and 300 million as clinically obese (BMI > 30 kg/m²) in 2002 (4). The reason for the increased prevalence of obesity is attributed to greater food abundance and lower levels of physical activity.

Pandemic Prevalence of Cardiovascular and Metabolic Risk Factors

Coronary heart disease (CHD) is associated with the same risk factors throughout the world, according to the large INTERHEART study (5). This international, case-control study enrolled 15,152 cases and 14,820 controls from 52 countries on every continent to assess potentially modifiable risk factors associated with acute myocardial infarction (AMI). As shown in Table 1, current smoking, raised apolipoprotein (Apo) B/Apo A1 ratio, hypertension, diabetes, abdominal obesity, and psychosocial factors conferred the greatest risk of AMI (5). Daily consumption of

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¹ Nonstandard abbreviations: WHO, World Health Organization; CHD, coronary heart disease; AMI, acute myocardial infarction; Apo, apolipoprotein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; NAFLD, non-alcoholic fatty liver disease.

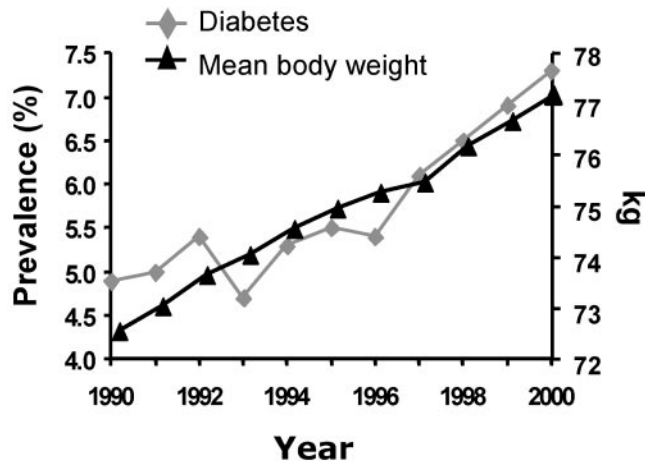


Figure 1: According to survey data from the Behavioral Risk Factor Surveillance System, the prevalence of diabetes increased from 4.9% in 1990 to 7.3% in 2000, a 49% increase (1,2). Between 1991 and 2000, the prevalence of obesity increased from 12.0% to 19.8%, a 61% increase (1,3).

vegetables and fruits and consumption of alcohol three or more times per week were protective. Worldwide, the two most significant risk factors were smoking and abnormal lipids, which accounted for two thirds of the risk of AMI. Psychosocial factors, abdominal obesity, diabetes, and hypertension ranked as the next most significant risk factors; however, their relative effect varied in different regions of the world. Interestingly, abdominal obesity had a greater relationship to AMI than did BMI. In contrast, BMI, the usual measure of obesity, was only moderately associated with AMI.

The INTERHEART study showed that, worldwide, nine easily measured and modifiable risk factors account for 90% of the risk of AMI. The investigators concluded that risk factor modification represents a viable approach to the prevention of CHD on a global scale (5).

BMI: A Reliable Indicator of Disease Risk?

The numerous medical complications associated with obesity extend to nearly every organ system and significantly increase the risk of serious disease and death (Table 2). The question of which clinical marker is most useful in predicting disease risk is somewhat controversial. Among the anthropometric variables, waist circumference is generally considered the most accurate indicator of cardiovascular disease (CVD) risk.

In the general population, the correlation between BMI and waist circumference is extremely high (6). However, in the elderly, BMI may be somewhat misleading, because fat tends to shift from peripheral to central sites, rendering waist-to-hip ratio a more accurate predictor of mortality risk than increased BMI (6,7).

A large prospective cohort study of more than one million U.S. adults documented a curvilinear relationship between BMI and mortality (6). Basically, the risk of mortality increased at both ends of the curve, with the very heavy (BMI > 32 kg/m²) and the very lean (BMI < 20 kg/m²) at greatest risk. In people who had never smoked and had no history of disease, the lowest rates of death from all causes were found at intermediate BMIs between 23.5 and 24.9 kg/m² in men and 22.0 and 23.4 kg/m² in women (6). Across the range of BMIs between 22.0 and 26.4 kg/m² in men and 20.5 and 24.9 kg/m² in women, the relative risk of

Table 1. Risk of AMI associated with risk factors in the overall population in the INTERHEART study (5)

Risk factor	Controls (%)	Cases (%)	Odds ratio (99% confidence interval)
Apo B/Apo A1 ratio	20.0	33.5	3.25 (2.81, 3.76)
Current smoking	26.8	45.2	2.87 (2.58, 3.19)
Diabetes	7.5	18.4	2.37 (2.07, 2.71)
Hypertension	21.9	39.0	1.91 (1.74, 2.10)
Abdominal obesity (upper tertile of waist circumference)	33.3	46.3	1.62 (1.45, 1.80)
Psychosocial			2.67 (2.21, 3.22)
Vegetables/fruit daily*	42.4	35.8	0.70 (0.62, 0.79)
Exercise*	19.3	14.3	0.86 (0.76, 0.97)
Alcohol intake ≥3 times/wk*	24.5	24.0	0.91 (0.82, 1.02)

Adapted with permission. Adjusted for all risk factors; odds ratios and confidence intervals were calculated for the association of risk factors to AMI. AMI, acute myocardial infarction; Apo, apolipoprotein.

* Protective factor.

Table 2. Medical complications of obesity

Cancer	Hypertension
Breast	Idiopathic intracranial hypertension
Uterus	Nonalcoholic fatty liver disease
Cervix	Steatosis
Colon	Steatohepatitis
Esophagus	Cirrhosis
Pancreas	Osteoarthritis
Kidney	Pancreatitis (severe)
Prostate	Phlebitis
Cataracts	Venous stasis
Coronary heart disease	
Dermatologic problems	
Diabetes	
Dyslipidemia	
Gallbladder disease	
Gout	
Gynecologic abnormalities	
Abnormal menses	
Infertility	
Polycystic ovary syndrome	

death was not significantly elevated. However, death rates increased in relationship to moderate and severe overweight. Increasing BMI was associated with an increased risk of death in all age groups and for all categories of causes of death. In contrast, the optimal BMI for longevity was in the achievable average range of between 20.5 and 24.9 kg/m² for men and women of all ages.

Weight Gain in Adulthood: How Much Is Too Much?

A clear relationship exists between weight gain in adulthood (age, 20 to 50 years) and the development of diabetes and CHD. How much weight gain is too much? Unfortunately, increasing evidence shows that even marginal to moderate weight gain in adulthood increases the risk of chronic disease (8). In the Nurses' Health Study (9–12) and the Health Professionals Follow-up Study (13), individuals who had weight gains ranging from 11 to 22 lb had a 1.5 to 3 times higher risk of chronic disease (e.g., CHD, hypertension, cholelithiasis, and type 2 diabetes) compared with those who maintained their weight within 4 lb of their weight at 18 to 20 years of age. Figure 2 depicts the relationship between weight gain in adulthood and increased risk of diabetes (8,10). As might be expected, risk increases exponentially with larger gains in weight (8). In

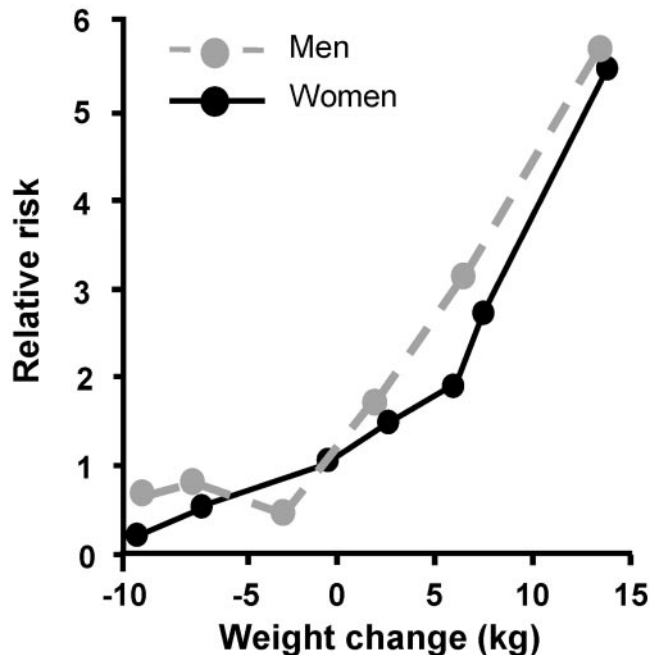


Figure 2: Relationship between weight gain in adulthood and the relative risk of type 2 diabetes in men and women (8). Data are for men who were followed for up to 10 years in the Health Professionals Follow-up Study and for women who were followed for up to 18 years in the Nurses' Health Study. Adapted with permission.

individuals >50 years, particularly men, the age-related conversion of muscle mass to fat may manifest itself as increased abdominal adiposity (e.g., increased waist circumference), even in the absence of weight gain (8).

The clustering of cardiovascular and metabolic risk factors, particularly when associated with weight gain in adulthood, is associated with an increased risk of CHD. An analysis of 16-year follow-up data from the Framingham Offspring Study revealed that weight gain in adulthood correlates with adverse cardiovascular and metabolic risk status and greatly increases the risk of CHD (14). Relatively small changes in weight of 2.25 kg, or ~5 lb, influence cardiovascular and metabolic risk (14). After adjustment for age and baseline level of obesity, weight loss of 5 lb or more favorably changed the cardiovascular and metabolic risk factor sum to a high degree ($p < 0.001$ for both men and women). Conversely, weight gain of 5 lb or more deleteriously affected cardiovascular and metabolic risk status ($p < 0.001$ for both men and women), as indicated by risk factor sums that declined 48% in men and 40% in women). The clustering of three or more cardiovascular and metabolic risk factors, the criteria for the diagnosis of metabolic syndrome, was observed in ~17% of both sexes and was associated with a greatly increased risk of CHD (30% in men and 56% in women) (14).

Table 3. Adult Treatment Panel III: individual risk factors for the metabolic syndrome* (16)

Risk factor	Defining level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting blood glucose	≥110 mg/dL [≥100 mg/dL (30)]

Adapted with permission.

* Diagnosis is established when at least three of these risk factors are present.

Clinical Definitions of Cardiovascular and Metabolic Risk

Initially described by Reaven as syndrome X in 1988 (15), the concept of cardiovascular and metabolic risk factor clustering has been codified by various organizations, most notably the National Cholesterol Education Program Adult Treatment Panel III (16), the WHO (17), and the International Diabetes Federation (18). There is debate as to whether the underlying cause of the metabolic syndrome is environmental (16), inflammatory (19), or metabolic (e.g., insulin resistance) (17). However, regardless of cause, a consensus exists as to the importance of weight reduction and exercise as the cornerstone of lifestyle modification approaches to primary and secondary CHD prevention.

The National Cholesterol Education Program Adult Treatment Panel III definition provides a simple clinical tool for the identification of cardiovascular and metabolic risk, even in seemingly low-risk individuals (Table 3) (16,20). According to recent estimates, ~47 million individuals in the United States have the metabolic syndrome (21).

The power of individual components to predict the metabolic syndrome is subject to tremendous variation. For example, an analysis of data from the Third National Health and Nutrition Examination Survey showed that 91% of individuals with a high waist circumference had the metabolic syndrome, as did 74% of those with high triglyceride levels and 77% with low high-density lipoprotein cholesterol (HDL-C) levels (21).

The San Antonio Heart Study assessed the ability of the National Cholesterol Education Program Adult Treatment Panel III vs. the WHO criteria for the metabolic syndrome in predicting all-cause and CVD mortality (20). Among the 2815 participants, 25 to 64 years of age at enrollment, 509 met both criteria, 197 met the National Cholesterol Education Program criteria only, and 199 met the WHO criteria only. During the follow-up period of 12.7 years, 229 deaths were recorded (117 from CVD). In the larger primary prevention group of 2372 individuals without diabetes or CVD at baseline, 132 deaths occurred (50 from CVD). To evaluate the effect of diabetes and sex on CVD mortality, sex-specific hazard ratios were determined (20). Patients with diabetes who met the National Cholesterol Education Program criteria for the metabolic syndrome had the highest risk of CVD mortality (8.19 for women, 3.09 for men; Table 4). Notably, the risk of CVD death for women with diabetes and the metabolic syndrome was nearly three times higher than that for men (20). Those without diabetes and without the metabolic syndrome had the lowest risk of CVD mortality. In lower-risk subjects, the simpler National Cholesterol Education Program metabolic syndrome definition

Table 4. Comparison of DM/MetS status and sex-specific hazard ratios for CVD mortality in the San Antonio Heart Study (20)

Baseline DM/MetS status*	Women without CVD [HR (95% CI)]†	Men without CVD [HR (95% CI)]†
No DM, No NCEP-MetS	1.00	1.00
No DM, Yes NCEP-MetS	2.07 (0.72, 6.0)	1.96 (0.99, 3.88)
Yes DM, No NCEP-MetS	3.53 (0.75, 16.7)	2.34 (0.70, 7.82)
Yes DM, Yes NCEP-MetS	8.19 (3.51, 19.1)	3.09 (1.49, 6.43)

Adapted with permission. DM, diabetes mellitus; MetS, metabolic syndrome; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; NCEP, National Cholesterol Education Program; NCEP-MetS, NCEP-defined MetS.

* No CVD at baseline (Cox models).

† Adjusted for age and ethnicity.

was a better predictor of all-cause and CVD mortality than was the WHO definition. Moreover, sex seemed to modify the predictive ability of the metabolic syndrome for CVD mortality. The CVD mortality hazard ratios for National Cholesterol Education Program–defined metabolic syndrome were 4.65 and 1.82 for women and men, respectively; corresponding hazard ratios for WHO-defined metabolic syndrome were 2.83 and 1.15 (20).

Finally, all components of the National Cholesterol Education Program metabolic syndrome criteria do not have equal power in identifying CHD risk. In a multivariate analysis of National Health and Nutrition Examination Survey data, the most significant predictors of CHD were low HDL-C, high blood pressure, and diabetes (22). Furthermore, the use of the metabolic syndrome in predicting diabetes risk was 4-fold higher than it was for predicting CHD risk. Data from the San Antonio Heart Study (23) showed that the National Cholesterol Education Program Adult Treatment Panel III metabolic syndrome criteria predicted diabetes accurately, independent of other risk factors including impaired glucose tolerance and fasting insulin. However, the addition of the 2-hour fasting glucose tolerance test further improved its predictive power (23,24). In contrast to CHD, a different set of metabolic syndrome traits predicts diabetes—namely, impaired glucose tolerance and obesity—whereas the major indicators of CHD risk are high blood pressure and low HDL-C level.

Obesity and Metabolic Syndrome in Children and Adolescents

The prevalence of obesity is rising among children and adolescents, with alarming implications for the nation's future cardiovascular health. In a Yale University study (25), investigators assessed the effect of different degrees of obesity on the prevalence of the metabolic syndrome in a multiethnic, multiracial cohort of 439 obese (244 moderately obese, 195 severely obese), 31 overweight, and 20 non-obese youngsters (mean age, 12 years) (25). Baseline measurements of cardiovascular and metabolic status included BMI, blood pressure, glucose tolerance, and lipid, adiponectin, and C-reactive protein (CRP) levels.

The results showed that values for glucose, insulin, insulin resistance, triglycerides, CRP, interleukin-6, and systolic blood pressure, as well as the prevalence of impaired glucose tolerance, increased significantly with increasing obesity (25). Correspondingly, adiponectin and HDL-C levels decreased with increasing obesity.

In all racial and ethnic groups, the percentage of youngsters with impaired glucose tolerance increased exponentially in relationship to the severity of obesity (25). The overall prevalence of the metabolic syndrome was 38.7% in moderately obese children and 49.7% in severely obese children. None of the non-obese or overweight children qualified for a diagnosis of metabolic syndrome.

The investigators concluded that biomarkers of an increased risk of adverse cardiovascular outcomes were already present in these youngsters (25). Echoing the truth of this statement, preliminary short-term follow-up revealed that full-blown type 2 diabetes had already developed in eight youngsters who had metabolic syndrome (25).

Liver Enzymes: A Novel Biomarker of Cardiovascular and Metabolic Risk

Recent evidence suggests that non-alcoholic fatty liver disease (NAFLD) may play as important a role as visceral fat in the development of the metabolic syndrome, insulin resistance, and type 2 diabetes. An Italian study evaluated the prevalence of insulin sensitivity in 30 patients with biopsy-confirmed NAFLD, 21 of whom had non-alcoholic steatohepatitis (26). The prevalence of obesity, metabolic syndrome components, insulin resistance, and/or type 2 diabetes was increased among patients with liver disease. The investigators therefore concluded that NAFLD should rank as an additional cardiovascular and metabolic risk factor, because it correlates with decreased insulin sensitivity independent of BMI.

In the large Insulin Resistance Atherosclerosis Study, the association between elevated liver enzymes and risk of type 2 diabetes was investigated among 906 individuals, none of whom had diabetes at study entry (27). The results showed that individuals with the highest elevations of alanine aminotransferase and aspartate aminotransferase had significantly greater risk of developing diabetes (27). Moreover, these liver markers predicted diabetes risk across all subgroups, regardless of sex, ethnicity, obesity, glucose tolerance status, or insulin sensitivity and independent of CRP, a marker of inflammation. CRP and liver markers not only predicted diabetes independent of each other, but also to the same degree. Therefore, when used in conjunction, these two markers may have additive predictive power in identifying patients at risk of developing diabetes. Overall, aspartate aminotransferase, alanine aminotransferase, and other markers of liver injury may provide clinically useful and cost-effective surrogate markers for NAFLD (27). In a more recent study, liver function tests were found to predict the development of the metabolic syndrome (28).

In terms of therapeutic options, study results suggest that insulin sensitizers (e.g., thiazolidinediones or metformin) may be associated with improvements in NAFLD/non-alcoholic steatohepatitis and reductions in liver fat; however, these medications need further evaluation in randomized controlled trials (29).

Conclusions

The prevalence of obesity and diabetes is increasing rapidly in both industrialized and developing nations. Obesity is also on the rise among children and adolescents.

Research has shown a clear relationship between cardiovascular and metabolic risk factors and the development and progression of CVD and diabetes. Obesity, particularly central obesity, is an independent risk factor for the development of CVD and diabetes. Weight gain in adulthood is associated with rising rates of multiple cardiovascular and metabolic risk factors and an increased risk of chronic diseases, including diabetes, CHD, hypertension, and cholelithiasis. In contrast, weight loss of 5 lb or more can favorably alter cardiovascular and metabolic risk status and prevent the progression to CHD.

Recent evidence suggests that liver enzymes may provide useful clinical surrogate markers for NAFLD, which is independently associated with the metabolic syndrome and with increased risk of type 2 diabetes. Fortunately, most of these cardiovascular and metabolic risk factors are modifiable; therefore, timely implementation of lifestyle changes and pharmacological approaches can play a pivotal role in the prevention of chronic disease.

Appendix

Question and Answer Section

Q: Do you think the metabolic syndrome has a single cause?

Dr. Haffner: Of the several plausible mechanisms hypothesized, the two most common are increased visceral fat and insulin resistance. Fat in other areas, for example, hepatic or intramuscular fat, also plays an important role. An operational definition does not require the identification of a single causative mechanism.

Dr. Smith: Although there may be multiple underlying etiologies (e.g., genetic, environmental, inactivity), they converge in the middle, in terms of lipid abnormalities and other clusters. The term metabolic syndrome provides an operational definition in that the components converge; however, they need not share the same underlying etiology.

Q: Isn't it true that the underlying cause of the metabolic syndrome is the failure of the adipose organ to handle excess energy?

Dr. Aronne: No, that's not entirely correct. Although the majority of individuals with the metabolic syndrome have central obesity, a very significant number of people with a BMI ≤ 25 kg/m² also have it.

Dr. Smith: We have not solved the hypothesis and reached the stage where we can attribute the entire concept of the metabolic syndrome to the adipose organ. I presented some data and there are more data that suggest that the fat cell is involved in the metabolic syndrome. But until we have hard data that prove that most, if not all, of this syndrome is due to failure of the adipose organ, we need to be cautious. In the convergent model I discussed, defects in fat oxidation in the skeletal muscle or in other tissues could

clearly support any given level of obesity. Therefore, in that setting, the defect would not be in the adipose organ, but instead downstream in the oxidizing tissues. We have to be careful about relying on any one hypothesis because, for example, signaling defects in multiple organs can cause insulin resistance and lipotoxicity. Although it would be nice to have a unifying one-size-fits-all explanation, I think we're going to discover that there will be multiple causes within each of these areas. The adipose organ probably will account for most, but not all, of the explanation.

Q: Could hyperactivation of the CB₁ receptor be the underlying cause of the metabolic syndrome?

Dr. Pi-Sunyer: There has been documentation of hyperactivity of the endocannabinoid pathway in obese animals who have elevated lipids and impaired glucose tolerance. Although this has not been documented in humans, it is certainly a very strong possibility.

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