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Metabolic Syndrome Pandemic

Scott M. Grundy

***Abstract*—**The metabolic syndrome is a multiplex risk factor that consists of several risk correlates of metabolic origin. In addition, to dyslipidemia, hypertension, and hyperglycermia, the syndrome carries a prothrombotic state and a proinflammatory state. Persons with the metabolic syndrome are at essentially twice the risk for cardiovascular disease compared with those without the syndrome. It further raises the risk for type 2 diabetes by about 5-fold. Although some investigators favor keeping risk factors separate for purposes of clinical management, others believe that identifying individuals with an aggregation of risk factors provides additional useful information to guide clinical management. In particular it focuses attention on obesity and sedentary life habits that are the root of the syndrome. This review addresses the prevalence of this clustering phenomenon throughout the world. Such seems appropriate because of the increasing prevalence of obesity in almost all countries. The available evidence indicates that in most countries between 20% and 30% of the adult population can be characterized as having the metabolic syndrome. In some populations or segments of the population, the prevalence is even higher. On the other hand, in parts of developing world in which young adults predominate, the prevalence is lower; but with increasing affluence and aging of the population, the prevalence undoubtedly with rise. **(*Arterioscler Thromb Vasc Biol*. 2008;28:629-636)**

Key Words: obesity ■ hypertension ■ diabetes ■ lipids ■ acute coronary syndrome

The metabolic syndrome (MetS) is a multiplex risk factor for atherosclerotic cardiovascular disease (ASCVD).[1,2] It consists of atherogenic dyslipidemia (ie, elevated triglycerides and apolipoprotein B-containing lipoproteins and low high-density lipoproteins [HDL]), elevations of blood pressure (BP) and glucose, and prothrombotic and proinflammatory states. Many persons with the MetS have insulin resistance that predisposes them to either prediabetes or type 2 diabetes. Obesity and physical inactivity are the driving force behind the syndrome[3]; but a second set of factors, metabolic susceptibility, usually is required for the MetS to become evident.[2] Susceptibility factors include adipose tissue disorders (typically manifest as abdominal obesity), genetic and racial factors, aging, and endocrine disorders. Genetic aberrations affecting specific metabolic risk factors can further modify expression of the syndrome. The MetS is often associated with other medical conditions, notably, fatty liver, cholesterol gallstones, obstructive sleep apnea, gout, depression, musculosketal disease, and polycystic ovarian syndrome.[1]

The risk for ASCVD accompanying the MetS is approximately doubled compared with an absence of the syndrome.[1] For example, a recent meta-analysis including 43 cohorts

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(172 573 individuals) reported that metabolic syndrome conveyed a relative risk (RR) for CVD events and death of 1.78.[4] In women the risk was highest (RR 2.63). In addition, risk was still associated with the syndrome after adjusting for traditional CVD risk factors (RR 1.54); this finding indicates that risk accompanying the syndrome cannot be explained entirely by the latter. Other reports support this conclusion.[5] In those without type 2 diabetes, the likelihood of developing diabetes is increased approximately 5-fold. The MetS appears to promote the development of ASCVD at multiple levels. Elevations of apo B-containing lipoproteins initiate atherogenesis and drive lesion development.[6] Atherosclerotic plaque development is accelerated by low levels of HDL, by elevated BP, by inflammatory cytokines, and likely by elevated plasma glucose.[7] More advanced plaques tend to become unstable, which in turn predisposes to plaque rupture.[8] When rupture occurs, a prothrombotic state promotes propagation of thrombi that can worsen cardiovascular syndromes.

An important point to make about the metabolic syndrome is that it is not a substitute for global risk assessment in determining absolute risk of individuals for the purpose of initiating preventive drug therapy. Instead the metabolic syndrome represents that part of global risk that can be attributed to underlying metabolic causes such as obesity and abnormal body fat distribution. Although the presence of the metabolic syndrome may influence choice of drug therapies, its presence essentially denotes the need to emphasize lifestyle management in clinical practice.

Criteria for MetS

The MetS, which is a clustering of risk factors, must be differentiated from the clinical criteria used to identify affected persons.[1] The purpose of the latter is to use simple measures to detect individuals who have risk-factor clustering. Detection criteria have evolved over the past decade. The recommended measurements for detection have been conditioned in part by views of the pathogenesis of the syndrome. For example, in 1998, the World Health Organization (WHO) task force on diabetes identified insulin resistance is the dominant cause of the MetS.[9] By these criteria, clinical indicators of insulin resistance were required for the diagnosis. But with growing evidence for a critical role for abdominal obesity, the latter has assumed a more important position among diagnostic criteria. The latter led to the National Cholesterol Education Program (NCEP) criteria for the MetS in which the need for demonstration of insulin resistance was replaced by an increased waist circumference (abdominal obesity).[6] In the past 2 years, clinical criteria have been largely harmonized. This harmonization is reflected in the American Heart Association (AHA)/ National Heart, Lung, and Blood Institute (NHLBI) update of the National Cholesterol Education Program (NCEP) criteria,[1] and the International Diabetes Federation (IDF) recommendations.[10] The WHO criteria[9] along with those of the AHA/NHLBI[1] and IDF[10] are summarized in Table 1. Recently a large number of studies have been carried out to determine the prevalence of the MetS in different populations. The majority of epidemiological studies have used NCEP criteria,[6] but there have been several comparisons of NCEP criteria with WHO and IDF recommendations for estimating prevalence.

Some investigators have questioned the clinical utility of the metabolic syndrome.[11] The claim is made that the primary clinical focus should remain on the individual metabolic risk factors and that aggregating them into a syndrome adds little to clinical management. The counter argument is that identification of risk-factor clustering changes the clinical focus to underlying causes, which calls for greater emphasis on lifestyle therapies to reduce long-term risk for CVD.[1] In spite of this disagreement over clinical strategy, most investigators agree that clustering of metabolic risk factors is a real and relatively common phenomenon. If the major purpose of the

Table 1. Previous Criteria Proposed for Clinical Diagnosis of the Metabolic Syndrome

Clinical Measure	WHO (1998)	NCEP (2001)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM or ↓ insulin sensitivity* plus any two of the following	None but any three of the following five features	None
Body weight	Males: waist to hip ratio >0.90; females: waist to hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥102 cm in men or ≥88 cm in women†	Increased WC (population specific) plus any two of the following
Lipid	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL	TG ≥150 mg/dL or on TG Rx
		HDL-C <40 mg/dL in men or <50 mg/dL in women	HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	≥110 mg/dL (includes diabetes)‡	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria		

WHO indicates World Heath Organization; NCEP, National Cholesterol Education Program Adult Treatment Panel III; IDF, International Diabetes Federation; IGT, impaired glucose intolerance; IFG, impaired fasting glucose; T2DM, type 2 diabetes; WC, waist circumference; BMI, body mass index; TG, triglycerides; HDL-C, HDL cholesterol.

*Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

†In Asian populations, the WC threshold for abdominal obesity is ≥90 cm in men or ≥80 cm in women.

‡The 2001 definition identified fasting plasma glucose of ≥110 mg/dL (6.1 mmol/L) as elevated. This was modified in 2004 to be ≥100 mg/dL (5.6 mmol/L), in accordance with the American Diabetes Associations updated definition of impaired fasting glucose (IFG).

metabolic-syndrome concept is to shift emphasis to earlier intervention with lifestyle therapies, it is reasonable to extend the concept to obese children and adolescents where the syndrome already is beginning to take hold. Although pediatricians are showing increasing interest in the concept, there is at present no agreement on how best to define and approach the problem clinically.[12]

Worldwide Prevalence of the MetS

A relatively high prevalence of the MetS is a worldwide phenomenon. This prevalence appears to be increasing because of a parallel rise in the prevalence of obesity. The likelihood of a further increase in the MetS can be anticipated because of projections of a greater prevalence of obesity in the future.[13] In the discussion to follow, the prevalence of obesity in various regions of the world will be reviewed. However, it must be noted that determining the prevalence of the metabolic syndrome in different regions depends on defining criteria. Most reports have used the NCEP definitions of the syndrome.[1,3] In some cases, the NCEP definition has been adjusted for waist circumference differences in different population groups. One of the major unresolved issues for defining the syndrome is that of the appropriate waist circumference. The primary difference between NCEP and IDF definitions is that waist-circumference cut points for Whites, Blacks, and Hispanics is higher in NCEP than in IDF. This could lead to a higher prevalence of the syndrome with the IDF definition. In some reports, this is true, but in others, the differences are less than might be expected.

United States and Canada

Because obesity is the major driver of MetS development, it must be noted that about 30% of all United States (US) adults are presently overweight (BMI 25 to 29.9 kg/m^2), and about 32% are obese (BMI $\geq$30 kg/m^2).[14] Among the latter, about 5% of the population is extremely obese (BMI $\geq$40 kg/m^2).[14] Further and more alarming, approximately 16% of female children and adolescents are classified as overweight, and for males, about 18%.[14] In Canada, 36% of adults are overweight and 23% are obese.[15] Notable is the 10% lower prevalence in obese adults in Canada compared with the US.

In 1988 to 1994, at least one-fourth of the population had the MetS by NCEP criteria. A similar prevalence was reported for Canada. The prevalence of the syndrome is strongly related to age. By age 60, the percentage affected in the USA was approximately 40%.[16] Men and women are affected about equally. Each of the metabolic risk factors—abdominal obesity, elevated TG, low HDL-C, elevated blood pressure, and elevated plasma glucose—occurs in approximately one third of the US population. The original NCEP threshold for elevated glucose was 110 mg/dL; at this cut point, only about 15% of the US population had a high glucose. In 2005, the AHA/NHLBI lowered the glucose

Table 2. Prevalence of Metabolic Syndrome in Europe

				Prevalence of MetS (% of population)		
Country and Reference	Population	Age Range (No.)	Criteria	Men	Women	Total
France (43)	Men women	35–64 (3359)	NCEP	23.0	16.9	
France (44)	Men	50–59 (10 592)	NCEP	29.7		
			IDF	38.9		
			WHO	35.5		
Germany (45)	Men women	(4816 men 2315 women)	NCEP IDF	23.5 31.6	17.6 22.6	
Netherlands (46)	Adult men women	50–75 (1364)	NCEP WHO	19.0 26.0	32.0 26.0	
Italy (47)	Men Women	45–64 (1877)	NCEP	24.1	23.1	22.2
Italy (48)	Men women	40–79 (888)	NCEP WHO			17.8 34.1
Italy (49)	Men Women	19+ (2100)	NCEP	15	18	
Italy (50)	Men Women	65–84 (5632)	NCEP	29.9*	55.2*	
Spain (51)	Men women	35–64 (2540)	NCEP IDF	22.3 27.7	30.7 33.6	
Portugal (52)	Men women	18–90 1436	NCEP	19.1	27.0	23.9
Greece (53)	Men Women	Adults (9669)	NCEP IDF			24.5 43.4
Croatia (54)	Men women	18–88 (996)	NCEP			34.0
UK (55)	Women	60–79 (3589)	NCEP IDF WHO		29.8 47.5 20.9	
UK (56)	Men women	40–69 (2346)	NCEP WHO			
Canary Islands (57)	Men women	30+ (1193)	NCEP WHO	20.3 26.5	21.1 17.6	
Netherlands (58)	Men women (CHD)	18–80 (1117)	NCEP			46
Spain (59)	Men women (HIV)†	41.9±9.2 (710)	NCEP			17.0
Greece (60)	Men women (FCHL)‡	Adults (706)	NCEP	63.0	37.0	41.8
Finland (61)	Depression and Anxiety	Adults 5698	NCEP	47	25	37

*In a subgroup with diabetes, 64.9% of men and 87.1% of women had NCEP MetS.
†HIV indicates Human immunodeficiency virus; ‡FCHL, familial combined hyperlipidemia.

threshold to 100 mg/dL.[1] This change led to an increase in elevated glucose to a level comparable to that of other risk factors. As a result of this change, the overall prevalence of the MetS was raised by about 6%.

Between NHANES 1988 to 94 and NHANES 1999 to 2000, the prevalence of the MetS increased. Ford et al[17] estimated that ≈50 million Americans had the MetS in 1990 and ≈64 million had the syndrome in 2000. Two factors appear to account for this increase. One of these is obesity; in 1988 to 1994 the prevalence of obesity was 22.5%, and in 1999 to 2000, it had increased to 30.5%.[18] A second factor is aging of the population.[19] For any level of BMI, the prevalence of the MetS in the US population rises with increasing age. This effect can be explained largely by age-related rises of blood pressure and glucose.[19]

Black Americans

Ford et al[16] reported that MetS is more common in Black women than in Black men. This contrasts with the similar gender prevalence for Whites. Black men in particular have a relatively low prevalence, using NCEP criteria, compared with other ethnic groups. Reasons for lower frequency in Black men are lower waist circumferences on average, lower triglycerides, and higher HDL-C levels.[20,21] The latter appear to be related to a genetic/racial predisposition to reduced activities of hepatic lipase.[22,23] Whether lower triglycerides and higher HDL-C protect against CVD in Black men is uncertain. On the other hand, Blacks in general are more insulin resistant than are Whites.[24,25] They are also more prone to hypertension[26] and to diabetes.[27,28] Thus, any protective effect of less dyslipidemia among US Blacks probably is negated by a higher frequency of other metabolic risk factors, notably insulin resistance, hypertension, and diabetes. Particularly in the case of Black men, NCEP criteria for the MetS may not provide a full picture of the metabolic disturbance that is common in this population.

Hispanic Americans

In 1988 to 1994, the highest prevalence of MetS among any ethnic group in the USA was found in Hispanics (32% of the population).[16] Hispanic women were especially prone to the syndrome with about 35% being affected. One reason for this relatively high prevalence of the MetS may be a greater insulin resistance.[29] In the Hispanic population, insulin resistance seems to be out of proportion to the severity of obesity. Support for excessive insulin resistance among Hispanics comes from the fact that this population has the highest rates of T2DM in the USA.[30,31] Although there is a trend for Hispanic Americans to be more obese than Whites, the difference is not great enough to account for the much higher

Table 3. Prevalence of Metabolic Syndrome in Asia

				Prevalence of MetS (% of population)		
Country and Reference	Population	Age Range (No.)	Criteria	Men	Women	Total
Central Asia						
India (62)	Men women	20–70 (26 001)	IDF NCEP WHO			25.8 18.3 23.0
India (63)	Men women	>20 (1123)	NCEP	22.9	39.9	31.6
India (64)	Men women	20–75 (475)	NCEP			41.1
Southeast Asia						
Thailand (65)	Men women	35+ (404)	NCEP			18.0
Thailand (66)	Men women	20–70 (1383)	NCEP	15.7	11.7	12.8
Singapore (67)	Men women	Adult (3954)	NCEP	14.1	12.3	
China						
(68)	Men women	20–90 (16 342)	NCEP with BMI ≥25 kg/m^2	15.7	10.2	13.2
(69)	Men women	18–66 (1513)	NCEP IDF WHO			9.6 7.4 13.4
(70)	Men women	25–64 (18 630)	NCEP NCEP modified for Asians (8)* IDF			5.8 9.5 8.5
(71)	Men women	50–85 (10 362)	NCEP IDF			15.7 25.8
(72)	Men women T2DM	30+ (1039)	NCEP IDF WHO			55.7 50.0 70.0
(73)	Men women Type 2 DM	16–95 (5202)	NCEP	23.9	12.8	16.8
(74)	Men women	20+ (560)	NCEP modified for Asians (8)*			FCHL - 36.7 FHTG - 33.3 FH - 17.6 Normolipidemic - 16.3%
Japan						
(75)	Men women	19–88 (8144)	NCEP	19.0	7.0	
(76)	Men women	20–79 (3264)	Japanese criteria	12.1	1.7	7.8
(77)	Men women	30–79 (6985)	NCEP	30.2	10.3	
(78)	Men women	40+ (11 941)	3+ metabolic risk factors			14.9

*Waist circumference threshold: ≥90 cm for men and ≥80 cm for women.

†FCHL indicates familial combined hyperlipidemia; FHTG, familial hypertriglyceridemia; FH, familial hypercholesterolemia.

prevalence of T2DM in the former.[32,33] In contrast to Blacks, Hispanics are more likely to have hypertriglyceridemia than are Whites, although they do not have a higher prevalence of low HDL-C.[16] The high frequency of hypertriglyceridemia in this population correlates with an increased prevalence of fatty liver.[34] The frequency of hypertension is lower in middle-aged Hispanic men than in either White or Black counterparts; this difference compared with Whites however disappears with aging. Hispanic women in contrast have similar hypertension rates as White women.[35] Thus the pattern of MetS in Hispanic American is one in which obesity appears to drive glucose intolerance and hyperglycemia.

Other Adult Populations

In the USA and Canada, several other ethnic groups have been examined to determine the prevalence of the MetS. Native Americans represent one population that is particularly susceptible to T2DM. This high susceptibility undoubtedly is related in part to a high prevalence of obesity; but like Hispanics, Native Americans appear to have insulin resistance out of proportion to the severity of obesity.[36] This predisposition to insulin resistance may account for the 35% prevalence of MetS among adult Native Americans.[37] A similar or even higher prevalence of MetS has been reported for aboriginal Ontario, Canada Oji-Cree.[38] Up to 50% of this population in Western Canada carry the MetS.[38] It is possible that there is a strong genetic component for MetS in this population because functional polymorphisms in 3 candidate genes for plasma lipoproteins and blood pressure—angiotensinogen (AGT T174 M), G protein beta3 (GNB3 825C>T), and apolipoprotein C3 (−455T>C)—were associated with MetS.[39] Among Arab American adults in the Detroit area, age-adjusted prevalence of MetS was 23%[40]; rates were similar for men and women aged 20 to 49 years but were significantly higher for women aged ≥50 years.

Children and Adolescents

Of particular concern is a rising prevalence of the MetS in US youth. This rise undoubtedly results from an increasing obesity in younger people.[41] According to Daniels et al[42] approximately 1 million US adolescents meet the NCEP criteria for MetS. This corresponds to a prevalence of about 4% of all adolescents. Among overweight adolescents, MetS rates rise to 30% to 50%.[42]

Metabolic Syndrome in Europe

A series of studies on the occurrence of the MetS in Europe have been reported.[43–61] Criteria to determine prevalence have included those proposed by NCEP, IDF, and WHO. The data have been presented in different ways, but overall a general picture of prevalence can be obtained (Table 2). It seems fair to say that approximately one-fourth of the adult European population has the MetS. Prevalence varies somewhat depending on the age group studied, geographic location, or characteristics of the population studied. When NCEP and IDF criteria were compared, the IDF criteria usually gave a higher prevalence. This undoubtedly was attributable to the lower waist circumference threshold to define abdominal obesity. WHO criteria sometimes but not invariably gave a higher prevalence than did NCEP.

Metabolic Syndrome in Asia

The prevalence of the MetS, as reported from several studies in Central Asia, Southeast Asia, China, and Japan[62–78] are

Table 4. Prevalence of Metabolic Syndrome in Latin America

				Prevalence of MetS (% of population)		
Country and Reference	Population	Age Range (No.)	Criteria	Men	Women	Total
Mexico (79)	Men women	20–69 (2158)	NCEP WHO			26.6 13.61
Brazil (80)	Girls – overweight and non- overweight	12–19 (388)	3+ risk factors		Normal weight 14% Overweight 21.4%	
Venezuela (81)	Hispanic Men Women	≥20 (3108)	NCEP			35.3
Ecuador (82)	Postmeno-pausal Women	≥40 (325)	NCEP		41.5	
Dominican Ancestry (83)	Obese Children and Adolescents	2–20 (428)	Multiple risk factors			14
US Virgin Islands (84)	Caribbean-Born Adults – No history of diabetes	(893)	NCEP			20.5
Brazil (85)	Japanese Brazilian Men Women	30–60 (721)	NCEP modified for Asians (8)*			53
Brazil (86)	Japanese Brazilian Men Women	40–79 (151)	NCEP	36.9	38.8	
Brazil (87)	Adults Going Under 1st Time Angiography	(385)	WHO	39.7	58.7	
Brazil (88)	Japanese Brazilians – Men Women	≥30 (877)	NCEP modified for Asians (8)*	49.8	43.0	
Brazil (89)	Men Women Spanish Migrants to Brazil	(479)	NCEP	29.6	22.6	26.3

*Waist circumference threshold: ≥90 cm for men and ≥80 cm for women.

summarized in Table 3. In India, prevalence is relatively high, again dependent somewhat on the criteria used. With NCEP criteria, less than one-fifth of the studied population in Southeast Asia has the MetS. This lower prevalence, compared with North American and European populations, may be attributable in part to a younger population. In China, the general population has a relatively low prevalence, particularly when the high waist circumference threshold of NCEP is one of the criteria used for abdominal obesity. In older Chinese subjects with type 2 diabetes, the prevalence is much higher,[71–73] as it is in persons with familial forms of hypertriglyceridemia.[74] Finally, in Japan, the reported prevalence varies considerably from one study to another. Surprisingly, 2 reports in men indicated a prevalence up to one-fourth of the population.[77,78]

Metabolic Syndrome in Latin America

According to available reports,[79–89] the prevalence of the MetS, as defined by NCEP or WHO, is relatively high (Table 4). At least one-fourth of the adult population has the MetS, and in some countries it appears to be even higher. In Brazil, there is a large population of migrant Japanese.[85,86,88] When waist circumference thresholds are lowered to current recommendations for Asians, the prevalence of metabolic syndrome by NCEP criteria is high.

Conclusions

The clustering of risk factors that constitute the MetS is found to be common in most countries of the world. In the Americas, in Europe, and in India, at least one-fourth of the adults carry the syndrome. Because the MetS at least doubles the risk for ASCVD, compared with the population without the syndrome, the MetS likely accounts for up to half of all ASCVD. But because it also is associated with a very risk for type 2 diabetes, or with diabetes itself, the cardiovascular risk imparted by the MetS may be even greater than current estimates indicate. For this reason, there is urgency for development of betters approaches to the prevention and management of the syndrome. It is not enough to say "just treat the established risk factors." More importantly, an effort must be made to strike at the underlying causes of the syndrome. Certainly reversal of the worldwide epidemic of obesity and physical inactivity must be a high priority. But in addition, better means to treat underlying susceptibility to the syndrome also are needed. Both approaches represent a great challenge to research in the cardiovascular and diabetes fields.

Disclosures

None.

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ABSTRACT

The metabolic syndrome represents a clustering of metabolic risk factors for cardiovascular disease. The available evidence indicates that in most countries between 20 and 30% of the adult population has the metabolic syndrome. Because of this relatively high prevalence, the metabolic syndrome accounts for an increasing proportion of cardiovascular risk worldwide.