TABLE 422-1 NCEP:ATPIII[a] 2001 AND HARMONIZING DEFINITION CRITERIA FOR THE METABOLIC SYNDROME

NCEP:ATPIII 2001	Harmonizing Definition[b]
Three or more of the following:	**Three of the following:**
• Central obesity: waist circumference >102 cm (M), >88 cm (F)	• Waist circumference (cm)
• Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication	**Men** / **Women** / **Ethnicity**: ≥94 / ≥80 / Europid, sub-Saharan African, Eastern and Middle Eastern; ≥90 / ≥80 / South Asian, Chinese, and ethnic South and Central American; ≥85 / ≥90 / Japanese
• Low HDL[c] cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication	• Fasting triglyceride level >150 mg/dL or specific medication
• Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication	• HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication
• Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes	• Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication
	• Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels)

[a]National Cholesterol Education Program and Adult Treatment Panel III. [b]In this analysis, the following thresholds for waist circumference were used: white men, ≥94 cm; African-American men, ≥94 cm; Mexican-American men, ≥90 cm; white women, ≥80 cm; African-American women, ≥80 cm; Mexican-American women, ≥80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europid cutoffs (≥94 cm for men and ≥80 cm for women) and on South Asian cutoffs (≥90 cm for men and ≥80 cm for women) were used. For participants who were considered "other Hispanic," the International Diabetes Federation thresholds for ethnic South and Central Americans were used. [c]High-density lipoprotein.

higher prevalence of CVD than in patients who have type 2 diabetes or impaired glucose tolerance but do not have this syndrome.

Cardiovascular Disease Individuals with the metabolic syndrome are twice as likely to die of cardiovascular disease as those who do not, and their risk of an acute myocardial infarction or stroke is threefold higher. The approximate prevalence of the metabolic syndrome among patients with coronary heart disease (CHD) is 50%, with a prevalence of ~35% among patients with premature coronary artery disease (before or at age 45) and a particularly high prevalence among women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., nutrition, physical activity, weight reduction, and—in some cases—pharmacologic therapy), the prevalence of the syndrome can be reduced.

Lipodystrophy Lipodystrophic disorders in general are associated with the metabolic syndrome. Both genetic lipodystrophy (e.g., Berardinelli-Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired lipodystrophy (e.g., HIV-related lipodystrophy in patients receiving antiretroviral therapy) may give rise to severe insulin resistance and many of the components of the metabolic syndrome.

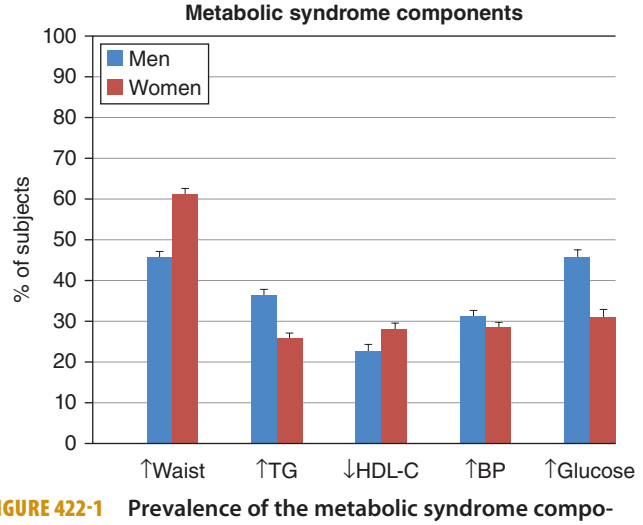

FIGURE 422-1 Prevalence of the metabolic syndrome components, from NHANES 2003–2006. NHANES, National Health and Nutrition Examination Survey; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure. The prevalence of elevated glucose includes individuals with known diabetes mellitus. *(Created from data in ES Ford et al: J Diabetes 2:1753, 2010.)*

ETIOLOGY

Insulin Resistance The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, which is caused by an incompletely understood defect in insulin action (Chap. 417). The onset of insulin resistance is heralded by postprandial hyperinsulinemia, which is followed by fasting hyperinsulinemia and ultimately by hyperglycemia.

An early major contributor to the development of insulin resistance is an overabundance of circulating fatty acids (Fig. 422-2). Plasma albumin-bound free fatty acids are derived predominantly from adipose-tissue triglyceride stores released by intracellular lipolytic enzymes. Fatty acids are also derived from the lipolysis of triglyceride-rich lipoproteins in tissues by lipoprotein lipase. Insulin mediates both antilipolysis and the stimulation of lipoprotein lipase in adipose tissue. Of note, the inhibition of lipolysis in adipose tissue is the most sensitive pathway of insulin action. Thus, when insulin resistance develops, increased lipolysis produces more fatty acids, which further decrease the antilipolytic effect of insulin. Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation take place in the liver.

Leptin resistance has also been raised as a possible pathophysiologic mechanism to explain the metabolic syndrome. Physiologically, leptin reduces appetite, promotes energy expenditure, and enhances insulin sensitivity. In addition, leptin may regulate cardiac and vascular function through a nitric oxide–dependent mechanism. However, when obesity develops, hyperleptinemia ensues, with evidence of leptin resistance in the brain and other tissues resulting in inflammation, insulin resistance, hyperlipidemia, and a plethora of cardiovascular disorders, such as hypertension, atherosclerosis, CHD, and heart failure.

The oxidative stress hypothesis provides a unifying theory for aging and the predisposition to the metabolic syndrome. In studies of insulin-resistant individuals with obesity or type 2 diabetes, the offspring of patients with type 2 diabetes, and the elderly, a defect in mitochondrial oxidative phosphorylation that leads to the accumulation of triglycerides and related lipid molecules in muscle has been identified.

Recently, the gut microbiome has emerged as an important contributor to the development of obesity and related metabolic disorders, including the metabolic syndrome. Although the mechanism remains