NCEP-Defined Metabolic Syndrome, Diabetes, and Prevalence of Coronary Heart Disease Among NHANES III Participants Age 50 Years and Older

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Although the individual components of the metabolic syndrome are clearly associated with increased risk for coronary heart disease (CHD), we wanted to quantify the increased prevalence of CHD among people with metabolic syndrome. The Third National Health and Nutrition Examination Survey (NHANES III) was used to categorize adults over 50 years of age by presence of metabolic syndrome (National Cholesterol Education Program [NCEP] definition) with or without diabetes. Demographic and risk factor information was determined for each group, as well as the proportion of each group meeting specific criteria for metabolic syndrome. The prevalence of CHD for each group was then determined. Metabolic syndrome is very common, with ~44% of the U.S. population over 50 years of age meeting the NCEP criteria. In contrast, diabetes without metabolic syndrome is uncommon (13% of those with diabetes). Older Americans over 50 years of age without metabolic syndrome regardless of diabetes status had the lowest CHD prevalence (8.7% without diabetes, 7.5% with diabetes). Compared with those with metabolic syndrome, people with diabetes without metabolic syndrome did not have an increase in CHD prevalence. Those with metabolic syndrome without diabetes had higher CHD prevalence (13.9%), and those with both metabolic syndrome and diabetes had the highest prevalence of CHD (19.2%) compared with those with neither. Metabolic syndrome was a significant univariate predictor of prevalent CHD (OR 2.07, 95% CI 1.66–2.59). However, blood pressure, HDL cholesterol, and diabetes, but not presence of metabolic syndrome, were significant multivariate predictors of prevalent CHD. The prevalence of CHD markedly increased with the presence of metabolic syndrome. Among people with diabetes, the prevalence of metabolic syndrome was very high, and those with diabetes and metabolic syndrome had the highest prevalence of CHD. Among all individuals with diabetes, prevalence of CHD was increased compared with those with metabolic syndrome without diabetes. However, individuals with diabetes without metabolic syndrome had no greater prevalence of CHD compared with those with neither. *Diabetes* 52:1210–1214, 2003

The frequent simultaneous presence of obesity, hyperlipidemia, diabetes, and hypertension was first described in the late 1960s (1). This association (i.e., diabetes, hypertension, and obesity with hyperlipidemia) was subsequently highlighted in the late 1970s by a number of German researchers, including Haller and colleagues (2,3). They coined the term "metabolic syndrome" and described its association with atherosclerosis. In 1991, Ferrannini et al. (4) described the same clustering of abnormalities in this cardiovascular and metabolic syndrome as being caused by insulin resistance and concluded that "insulin resistance syndrome" was the appropriate name for this condition. At about the same time, Reaven (5,6) agreed that insulin resistance was the cause of these abnormalities. He initially did not include abdominal obesity, however, and he used the term "syndrome X." It appears that metabolic syndrome, insulin resistance syndrome, and syndrome X all refer to the same clustering of risk factors associated with atherosclerosis and coronary heart disease (CHD). In fact, Meigs et al. (7) found that among nondiabetic subjects from the Framingham Offspring Study, a clustering of risk factors, including hyperinsulinemia, dyslipidemia, hypertension, and glucose intolerance (rather than hyperinsulinemia alone), characterized the underlying features of the insulin resistance syndrome.

The pathophysiology of this syndrome remains a subject of continuing controversy, although some have suggested a causal relationship with insulin resistance and/or visceral adiposity. At the same time, it has become increasingly apparent that even small increases in fasting or postprandial glucose values (including impaired glucose tolerance or impaired fasting glucose) impart an increased risk for cardiovascular morbidity and mortality (8–14). In the Quebec Prospective Study, Lamarche et al. (15) showed that even without hyperglycemia, elevated levels of insulin (i.e., insulin resistance), small dense LDL cholesterol, and apolipoprotein B were associated with risk for ischemic heart disease.

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provided a definition for metabolic syndrome (16). The NCEP criteria are practical for physicians to use, since the variables defining

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ATP, Adult Treatment Panel; CHD, coronary heart disease; NCEP, National Cholesterol Education Program; NCHS, National Center for Health Statistics; NHANES III, Third National Health and Nutrition Examination Survey.

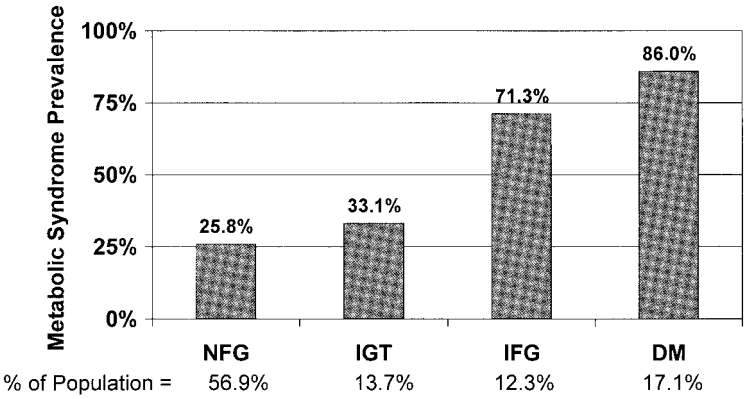

FIG. 1. Age-adjusted prevalence of metabolic syndrome in the U.S. population over 50 years of age categorized by glucose intolerance (NFG, normal fasting glucose; IGT, impaired glucose tolerance without impaired fasting glucose; IFG, impaired fasting glucose with or without impaired glucose tolerance; DM, diabetes mellitus).

metabolic syndrome are commonly available in clinical practice. Ford et al. (17) have previously shown that metabolic syndrome is common in people ≥50 years of age. Since glucose intolerance is an important part of metabolic syndrome and increases with age, this report will focus on the interactions among metabolic syndrome, hyperglycemia, and prevalence of CHD. We used Third National Health and Nutrition Examination Survey (NHANES III) data to evaluate the prevalence of CHD in individuals ≥50 years of age with metabolic syndrome, with and without diabetes, using the NCEP definition.

RESEARCH DESIGN AND METHODS

NHANES III was conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, in two phases: phase 1 (1988–1991) and phase 2 (1991–1994) (17–19). For this analysis, subjects surveyed during either phase are included. The survey was a stratified probability sample of the civilian, noninstitutionalized U.S. population. African Americans, Mexican Americans, and the elderly were oversampled to provide more accurate estimates of their characteristics within their respective populations and the population as a whole. Each respondent was assigned a weight based on geographic and demographic characteristics to allow the calculation of population-based estimates. A subset of adults ≥50 years of age representing 76.1 million Americans was used for this analysis.

An adult in-home questionnaire was administered to sampled subjects ≥17 years of age. Physical exams were conducted on those subjects who were ambulatory and who consented to the examination given at a date subsequent to the in-home interview. Adults ≥50 years of age who were scheduled for and received morning physical exams after a fast of at least 9 h were retained for analysis (n = 3,510). During NHANES III, oral glucose tolerance testing was conducted on approximately one-half of the examinees aged 40–74 years. This subsample most closely conformed to the World Health Organization criteria for oral glucose tolerance testing to identify diabetes and was the population used to estimate the prevalence of diabetes and impaired glucose tolerance.

The NCEP ATP III panel defined metabolic syndrome as the presence of three or more of the following risk determinants: *1*) increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women); *2*) elevated triglycerides (≥150 mg/dl); *3*) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); *4*) hypertension (≥130/≥85 mmHg); and *5*) impaired fasting glucose (≥110 mg/dl) (16).

We determined the prevalence of metabolic syndrome based on fasting glucose levels and glucose tolerance and then stratified the population into four groups (no metabolic syndrome or diabetes, metabolic syndrome without diabetes, metabolic syndrome with diabetes, and no metabolic syndrome with diabetes) using the NCEP definition of the metabolic syndrome and either self-reported history of diabetes or a fasting plasma glucose value ≥7.0 mmol/l (≥126 mg/dl) (16,20). Serum lipoproteins were evaluated as part of the blood biochemistry panel of the laboratory exam. LDL cholesterol was calculated using the Friedewald equation for those with serum triglyceride levels ≤400 mg/dl (21). Blood pressure is reported as the average of six readings, three taken during the household interview and three taken during the physical exam. The NCEP metabolic syndrome cutpoint for blood pressure is ≥130/85 mm/Hg. Individuals reporting a history of hypertension and current blood pressure medication use were defined as having hypertension regardless of measured blood pressure values. BMI was calculated as the weight of the individual in kilograms divided by the square of the height in centimeters. Individuals with a history of diabetes or glycemic medication use were defined as having diabetes regardless of measured fasting glucose values. Insulin measurements were performed using the Pharmacia Diagnostics radioimmunoassay kit. Insulin sensitivity was calculated using the formula of McAuley et al. (22) as the exponent of [2.63 − 0.28 ln(insulin mU/l) − 0.31 ln(triglyceride mmol/l)] and the homeostasis model assessment of insulin resistance (23).

As a result of low prevalence of CHD in the population <50 years of age (3.1% for <50 years vs. 12.3% for ≥50 years, unadjusted rates) and since metabolic syndrome clusters with age, we chose to focus our analysis on those ≥50 years of age. Presence of CHD is defined as self-reported myocardial infarction or a positive response to the angina pectoris section of the Rose Questionnaire (24). Our definition of CHD was based upon information available in the NHANES III database, but probably represents an underestimate of the true prevalence. Defining CHD only as self-reported without including information from the Rose Questionnaire reduces the prevalence of CHD by 2–3% but does not otherwise change our results.

Statistical analysis. All data were analyzed using SAS version 8e and SAS-callable SUDAAN version 8.0.1 (25,26). SUDAAN uses characteristics of the sample design and sample weights to calculate appropriate estimates of variance. The CROSSTAB and DESCRIPT procedures of SUDAAN were used to produce frequencies of categorical variables and means ± SE of continuous variables. Overall tests of significance across the four study groups were evaluated by ANOVA using the MULTILOG and REGRESS procedures. Summary statistics are presented as means ± SE for continuous measures and frequency percentage for all discrete measures. Age-adjusted CHD prevalence rates were computed by the direct method using the age distribution of the U.S. population based on the 2000 U.S. Census.

For Fig. 2, tests of significance were calculated using pairwise comparisons adjusted for multiple comparisons by the method of Bonferroni. A multivariate logistic model predicting CHD was developed using the RLOGIST procedure in SUDAAN. The independent variables of interest, the individual risk factors of metabolic syndrome as defined by NCEP, diabetes, and an indicator variable for metabolic syndrome (a proxy for the interactions of the individual factors) were fit simultaneously. The odds ratios and 95% CIs for having CHD given the presence of any one risk factor, controlling for all others, are presented in Table 3.

The attributable risk of CHD was calculated as the difference in prevalence between the population without either diabetes or metabolic syndrome and the appropriate group (i.e., metabolic syndrome without diabetes, diabetes without metabolic syndrome, diabetes and metabolic syndrome) divided by the prevalence of CHD in the appropriate group.

RESULTS

Age-adjusted prevalence of metabolic syndrome in the U.S. population ≥50 years of age categorized by glucose intolerance is shown in Fig. 1. There is a stepwise increase in prevalence of metabolic syndrome with worsening glucose tolerance from 26% in those with normal fasting glucose rising to 86% in those with diabetes. As can be seen in Table 1, metabolic syndrome is very common in the U.S. population over the age of 50 years, with ~43.5% meeting the NCEP criteria. In contrast, diabetes without metabolic syndrome is uncommon in the over-50 population (only ~13% of diabetic patients do not meet criteria for metabolic syndrome).

For most cardiovascular risk factors, the group with

TABLE 1
Demographic and laboratory characteristics among U.S. population ≥50 years

	No diabetes		Diabetes			
	No metabolic syndrome	Metabolic syndrome	No metabolic syndrome	Metabolic syndrome	*P* *	Total
Percentage of population	54.2%	28.7%	2.3%	14.8%		
Factor						
% Male	45.5	42.2	55.7	48.2	0.1218	45.2
Age (years)	63.4 ± 0.4	65.2 ± 0.6	68.5 ± 0.8	65.5 ± 0.6	<0.0001	64.3 ± 0.3
% Smoker	22.3	19.0	24.9	16.1	0.2757	20.5
LDL cholesterol (mg/dl)	138.3 ± 1.4	143.9 ± 1.7	135.3 ± 3.5	138.8 ± 2.2	0.0322	139.9 ± 1.1
HDL cholesterol (mg/dl)	56.5 ± 0.6	44.0 ± 0.7	58.8 ± 2.2	42.4 ± 1.1	<0.0001	50.9 ± 0.5
Triglycerides (mg/dl)	119.9 ± 2.5	211.9 ± 5.4	118.0 ± 6.3	231.5 ± 9.0	<0.0001	162.6 ± 3.3
Systolic BP mm/Hg	129.1 ± 0.8	140.3 ± 0.7	129.7 ± 3.0	139.7 ± 1.1	<0.0001	133.9 ± 0.6
Diastolic BP mm/Hg	73.9 ± 0.3	78.3 ± 0.6	72.3 ± 1.2	75.0 ± 0.6	<0.0001	75.3 ± 0.3
BMI	25.4 ± 0.2	29.6 ± 0.3	24.7 ± 0.8	30.9 ± 0.4	<0.0001	27.4 ± 0.2
Insulin sensitivity	7.4 ± 0.1	5.5 ± 0.1	6.7 ± 0.2	4.9 ± 0.1	<0.0001	6.5 ± 0.1
HOMA-IR	2.1 ± 0.1	3.6 ± 0.1	10.0 ± 3.0	11.5 ± 0.9	<0.0001	4.1 ± 0.2

Data are means ± SE unless otherwise indicated. *Statistical significance of differences across the groups (ANOVA). BP, blood pressure; HOMA-IR, homeostasis model assessment for insulin resistance.

metabolic syndrome and without diabetes was more comparable to the diabetes with metabolic syndrome group than to both groups without metabolic syndrome. An exception to this observation was HbA_{1c} levels, where the two diabetes groups were comparable. The two groups without metabolic syndrome were also very similar regardless of absence or presence of diabetes. Insulin resistance was highest and insulin sensitivity was lowest in the diabetes with metabolic syndrome group (4.9 ± 0.1), followed by the metabolic syndrome without diabetes group (5.5 ± 0.1). Insulin resistance was lowest and insulin sensitivity was highest in the group without metabolic syndrome or diabetes (7.4 ± 0.1, $P < 0.0001$).

The proportion of each group meeting each NCEP criterion for metabolic syndrome is shown in Table 2. Again, the characteristics of the two metabolic syndrome groups are comparable with the exception of fasting glucose (by definition) and are different from the two groups without metabolic syndrome.

Figure 2 shows the age-adjusted prevalence of CHD in the various groups. The overall prevalence in this age group was 11.7%. Americans over 50 years of age without metabolic syndrome and diabetes had the lowest CHD prevalence (8.7%), and those with both metabolic syndrome and diabetes had the highest (19.2%). Individuals with diabetes in the absence of metabolic syndrome did not have an incremental increase in CHD prevalence compared with individuals with neither (7.5 vs. 8.7%, respectively). Differences between the groups, both overall and using pairwise comparisons, were all statistically significant ($P < 0.001$).

Not surprisingly, metabolic syndrome was a significant predictor of prevalent CHD in univariate analysis (OR 2.07, 95% CI 1.66–2.59). However, as shown in Table 3, blood pressure, HDL cholesterol, and diabetes, but not presence of metabolic syndrome, were significant predictors of prevalent CHD in multivariate analyses.

As shown in Table 4, the excess prevalence of CHD attributable to metabolic syndrome and/or diabetes was 37.4% (1.1 million cases of CHD) in the group with metabolic syndrome without diabetes and 50.3% (1.1 million cases of CHD) in the group with both metabolic syndrome and diabetes. The entire excess prevalence of CHD among those with diabetes was in the group with both diabetes and metabolic syndrome.

DISCUSSION

This analysis examined CHD prevalence by metabolic syndrome criteria from the NCEP and diabetes status based on 1997 American Diabetes Association criteria using NHANES III, the most recent large clinical survey of a representative sample of the U.S. population, which collected all necessary information to characterize individ-

TABLE 2
Criteria for metabolic syndrome among U.S. population ≥50 years

	No diabetes		Diabetes		
	No metabolic syndrome	Metabolic syndrome	No metabolic syndrome	Metabolic syndrome	Total
Percentage of population	54.2%	28.7%	2.3%	14.8%	
Criterion					
% Waist circumference (M >102 cm; F >88 cm)	34.4	82.0	18.5	86.0	55.0
% Triglycerides ≥150 mg/dl	18.0	77.8	5.1	72.1	42.8
% HDL cholesterol (M <40 mg/dl; F <50 mg/dl)	16.5	70.7	2.6	69.7	39.5
Blood pressure ≥130/85 mm/Hg (%)	45.3	86.2	43.0	82.7	62.5
Fasting glucose >110 (%)	6.2	30.9	83.0	90.2	27.2

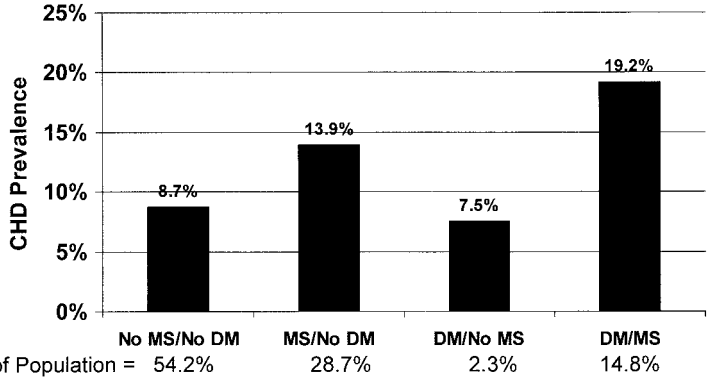

FIG. 2. Age-adjusted prevalence of CHD in the U.S. population over 50 years of age categorized by presence of metabolic syndrome and diabetes. Combinations of metabolic syndrome (MS) and diabetes mellitus (DM) status are shown.

uals by metabolic status. The prevalence of metabolic syndrome increases with increasing glucose intolerance. The prevalence of CHD markedly increases with the presence of metabolic syndrome. The prevalence of CHD among all participants with diabetes was increased compared with the prevalence among those with metabolic syndrome without diabetes. However, individuals with diabetes without metabolic syndrome had about the same prevalence of CHD as those with neither.

One possible reason for the excess prevalence of CHD associated with metabolic syndrome is the direct effect of insulin resistance on the heart and arteries (27). It is more likely that the bulk of the increased prevalence is mediated by known cardiovascular risk factors. Indeed, all five metabolic syndrome criteria are established cardiovascular risk factors. We know that the presence of multiple risk factors confers increased risk (28). However, it is unclear whether the metabolic syndrome confers elevated risk beyond the sum of its parts (29). Our multivariate analysis would suggest that the risk from metabolic syndrome is derived from its individual components, especially HDL cholesterol and blood pressure. However, modeling metabolic syndrome as the sole predictor of CHD yields more than a twofold increased risk compared with not having metabolic syndrome and is a convenient way to encapsulate a number of proven risk factors.

It has been argued that the excess prevalence of CHD seen in those with diabetes is directly associated with hyperglycemia. In our study, metabolic syndrome has been demonstrated to be much more important, with no increase in prevalence of CHD seen in people with diabetes in the absence of metabolic syndrome. Although one of the components of metabolic syndrome is fasting hyperglycemia and many of the subjects in this study with metabolic syndrome without diabetes still may have had hyperglycemia in the nondiabetic range, modestly increased glucose alone is unlikely to account for the increased CHD risk. Because *1*) most people with diabetes have type 2 diabetes and metabolic syndrome and *2*) most individuals with impaired fasting glucose also have metabolic syndrome, our work is consistent with our previous study using NHANES III data that showed an increased CHD prevalence in those with diabetes and impaired fasting glucose (30).

There are limitations to this analysis. Since the case fatality rate among people with diabetes is higher than in those without diabetes, this cross-sectional study is subject to survival bias, which would underestimate the impact of diabetes on CHD. The same may also be true for metabolic syndrome in the absence of diabetes. The NCEP criteria for metabolic syndrome have face validity, but have not yet been formally validated or studied. Since NHANES III was a cross-sectional study, we cannot infer causality from these associations. These results should be considered hypothesis-generating, which requires prospective studies among those with diabetes to demonstrate if those without the metabolic syndrome indeed have a lower cardiovascular risk than those with the syndrome. More recent studies have shown that there is a continuing epidemic of diabetes and obesity and suggest that NHANES III data, even adjusted for recent census data, may be underestimating the prevalence of diabetes and metabolic syndrome (31).

The prevalence of CHD markedly increases with presence of metabolic syndrome. Among people with diabetes, prevalence of metabolic syndrome was very high, and those with diabetes and metabolic syndrome had the highest prevalence of CHD. Among all individuals with diabetes, prevalence of CHD was increased compared to those with metabolic syndrome without diabetes. How-

TABLE 3
Prediction of CHD prevalence using multivariate logistic regression

Variable*	Odds ratio	Lower 95% limit	Upper 95% limit
Waist circumference	1.13	0.85	1.51
Triglycerides	1.12	0.71	1.77
HDL cholesterol*	1.74	1.18	2.58
Blood pressure*	1.87	1.37	2.56
Impaired fasting glucose	0.96	0.60	1.54
Diabetes*	1.55	1.07	2.25
Metabolic syndrome	0.94	0.54	1.68

*Significant predictors of prevalent CHD.

TABLE 4
Attributable risk of metabolic syndrome and diabetes for CHD in U.S. population ≥50 years

	No diabetes	Diabetes	
	Metabolic syndrome	No metabolic syndrome	Metabolic syndrome
Total population	21,841,000	1,750,000	11,263,000
Population with CHD	3,036,000	131,000	2,162,496
Attributable risk	37.4%	NM	54.7%

NM, not meaningful.

ever, individuals with diabetes without metabolic syndrome had no greater prevalence of CHD compared with those with neither.

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