

**Global Coronary Heart Disease Risk Assessment of U.S. Persons With the Metabolic
Syndrome**

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Brief title: Global Risk Assessment and Metabolic Syndrome

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Objective: While metabolic syndrome (MetS) is related to an increased risk of coronary heart disease (CHD) events, persons with MetS encompass a wide range of CHD risk levels. This study describes the distribution of 10-year CHD risk among U.S. adults with MetS.

Research Design and Methods: MetS was defined by the modified National Cholesterol Education Program / Adult Treatment Panel (NCEP/ATP III) definition among 4293 U.S. adults aged 20-79 in the U.S. National Health and Nutrition Examination Survey 2003-2004. Low, moderate, moderately high, and high risk status were defined as <6%, 6-10%, 10-20%, and >20% probability of CHD in 10 years (based on NCEP/ATP III Framingham risk score algorithms), respectively; those with diabetes or pre-existing cardiovascular disease were assigned to high risk status.

Results: The weighted prevalence of MetS by NCEP criteria in our study was 29.0% overall (30.0% in men (M) and 27.9% in women (F), $p=0.28$). 38.5% (M: 30.7%, F: 46.9%) were classified as low risk, 8.5% (M: 7.9%, F: 9.1%) moderate risk, 15.8% (M: 23.4%, F: 7.6%) moderately high risk, and 37.3% (M: 38.0%, F: 36.5%) high risk. The proportion at high risk increased with age but was similar between Hispanics, non-Hispanic whites, and non-Hispanic blacks.

Conclusions: While many MetS subjects are at low calculated risk for CHD, about half are at moderately high or high risk, reinforcing the need for global risk assessment in persons with MetS to appropriately target intensity of treatment for underlying CHD risk factors.

The metabolic syndrome (MetS) is a cluster of risk factors often linked to insulin resistance that has been shown to increase the risk for development of cardiovascular disease (CVD). Persons with MetS are at an increased risk of coronary heart disease (CHD) and CVD mortality (1,2). Global risk assessment using Framingham risk prediction algorithms is often the initial evaluation of CHD risk in subjects with multiple risk factors, including those with MetS (3). While it is often assumed that persons with MetS are at high risk of CVD, many have only borderline elevations in risk factors so may actually be at either low or intermediate risk of CVD (4). Therefore, assessment of global risk of CHD in persons with MetS may be helpful to most appropriately target the intensity of cardiometabolic risk factor interventions for prevention of diabetes (DM) or cardiovascular disease.

The aim of this paper is to calculate the global risk of CHD in adults with MetS in the United States in order to better characterize the diversity in their risk of CHD using the data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004. In addition, we will examine the global risk of CHD in persons with MetS across gender, ethnicity and age groups, as well as examine goal attainment and distance to recommended levels for key CHD risk factors.

Research Design and Methods

Among 4,293 adults aged 20-79 in the National Health and Nutrition Examination Survey (NHANES) 2003-2004, 3,034 had complete risk factor data allowing calculation of 10-year risk of a hard CHD event (non-fatal myocardial infarction or CHD death) according to National Cholesterol Education Program / Third Adult Treatment Panel (NCEP/ATP

III) Framingham risk score criteria (5). We defined MetS by the modified NCEP definition if three or more of the following were present: 1) waist circumference ≥ 102 cm for men or ≥ 88 cm for women, 2) triglyceride level ≥ 1.69 mmol/l (150 mg/dl) if fasting, 3) HDL-cholesterol level ≤ 1.04 mmol/l (40 mg/dl) if male or ≤ 1.29 mmol/l (50 mg/dl) if female, 4) blood pressure $\geq 130/85$ mm Hg or on antihypertensive treatment, and 5) fasting glucose level ≥ 5.6 mmol/l (100 mg/dl), or on drug treatment for elevated glucose. Participants were classified as not having MetS after confirming the absence of at least three MetS risk factors. We also conducted similar analyses among persons identified with MetS by the International Diabetes Federation (IDF) criteria requiring increased waist circumference as defined above plus two or more of the other criteria (based on the same cut points as shown above, except for a lower waist circumference cutpoint for Hispanics of ≥ 80 cm for women and ≥ 90 cm for men as recommended by the IDF for persons of Central or South American ancestry) (6). DM was defined as having a fasting glucose level ≥ 6.99 mmol/l (126 mg/dl), after a 12-hour fast, a non-fasting glucose level of ≥ 11.1 mmol/l (200 mg/dl), use of oral hypoglycemic agents or insulin, or self-reported diagnosis of DM. We examined the proportion of persons with and without MetS among each risk group who were at low (<6%), moderate (6-9%), moderately high (10-20%), high (>20%) 10-year probability for CHD based on Framingham risk algorithm (5), and classified according to the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) scientific statement on metabolic syndrome (3) defining moderately high risk as 10-20% and high risk as >20% 10-year probability of CHD. While this statement also defined moderate risk as <10% with 2 or more risk

factors present, “intermediate” risk has been previously suggested to be a CHD risk of 0.6-2.0% per year (7), so we have therefore defined moderate risk as 6-10% and low risk as <6% risk in 10 years for the purposes of this manuscript. Persons with pre-existing DM (as defined above) or self-reported CVD (including heart attack, heart failure, or stroke) were assigned to the high-risk group. We stratified our analyses by age group, gender and ethnicity.

We also examined the percent of MetS subjects not at recommended levels for HDL-C, triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, and LDL-cholesterol. Mean distance from recommended levels for each of these risk factors were calculated among all those out of goal. Distance from goal was calculated as the difference between the actual levels and recommended goal. Goals for blood pressure were <140/90 mmHg, or <130/80 mmHg if DM or chronic kidney disease was present. LDL-C goal for those at low risk was <160 mg/dl; moderate to moderately high risk (6-20%) was <130 mg/dl; and high risk (>20%, DM or CVD) was <100 mg/dl. Goals for fasting glucose were <100 mg/dl, HDL-C \geq 40 mg/dl (M) and \geq 50 mg/dl (F), and for triglycerides were <150 mg/dl, based on revised AHA/NHLBI MetS recommendations (5).

LDL-C was calculated using the Friedwald equation ($LDL-C = \text{total cholesterol} - HDL-C - [1/5] \text{triglycerides}$) if triglycerides were under 400 mg/dL. HDL-C levels were measured by a precipitation method using a heparin-manganese (Mn) chloride mixture on a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Total cholesterol and triglycerides were measured enzymatically after hydrolyzation to glycerol on a Hitachi 704 Analyzer. Glycohemoglobin was measured using a glycohemoglobin

analyzer. Blood pressure was measured using a mercury sphygmomanometer and taking the average of four readings. Detailed specimen and data collection are discussed in the NHANES Laboratory/Medical Technologists Procedures Manual (8).

Cross tabulation procedures with SUDAAN software were used for population-weighted percentages. Chi-square test of proportions and ANOVA tests for comparing means were used to compare extent of positive risk factors for each parameter by gender and ethnicity. SAS statistical software version 9.1.3 (SAS Institute, Cary, North Carolina) as well as SUDAAN statistical software version 9.0.1 (Research Triangle Park, North Carolina) was used for analysis and computation of weighted estimates for projection to the U.S. population in 2003-2004.

Results

10-year Global Risk of Persons with Metabolic Syndrome

The 2003-2004 NHANES weighted prevalence of MetS as defined by the AHA/NHLBI modified NCEP/ATP III definition was 29.0% (the unweighted prevalence was 32.0%, based on 971 of 3034 subjects being classified with MetS). Among those with MetS, 38.5% had a calculated 10-year risk for CHD of <6% (low), 8.5% had 10-year CHD risk of 6-9% (moderate), 15.8% had 10-year CHD risk of 10-20% (moderately high), and 3.5% had 10-year CHD risk of >20% (high). The remaining 33.7% of MetS subjects had DM and/or CVD, which would put them in the highest risk category. This contrasts with those without MetS, where a significantly higher proportion were at low risk (79.7%) and lower proportions were at moderate (6.3%), moderately high (8.2%), and high risk (0.9%), or had DM and/or CVD (4.9%) ($p < 0.001$) (Figure 1). Logistic regression

shows the odds of being categorized as high risk in those subjects with Mets is 9.68 (95% CI =7.53-12.45), unadjusted, and after age adjustment, while this is attenuated, it remains highly significant: Odds = 6.05 (4.61-7.93).

While a similar proportion of male vs. female MetS subjects were categorized as high CHD risk (>20% 10-year risk of CHD, DM and/or CVD)(38.0% vs. 36.5%), 23.4% of males but only 7.6% of females were classified as moderately high risk ($p<0.001$ between males and females across risk categories). There were, however, no significant differences in CHD risk distribution when comparing different ethnic groups (Figure 2), with the proportion at high risk among Hispanics, non-Hispanic whites, and non-Hispanic blacks being 35.6%, 36.3%, and 41.6%, respectively ($p=0.27$). Among persons with MetS, from logistic regression analyses both unadjusted and age-adjusted, there were no significant differences in the likelihood of high risk status by gender or ethnicity (results not shown). Across age groups, the proportion of individuals with MetS at high risk (>20% 10-year risk or DM/CVD) increased dramatically with age from 4.4% in those aged 20-29 to 75.8% in those aged 70-79 among men and 17.1% to 55.0%, respectively, among women ($p<0.001$ when comparing risk category distribution by age for both men and women) (Figure 3).

A very similar risk distribution was calculated for MetS subjects identified under the International Diabetes Federation criteria, where an overall weighted prevalence of 26.8% (unweighted prevalence 29.0%) for MetS was obtained. 39.6% of subjects were at low risk, 8.5% at moderate, 15.5% at moderately-high, 3.4 at high, and 33.2% with DM or CVD when using the International Diabetes Federation criteria for MetS. By gender, 37.1% of men

and 35.9% of women, and by ethnicity, 34.3% of Hispanics, 35.6% of non-Hispanic whites, and 40.7% of non-Hispanic blacks ($p<0.001$ across gender) were defined to be at high risk, comparable to the proportions obtained using the NCEP definition above.

Prevalence of Metabolic Syndrome Risk Factors

Among individuals with MetS (classified by the NCEP ATP III definition), the most common risk factor components were increased waist circumference (93.4% of MetS subjects) followed by elevated triglycerides (64.6% of MetS subjects). Elevated LDL-C, while among the least common of the associated risk factors, was still present in 40.2% of MetS subjects. When comparing MetS subjects with DM to those without DM, those with DM showed a trend towards lower prevalence of abnormal HDL (50.1% vs 62.8% in those MetS subjects without DM) and triglycerides (59.3% vs. 65.9%).

Mean levels, proportion not at goal, and distance from goal of selected risk factors in MetS subjects

Mean levels of CVD risk factors for subjects with and without MetS are shown in Table 1. 34.4% of all MetS persons had systolic blood pressure not at recommended levels, while 17.9% were above recommended levels for diastolic pressure. Of those not at goal for blood pressure, mean blood pressures were 151 mmHg for systolic and 91 mmHg for diastolic, with an average distance from goal of 16 mmHg for systolic and 5 mmHg for diastolic blood pressure. 40.2% of all persons with MetS had LDL-C that was not controlled to recommended levels, with a mean LDL-C of 154 mg/dl (averaging 37 mg/dl from goal) in those not at goal. Overall, 53.4% of men and 68.1% of women with MetS were below their recommended HDL-C

levels, and 56.3% were not at goal for fasting glucose, with these persons averaging 23 mg/dl from goal. Expectedly, subjects without MetS had significantly lower levels of all measures (significantly higher for HDL-C), with significantly lower proportions not at goal or recommended levels (Table 1).

Conclusions

While persons with MetS are at greater risk of CHD events as compared to those without MetS (1,2), the heterogeneity in CHD risk among persons with MetS has not been fully described. The present study is unique in describing the overall risk distribution of all persons with MetS and shows a sizeable proportion of individuals with MetS are actually at low global risk of CHD. However, more than one-third of adults with MetS are in the high risk group (the majority classified as such because of pre-existing DM or CVD, and fewer subjects with multiple risk factors providing an estimated 10-year risk of CHD of >20%). Previous estimates of global risk in persons with MetS (4) were based on an earlier NHANES survey (1988-1994), and included persons age 30-74 without known DM or CVD; therefore, the full-spectrum of risk was not fully appreciated in that report. Moreover, our study is unique in showing the distance of MetS and non-MetS risk factors from recommended or goal levels and has shown one-third of MetS subjects are not at recommended blood pressure levels, 40% not at recommended LDL-C goals, and over half of MetS subjects have above normal levels of triglycerides, HDL-C, and glucose. Such information may be of use to clinicians in deciding how they should approach risk assessment in persons with MetS, as well as how aggressively to treat.

There are several limitations to our study. First, while the NCEP/ATP III risk

algorithm used in this study incorporated many criteria found in the Framingham coronary disease prediction algorithm, it did not include triglycerides, obesity, and hypertriglyceridemia, which could potentially affect risk estimation in MetS subjects in the multiethnic U.S. population, even though these factors did not add to prediction of CHD in the original Framingham cohort of primarily Caucasian subjects. While the Framingham risk equation has been validated in some ethnic populations in previous reports (9), it may or may not be fully applicable for multiethnic populations such as those in the most recent NHANES 2003-2004 survey. Our analysis did not show estimated CHD risk to differ by ethnicity among persons with MetS. In populations such as Hispanics who have lower CHD rates (10), it is also possible we may have overestimated risk in our subset of Hispanics. Conversely, despite blacks having poorer CVD outcomes, our analysis did not identify estimated CHD risk to be significantly greater among blacks with MetS. Certain factors that may relate to poorer outcomes in blacks (e.g., left ventricular hypertrophy), being neither part of the MetS definition nor the Framingham risk algorithms used, may help explain this. Second, NCEP/ATP III algorithm does not take into account family history of premature CHD or new markers (e.g., C-reactive protein) or subclinical measures of CHD which may be more common in MetS subjects, thereby potentially underestimating risk in certain persons. For example, it has been shown that within a given calculated risk strata (e.g., 10-20% CHD risk), actual CHD event risk varied several-fold according to level of coronary calcium score (11). Additionally, as information on CVD was based on self-report, it is possible that these could be underestimated, which would result in a

lower overall risk of CHD than may actually be the case. Finally, this study only addresses 10 year risk for CHD; lifetime CHD risk is substantially greater and may be a more relevant endpoint for the purposes of targeting therapy (12).

In conclusion, a wide spectrum of estimated risk of CHD exists in U.S. adults with MetS; about one third of MetS subjects are at high risk of CHD (either due to pre-existing CHD, DM, or >20% calculated risk of CHD), and approximately one-half are at 10% or greater risk for CHD. These proportions are significantly higher in persons with, versus without MetS. Specifically, more than one third of men with MetS have high risk of CHD in 10 years. Finally, many persons with MetS remain a significant distance from recommended or normal levels of lipids, blood pressure, and/or glucose. These findings highlight the importance of global risk assessment in persons with MetS in order to appropriately intensify treatment of their cardiometabolic risk factors.

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Table 1. Mean and distance to goal or recommended levels of cardiovascular risk factors in persons with and without metabolic syndrome

	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Triglycerides (mg/dL)	Waist Circumference (cm)	HDL (mg/dL)	Fasting glucose (mg/dL)	LDL-C (mg/dL)
Overall mean (median)							
MetS	131‡ (132)	75‡ (73)	204‡ (171)	M: 114‡ (110) F: 106‡ (104)	M: 40‡ (39) F: 48‡ (46)	108‡ (103)	124‡ (122)
Non-MetS	117 (116)	70 (69)	101 (89)	M: 94 (94) F: 88 (87)	M: 52 (51) F: 64 (63)	88 (88)	117 (116)
Proportion not at goal or recommended levels							
MetS	34.4‡	17.9‡	64.6‡	M: 90.1‡ F: 96.9‡	M: 53.4‡ F: 68.1‡	56.3‡	40.2‡
Non-MetS	7.4	3.8	11.5	M: 19.9 F: 42.6	M: 10.2 F: 17.8	7.9	18.5
Mean (median) among subjects not at goal or recommended levels							
MetS	151 (149)	91 (91)	261 (205)	M: 116‡ (112) F: 107‡ (105)	M: 35 (36) F: 41† (42)	123‡ (112)	154 (150)
Non-MetS	152 (149)	93 (92)	231 (201)	M: 111 (109) F: 101 (99)	M: 34 (33) F: 43 (44)	110 (104)	163 (161)
Mean (median) distance from goal among subjects not at goal or recommended levels							
MetS	16 (13)	5 (3)	111 (55)	M: 14‡ (10) F: 19‡ (17)	M: 5 (4) F: 9† (8)	23‡ (12)	37 (29)
Non-MetS	14 (11)	5 (3)	81 (51)	M: 9 (7) F: 13 (11)	M: 6 (5) F: 7 (6)	10 (4)	29 (23)

Goals or recommended levels for systolic/diastolic blood pressure are <140/90 mmHg or <130/80 mmHg for those with DM or CKD, triglycerides <150 mg/dl, waist circumference <102 cm for men or <88 cm for women, HDL-C ≥40 mg/dl for men and ≥50 mg/dl for women, glucose <100 mg/dl, and LDL-C <100 mg/dl for CVD, DM, or high risk (>20% 10 year risk), <130 mg/dl for moderate risk (6-20% 10 year risk), <160 mg/dl for low risk (<6% 10 year risk). †p<0.01, ‡p<0.001.

Figure 1. Proportion of persons with and without MetS classified by 10-year CHD risk group: low (<6%), moderate (6-<10%), moderately high (10-20%), and high (>20% or DM/CVD) risk groups. $p < 0.001$ comparing distribution of risk groups between those with vs. without MetS. DM=diabetes, CVD=cardiovascular disease.

Figure 1.

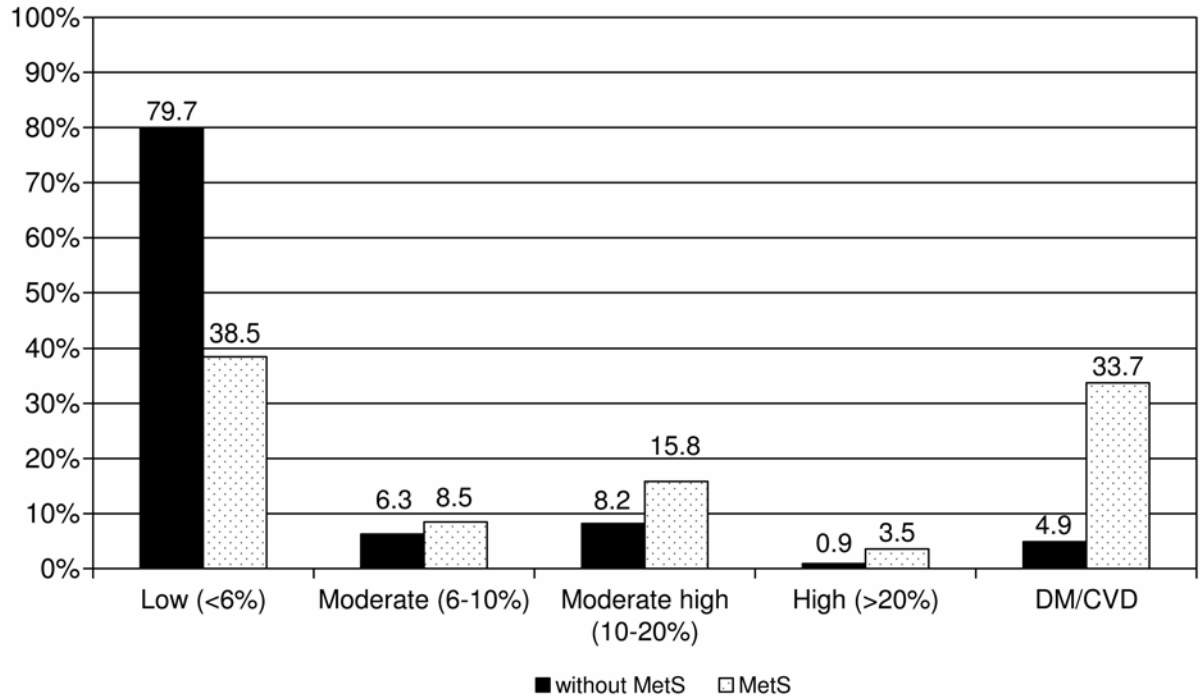


Figure 2. Distribution of 10-year estimated risk for coronary heart disease: low (<6%), moderate (6-<10%), moderately high (10-20%) and high (>20% or diabetes or cardiovascular disease) persons with MetS stratified by gender and race. $p < 0.001$ comparing distribution of risk groups between men and women.

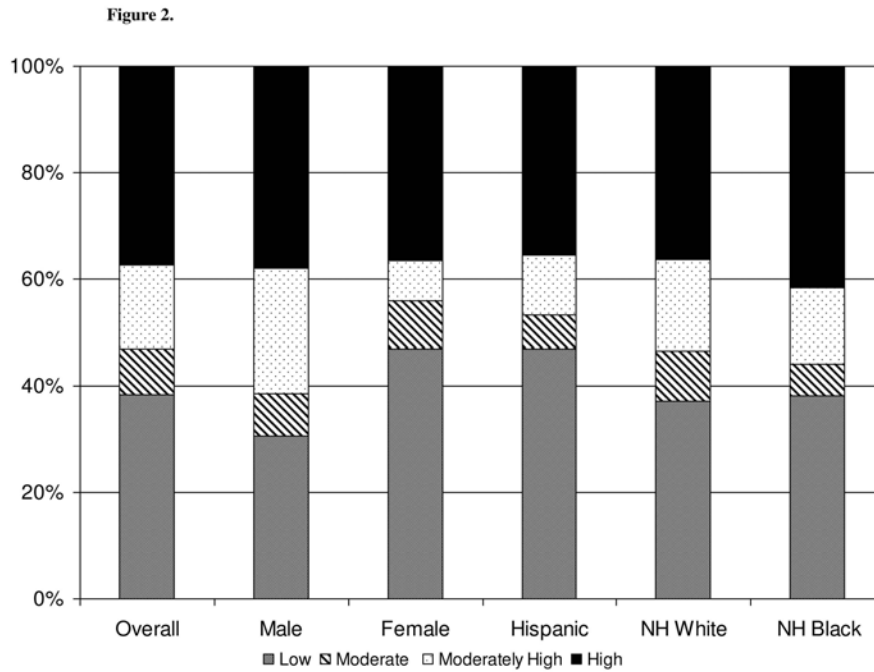


Figure 3. Distribution of 10-year estimated risk for coronary heart disease by age group stratified by gender: low (<6%), moderate (6-<10%), moderately high (10-20%) and high (>20% or diabetes or cardiovascular disease). $p < 0.001$ comparing distribution of risk groups across age groups for both men and women.

Figure 3.

