Prevalence and Characteristics of the Metabolic Syndrome in the San Antonio Heart and Framingham Offspring Studies

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The metabolic syndrome may be a common phenotype increasing risk for type 2 diabetes and cardiovascular disease. We assessed the prevalence and characteristics of the metabolic syndrome among population-based samples of 3,224 white subjects attending Framingham Offspring Study (FOS) exam 5 (1991–1995) and 1,081 non-Hispanic white and 1,656 Mexican-American subjects attending the San Antonio Heart Study (SAHS) phase II follow-up exam (1992–1996). Subjects were ~50% women, aged 30–79 years, without diabetes, and classified with the metabolic syndrome according to criteria for obesity, dyslipidemia, hyperglycemia, and hypertension proposed by the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) or the World Health Organization (WHO). We used regression models to estimate rates across ethnic groups and to assess the association of the metabolic syndrome with insulin resistance and predicted 10-year coronary heart disease (CHD) risk. Among FOS white subjects, the age- and sex-adjusted prevalence of the metabolic syndrome was 24% by both ATP III and WHO criteria; among SAHS non-Hispanic white subjects, 23 and 21%, respectively; and among SAHS Mexican-American subjects, 31 and 30%. Rates were highest among Mexican-American women (ATP III, 33%) and lowest among white women (21%). Subjects with the metabolic syndrome by ATP III criteria had higher age-, sex-, and ethnicity-adjusted levels of fasting insulin (11.3 μU/ml), homeostasis model assessment of insulin resistance (2.7), and predicted CHD risk (11.8%) than those without the syndrome (5.9 μU/ml, 1.3, and 6.4%, respectively; all $P = 0.0001$); differences were similar using WHO criteria. We conclude that the metabolic syndrome typically affects 20–30% of middle-aged adults in the U.S. By any criteria, subjects with the metabolic syndrome are more insulin resistant and at increased predicted risk for CHD versus those without the metabolic syndrome. *Diabetes* 52:2160–2167, 2003

The concept of a cluster of metabolic disorders encompassing risk factors for type 2 diabetes and cardiovascular disease (CVD) has become well established during the past 15 years since the proposal of "syndrome X" or the "insulin resistance syndrome" (1,2). During this period, prospective data have shown that central and total obesity, elevated levels of triglycerides and depressed levels of HDL cholesterol, hypertension, glucose intolerance, and insulin resistance predict the development of type 2 diabetes and CVD (3–6). Clustering analyses confirm that these traits occur simultaneously to a greater degree than would be expected by chance alone (7,8), and factor analyses suggest that these diverse traits reflect a limited number of underlying physiological phenotypes (9,10). This evidence supports the existence of a discrete disorder meriting appellation as a "metabolic syndrome." Central to the syndrome is an obesity-hyperinsulinemia-dyslipidemia phenotype, which itself has been shown to predict incident development of both type 2 diabetes and CVD (11–13). There is also evidence of a genetic basis for the metabolic syndrome (14).

Despite these advances, however, there has been no uniform case definition for the syndrome, which has impeded epidemiological investigation of its prevalence and characteristics across diverse populations. Recently, the World Health Organization (WHO) (15) and the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) (16) proposed working criteria for the metabolic syndrome. These criteria are similar in their focus on obesity, dyslipidemia, hyperglycemia, and hypertension; however, they have potentially substantive differences in their specific constituent traits and trait threshold criteria. Whether these similarities and differences translate into important differences in overall metabolic syndrome prevalence, insulin resistance, or predicted risk of coronary heart disease (CHD) is not well specified. In this report, we address these questions in the population-based

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2hPG, 2-h postchallenge glucose; ATP III, Third Report of the National Cholesterol Education Program's Adult Treatment Panel; CHD, coronary heart disease; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; FFM, fat-free mass; FOS, Framingham Offspring Study; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; SAHS, San Antonio Heart Study; UACR, urine albumin/creatinine ratio; WHO, World Health Organization; WHR, waist-to-hip ratio.

Framingham Offspring Study (FOS) and San Antonio Heart Study (SAHS).

RESEARCH DESIGN AND METHODS

Participants

Framingham Offspring Study. Participants in the FOS, a long-term, community-based, prospective observational study, are the children and spouses of the children of the original Framingham Heart Study cohort (17,18). Virtually all subjects are white and of mixed European Caucasian ancestry. Data for the present study was taken from the 5th Offspring exam (1991–1995), for which 3,799 participants (85% of eligible subjects) fasted overnight, provided plasma samples for insulin, glucose, lipid, and other measurements, and had a standardized medical history and physical. Subjects without diagnosed diabetes had a 2-h, 75-g oral glucose tolerance test (OGTT). Subjects were considered to have diagnosed diabetes if they reported current or past hypoglycemic drug therapy or if fasting plasma glucose (FPG) was ≥7.0 mmol/l at any two prior exams. Nondiabetic subjects were classified into glucose tolerance categories based on OGTT results using 1997 ADA and 1998 WHO criteria (15,19). Subjects were classified as having previously undiagnosed diabetes if either the FPG was ≥7.0 mmol/l or the 2-h postchallenge glucose (2hPG) level was ≥11.1 mmol/l; with impaired fasting glucose (IFG) if the FPG was 6.1–6.9 mmol/l and the 2hPG was 7.8–11.0 mmol/l; with impaired glucose tolerance (IGT) if the FPG was <6.1 mmol/l and the 2hPG was 7.8–11.0 mmol/l; and with normal glucose tolerance if the FPG was <6.1 mmol/l and the 2hPG was <7.8 mmol/l. Height, weight, waist circumference (at the umbilicus), and hip circumference (at the greater trochanter) were measured, BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2), and the waist-to-hip ratio (WHR) was calculated. The average of two blood pressure measurements, taken after subjects had been seated for at least 5 min, was calculated. Participants who reported smoking at least one cigarette per day during the year before the examination were classified as current smokers.

Plasma glucose was measured in fresh specimens with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA). Glucose assays were run in duplicate; the intra-assay coefficient of variation was <3%. Fasting insulin levels were measured as total immunoreactive insulin (Coat-A-Count Insulin; Diagnostic Products, Los Angeles, CA). Cross-reactivity of this assay with pro-insulin at mid-curve is at least 70%, and the the intra- and inter-assay coefficients of variation ranged from 5.0 to 10.0%. Plasma insulin levels were calibrated to serum level equivalents and further calibrated with insulin levels in the SAHS, as described previously (20). Calibrated fasting serum insulin levels were used to calculate levels of insulin resistance using the homeostatic model, where homeostasis model assessment of insulin resistance (HOMA-IR) = fasting insulin × glucose/22.5 (21), or insulin sensitivity (adjusted for fat-free mass [FFM] − IS) as a function of fasting insulin and triglycerides, where $\text{FFM} - \text{IS} = e^{[2.63 - 0.28(\log \text{fasting insulin}) - 0.31(\log \text{triglycerides})]}$ (22). The fasting total plasma cholesterol and plasma triglyceride levels were measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of LDL and VLDL cholesterols with dextran sulfate-magnesium (23). We also exchanged samples with the SAHS to compare lipid measurements; correlations between total cholesterol and fasting triglyceride levels in the two studies were >0.9. LDL cholesterol was estimated indirectly where triglyceride levels were <4.52 mmol/l (24). The Framingham laboratory participates in the lipoprotein cholesterol laboratory standardization program administered by the Centers for Disease Control in Atlanta, Georgia. The urine albumin/creatinine ratio (UACR) was assessed at the 6th FOS exam (1995–1998) from a single void urine sample. The urine albumin concentration was measured by immunoturbimetry (Tina-quant Albumin assay; Roche Diagnostics, Indianapolis, IN) and the urine creatinine concentration using a modified Jaffe method. We classified subjects with microalbuminuria if the UACR was >30 mg/g. The FOS has ongoing approval from the Institutional Review Board of the Boston University School of Medicine, and all participants provided written informed consent.

San Antonio Heart Study. The SAHS is a long-term, community-based, prospective observational study of diabetes and CVD in Mexican Americans and non-Hispanic whites (25,26). The study initially enrolled 3,301 Mexican-American and 1,857 non-Hispanic white men and nonpregnant women in two phases between 1979 and 1988. Participants were 25–64 years of age at enrollment and were randomly selected from low-, middle-, and high-income neighborhoods in San Antonio, Texas. A 7- to 8-year follow-up exam began in 1987 and was completed in the fall of 1996. A total of 3,682 individuals (73.7% of survivors) from the two phases completed the follow-up examination. Data for the present study come from subjects seen between 1988 and 1996 during the follow-up study. The clinical examination, informed consent procedures, definitions of clinical characteristics, and laboratory analysis methods were essentially identical to those used in the FOS. UACR data were not available for SAHS participants. The SAHS has ongoing approval from the Institutional Review Board of the University of Texas Health Sciences Center, San Antonio.

Measurements

Metabolic syndrome trait, metabolic syndrome, and CVD risk factor criteria. We applied published criteria to classify subjects with the metabolic syndrome, with the following exceptions: First, we excluded subjects with diagnosed or OGTT-detected diabetes (except where explicitly stated in RESULTS). The WHO explicitly and the ATP III implicitly include type 2 diabetes as part of glucose intolerance traits, but we consider diabetes to be a *consequence* and not a *component* of the syndrome. Second, the WHO specifies use of a glucose clamp to assess insulin resistance, but we followed the recommendations of the European Group for the Study of Insulin Resistance (EGIR) and defined insulin resistance as a fasting insulin level exceeding the 75th percentile of the distribution in the nondiabetic population (27). Third, we included subjects with treated hypertension among those with elevated blood pressure traits. Lastly, microalbuminuria data were not available for SAHS participants, so we calculated the prevalence of the WHO-defined metabolic syndrome without considering this trait for across-population comparisons.

We classified subjects with the metabolic syndrome by WHO criteria (15) according to the following schema:

IFG and/or IGT and/or insulin resistance and two or more of the following:

- WHR >0.90 (men), >0.85 (women), or BMI ≥30 kg/m^2;
- Triglyceride ≥1.7 mmol/l or HDL cholesterol <0.9 mmol/l (men), <1.0 mmol/l (women);
- Blood pressure ≥140/90 mmHg (or treated hypertension);
- Microalbuminuria.

We classified subjects with the metabolic syndrome by ATP III criteria (16) according to the following schema:

Any three of the following:

- FPG ≥6.1 mmol/l;
- Waist circumference ≥102 cm (men), ≥88 cm (women);
- Triglycerides ≥1.7 mmol/l;
- HDL cholesterol <1.0 mmol/l (men), <1.16 mmol/l (women);
- Blood pressure ≥130/85 mmHg (or treated hypertension).

We also assessed the prevalence of the metabolic syndrome according to two different modifications of the ATP III criteria. In one, we replaced the large waist trait with the BMI ≥30 kg/m^2 trait, as waist measurement is not uniformly used in clinical care. In the other, we required a large waist circumference and high triglyceride and/or low HDL cholesterol levels (for a sum of at least two traits), and either hyperglycemia or elevated blood pressure, for a sum total of any three traits, as factor analyses of metabolic syndrome traits suggest that the obesity-dyslipidemia trait is a key characteristic of the syndrome (9,10).

We assessed CVD risk according to the prevalence of the following risk factors: 2hPG ≥7.8 mmol/l, LDL cholesterol ≥100 mg/dl, total/HDL cholesterol ratio >5.0, and current cigarette smoking. In addition, we used the Framingham Risk Score to predict the 10-year risk for CHD events (28).

Statistical analysis. From 3,799 FOS white, 1,339 SAHS non-Hispanic white, and 2,343 SAHS Mexican-American subjects examined overall, we excluded 18 FOS subjects aged <30 or >79 years; 351, 127, and 499, respectively, with diabetes; and 206, 131, and 188, respectively, with missing covariables. We stratified the primary analyses by sex and ethnicity. Insulin, HOMA-IR, FFM-IS, and triglyceride levels were log-transformed before statistical analysis and back-transformed for reporting. Prevalence estimates were age-adjusted (or age-, sex-, and/or ethnicity-adjusted where indicated) using logistic regression (29). We used logistic regression models to contrast trait or syndrome prevalence estimates by sex and ethnic group; likewise, we used linear regression models to contrast continuously distributed risk factor levels. Analyses were performed using SAS (30). Statistical significance was defined as a two-tailed P value <0.05.

RESULTS

Among 3,224 FOS white subjects, the mean age was 54 years and 53% were women. Among 1,081 SAHS non-Hispanic white subjects, the mean age was 52 years and 56% were women. Among 1,656 SAHS Mexican-American

TABLE 1
Prevalence of metabolic syndrome traits and the metabolic syndrome according to (NCEP ATP III) and WHO criteria by sex and ethnicity among nondiabetic men (M) and women (W) aged 30–79 years, Framingham Offspring and San Antonio Heart Studies

	Framingham Offspring		San Antonio				*P*			
	White		Non-Hispanic white		Mexican American					
	Men	Women	Men	Women	Men	Women	FW vs. NHW*	FW vs. MA*	NHW vs. MA*	M vs. W†
n	1,503	1,721	470	611	682	974				
NCEP ATP III										
FPG ≥6.1 mmol/l (%)	8.1	5.6	3.2	1.4	6.5	3.7	0.0001	0.02	0.0006	0.0001
Waist circumference ≥102 cm (M), ≥88 cm (W) (%)	31.0	33.8	32.8	39.3	31.2	56.4	0.03	0.0001	0.0001	0.0001
Triglycerides ≥1.7 mmol/l (%)	37.3	26.7	36.6	27.3	48.9	36.8	1.0	0.0001	0.0001	0.0001
HDL cholesterol <1.0 mmol/l (M), <1.16 mmol/l (W) (%)	40.6	34.7	55.5	51.6	53.6	60.4	0.0001	0.0001	0.03	0.1
Blood pressure ≥130/85 mmHg (%)	48.8	36.9	36.7	32.0	44.1	36.9	0.0001	0.1	0.0009	0.0001
NCEP ATP III metabolic syndrome (%)	26.9	21.4	24.7	21.3	29.0	32.8	0.5	0.0001	0.0001	0.02
NCEP ATP III with BMI instead of waist circumference (%)	25.2	17.8	22.1	15.0	28.4	26.8	0.03	0.0001	0.0001	0.0001
NCEP ATP III requiring obesity-dyslipidemia (%)	14.5	13.7	9.0	13.4	13.6	20.9	0.03	0.0009	0.0001	0.02
WHO										
IFG-IGT (%)	16.4	15.4	14.2	17.1	19.1	27.1	0.9	0.0001	0.0001	0.045
Insulin resistance (%)‡	32.2	20.1	24.1	14.8	28.7	26.1	0.0001	0.2	0.0001	0.0001
Waist-to-hip ratio >0.9 (M), >0.85 (W) (%)	86.1	38.2	87.7	46.9	90.6	64.2	0.0002	0.0001	0.0001	0.0001
BMI ≥30 kg/m^2 (%)	26.3	19.3	23.4	19.5	31.5	37.0	0.4	0.0001	0.0001	0.008
Triglycerides ≥1.7 mmol/l (%)	37.3	26.7	36.6	27.3	48.9	36.8	1.0	0.0001	0.0001	0.0001
HDL cholesterol <0.90 mmol/l (M), <1.0 mmol/l (W) (%)	21.3	9.5	34.4	19.6	36.1	25.6	0.0001	0.0001	0.02	0.0001
Blood pressure ≥140/90 mmHg (%)	32.2	25.8	25.1	22.3	26.9	24.4	0.0005	0.02	0.2	0.0001
Microalbuminuria (UACR >30 mg/g) (%)§	7.8	11.7	NA	NA	NA	NA	NA	NA	NA	0.001
WHO metabolic syndrome (%)	30.3	18.1	24.7	17.2	32.0	28.3	0.0001	0.04	0.0001	0.0001
WHO including micro-albuminuria (%)§	31.8	19.7	NA§	NA	NA	NA	NA	NA	NA	0.0001

Data are age-adjusted percentages. *Age, sex-adjusted contrast of ethnicity; FW, Framingham Offspring Study white; NHW, San Antonio Heart Study non-Hispanic white; MA, San Antonio Heart Study Mexican American. †Age, ethnicity-adjusted contrast of sex. ‡Insulin resistance = fasting insulin level >75th percentile in the nondiabetic population. FW; n = 3,145; NHW; n = 1,005; MA; n = 1,595 due to missing fasting insulin levels. §n = 3,224 for FW; microalbuminuria data not available for NHW and MA subjects.

subjects, the mean age was 50 years and 58% were women. Age-adjusted metabolic syndrome trait prevalences, stratified by sex and ethnicity, are displayed in Table 1. There was substantial heterogeneity by sex and ethnicity in the prevalence of all traits. Syndrome traits were generally more common among men compared with women (with the exception of large waist circumference) and more common among SAHS Mexican-American compared with white subjects. There was heterogeneity even among white populations, with FOS whites having a greater prevalence of hyperglycemia, insulin resistance, and hypertension but a lower prevalence of a large waist circumference or low HDL cholesterol levels compared with SAHS non-Hispanic white subjects. Some traits were much more common (for instance, obesity and hypertension) than others (for instance, hyperglycemia).

Metabolic syndrome trait heterogeneity translated into substantial sex and ethnic variation in the prevalence of the syndrome itself, although by any definition the syndrome was very common, affecting 20–24% of white subjects and over 30% of SAHS Mexican-American subjects (Table 1). Replacing a high BMI for a large waist circumference as the obesity trait in the ATP III criteria produced a small decrease in the prevalence of the syndrome; this decrement was greater among women than among men. The syndrome prevalence was substantially lower using the ATP III criteria modified to require the central obesity-dyslipidemia trait. In SAHS subjects, this modification changed the prevalence such that the syndrome became more common among women than among men. Adding microalbuminuria to the WHO criteria very slightly increased the prevalence of the syndrome in the FOS population.

For the sake of comparison with other studies (31), we also estimated the prevalence of the metabolic syndrome including subjects with diagnosed and OGTT-detected diabetes in the sample: among FOS whites (adding 180 diabetic subjects with complete data), 26.7% had the syndrome by ATP III criteria and 26.6% by WHO criteria; among SAHS non-Hispanic white subjects (adding 110), 28.0 and 26.4%, respectively; and among SAHS Mexican-American subjects (adding 414), 41.4 and 41.1%, respectively.

TABLE 2
Levels of insulin resistance and CVD risk among subjects with the metabolic syndrome according to NCEP ATP III and WHO criteria, by ethnicity, among nondiabetic men and women aged 30–79 years, Framingham Offspring and San Antonio Heart Studies

	Framingham Offspring and San Antonio white		San Antonio Mexican American		*P* with vs. without white*	*P* with vs. without MA*
	Without syndrome	With syndrome	Without syndrome	With syndrome		
NCEP ATP III metabolic syndrome						
n	3,258	1,047	1,172	484		
2hPG ≥7.8 mm (%)	14.6	35.1	8.7	25.4	0.0001	0.0001
Total/HDL cholesterol ratio >5.0 (%)	35.8	75.4	20.8	65.3	0.0001	0.0001
LDL cholesterol >100 (%)†	83.0	80.0	77.6	82.8	0.3	0.002
Smoking (%)	18.5	16.9	18.8	20.1	0.4	0.4
Fasting insulin (mean μU/ml)‡	5.3	10.9	6.8	11.1	0.0001	0.0001
HOMA-IR (mean)‡	1.2	2.6	1.5	2.6	0.0001	0.0001
Fat-free mass–adjusted insulin sensitivity (mean)‡	2.1	1.4	1.8	1.4	0.0001	0.0001
Predicted CHD risk (mean %)	6.7	12.6	6.4	10.7	0.0001	0.0001
WHO metabolic syndrome						
n	3,291	1,014	1,219	437		
2hPG >7.8 mm (%)	8.5	50.4	4.9	39.1	0.0001	0.0001
Total/HDL cholesterol ratio >5.0 (%)	41.2	64.3	24.3	54.5	0.0001	0.0001
LDL cholesterol >100 (%)†	83.5	79.0	78.1	80.7	0.2	0.1
Smoking (%)	19.0	15.9	19.7	16.9	0.1	0.051
Fasting insulin (mean μU/ml)‡	5.1	13.6	6.3	13.4	0.0001	0.0001
HOMA-IR (mean)‡	1.2	3.3	1.4	3.2	0.0001	0.0001
Fat-free mass–adjusted insulin sensitivity (mean)‡	2.1	1.3	1.9	1.3	0.0001	0.0001
Predicted CHD risk (mean %)	7.0	11.8	6.8	9.8	0.0001	0.0001

Data are age- and sex-adjusted proportions or means. Means for insulin, HOMA-IR, and insulin sensitivity are back-transformed from log levels. *Age- and sex-adjusted contrasts; †n = 4,481 for LDL cholesterol levels due to elevated triglyceride levels or missing LDL values; ‡n = 5,745 for insulin-related measures due to missing fasting insulin values.

By any criteria, subjects with the metabolic syndrome were more insulin resistant and at greater predicted risk of CHD than subjects without the syndrome. Those with the metabolic syndrome by ATP III criteria compared with those without the syndrome had higher age-, sex-, and ethnicity-adjusted levels of fasting insulin (11.3 vs. 5.9 μU/ml), HOMA-IR (2.7 vs. 1.3), and predicted CHD risk (11.8 vs. 6.4%; all $P = 0.0001$). Those with the metabolic syndrome by WHO criteria compared with those without the syndrome had higher adjusted levels of fasting insulin (13.7 vs. 5.5 μU/ml), HOMA-IR (3.3 vs. 1.2), and predicted CHD risk (11.2 vs. 6.9%; all $P = 0.0001$). Risk factor levels stratified by sex and ethnicity are shown in Table 2. Subjects with the metabolic syndrome by ATP III or WHO criteria were two to four times more likely to have postchallenge hyperglycemia or elevated total/HDL cholesterol ratios, and had two- to fourfold more adverse levels of fasting insulin, HOMA-IR, or insulin sensitivity. Predicted 10-year CHD risk was 2–5% higher among subjects with the metabolic syndrome. Proportions of subjects with elevated LDL cholesterol or cigarette smoking tended to be similar across groups. These patterns were similar in analyses of modified ATP III criteria, where elevated BMI replaced a large waist circumference as the obesity trait, or the obesity-dyslipidemia traits were required to establish a case of the metabolic syndrome (not shown).

We also found that different metabolic syndrome criteria did not necessarily identify the same groups of people. Among FOS whites with the metabolic syndrome by ATP III criteria, 66.5% also met WHO criteria (and 33.5% did not), whereas among FOS whites without the syndrome by ATP III criteria, 11.0% had the syndrome by WHO criteria (Fig. 1, top panels). The κ statistic (0.56) indicated moderate agreement between the two definitions among FOS whites. Among SAHS non-Hispanic whites meeting ATP III criteria, 57.7% also met WHO criteria (and 42.3% did not); among SAHS non-Hispanic whites without the ATP III syndrome, 9.5% met WHO criteria; the κ was 0.50. Among SAHS Mexican Americans meeting ATP III criteria, 59.3% also met WHO criteria (and 40.7% did not); among SAHS Mexican Americans without the ATP III syndrome, 14.6% met WHO criteria; the κ was 0.45. Subjects with the metabolic syndrome by WHO criteria but not ATP III criteria were more insulin resistant than those with the syndrome by ATP III but not WHO criteria (Fig. 1, middle panels): among FOS whites, HOMA-IR levels were 2.85 vs. 1.65; among SAHS non-Hispanic whites, 2.42 vs. 1.33; and among SAHS Mexican Americans, 2.81 vs. 1.75, respectively (all $P = 0.0001$). Conversely, subjects with the metabolic syndrome by WHO but not ATP III criteria were at lower predicted risk of CHD than those with the syndrome by ATP III but not WHO criteria (Fig. 1, bottom panels): among FOS whites, predicted risk was 8.9 vs. 11.9%; among SAHS non-Hispanic whites, 8.3 vs. 10.6%; and among SAHS Mexican Americans, 7.6 vs. 10.0%, respectively (all $P \leq 0.007$).

DISCUSSION

Increased understanding of insulin resistance–associated traits has enabled recent expert group proposals for case definitions of the metabolic syndrome. Among men and women aged 30–79 participating in the population-based

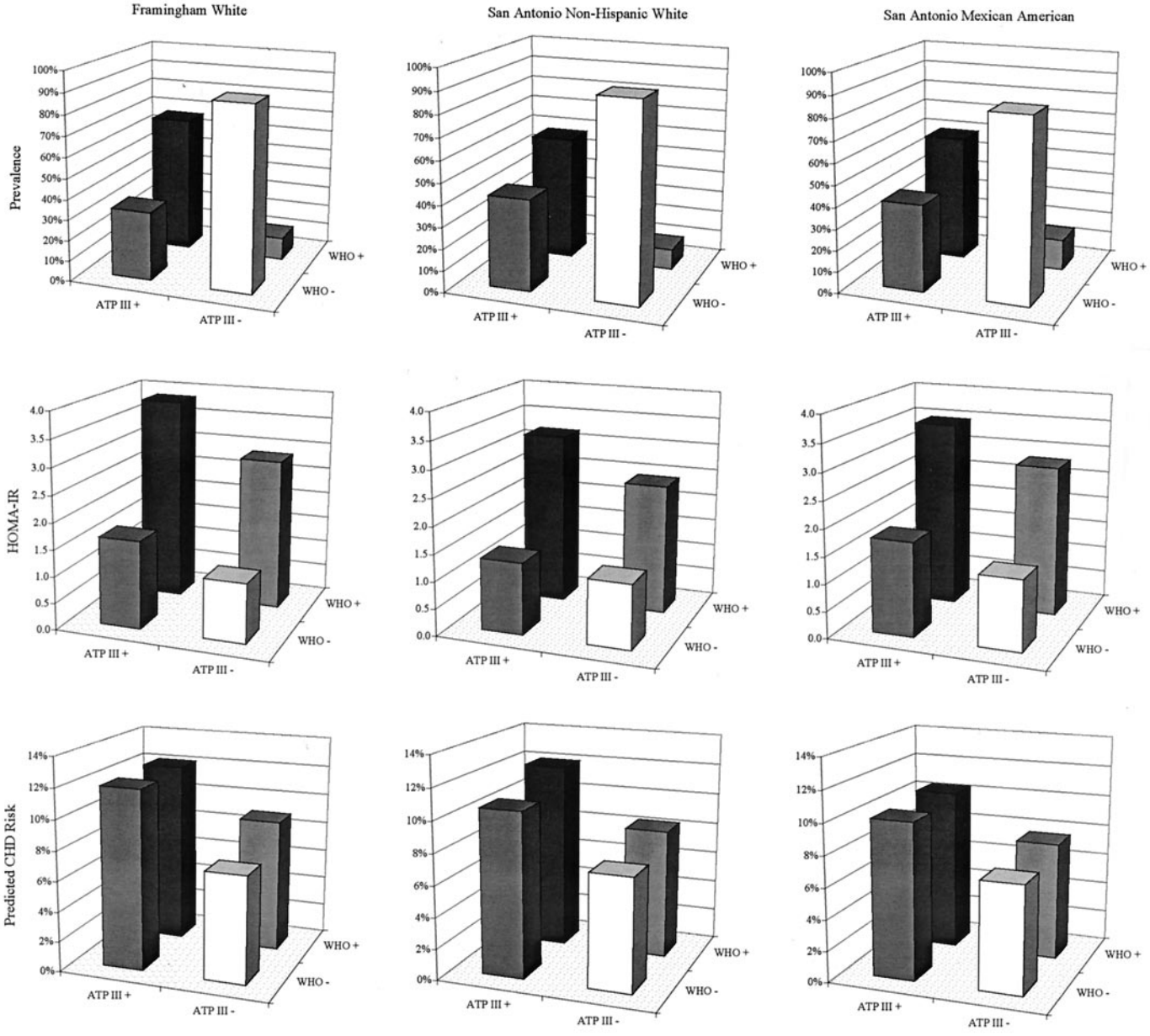

FIG. 1. The prevalence (top panels), HOMA-IR (middle panels), and predicted 10-year risk of CHD (bottom panels) among Framingham Study white (left-hand column), San Antonio non-Hispanic white (middle column), and San Antonio Mexican American (right-hand column) subjects concordant without the metabolic syndrome by either ATP III or WHO criteria (white bars), discordant with the syndrome by ATP III but not WHO criteria or by WHO but not ATP III criteria (gray bars), or concordant with the syndrome by both ATP III and WHO criteria (black bars). Prevalence reflects the proportion of subjects with (or without) the ATP III metabolic syndrome also meeting (or not meeting) WHO syndrome criteria. In all subjects, differences comparing discordant groups are significant: for HOMA-IR, $P = 0.0001$, and for predicted CHD risk, $P \leq 0.007$.

FOS and SAHS studies, we found that the metabolic syndrome was very common. Prevalence rates were similar by either the ATP III or WHO criteria, with 17–33% of men and women in two different ethnic groups affected. The syndrome was most prevalent among Mexican Americans. These rates from the early 1990s may underestimate the current prevalence of the syndrome in the U.S., as over the past decade there has been an epidemic increase in the prevalence of obesity and glucose intolerance (32,33). Our analysis also demonstrates that the metabolic syndrome is a heterogeneous disorder, with substantial variability in the prevalence of component traits within and across populations. Furthermore, there is imperfect agreement of classification by different syndrome criteria, leading to significant differences in insulin resistance and predicted CHD risk depending on the criteria employed.

Our study confirms findings by Ford and colleagues (31,34) in which the prevalence of the syndrome using ATP III or WHO criteria was determined among participants in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994). As in our study, there was substantial sex and racial/ethnic heterogeneity in the NHANES III sample in the distribution of metabolic syndrome traits and in the syndrome itself. Ford and colleagues also reported that the metabolic syndrome increased the risk of prevalent self-reported CHD by ~1.6- to 2.5-fold relative to those without the syndrome. In this report, we demonstrate that subjects with the syndrome

are relatively insulin resistant as well as being at increased predicted risk for CHD compared with those without the syndrome, even when constituent traits of the syndrome vary under different diagnostic criteria. In Ford's analyses, subjects with diabetes (both medication treated and on the basis of hyperglycemia) were included, whereas we excluded diabetic subjects. Other NHANES III data show that the prevalence of diagnosed and undiagnosed diabetes is 11–14% in non-Hispanic whites and 20–24% in Mexican Americans. If subjects with diabetes were removed from Ford's data, metabolic syndrome prevalence rates would probably be modestly lower, as hyperglycemia makes only a small marginal independent contribution to the joint prevalence of insulin resistance–related traits (9). Our study also provides population-based prevalence estimates of the WHO-defined metabolic syndrome. Comparable U.S. data are not available, although data from the high-risk Botnia Study (a large family study of type 2 diabetes in Finland and Sweden) provide some contrast to our results (35). Among 2,149 men aged 35–70 years, the prevalence of the WHO metabolic syndrome was 15% among men and 10% among women with normal glucose tolerance, and 64% among men and 42% among women with IFG/IGT. Botnia and NHANES III data support our conclusion that the metabolic syndrome is very common in Western populations by either WHO or ATP III criteria.

The NHANES III and Botnia data confirm the high degree of syndrome trait heterogeneity we found in our sample. Despite this trait heterogeneity, we found that subjects with the metabolic syndrome, by any criteria, were more insulin resistant, had higher levels of most CVD risk factors, and had significantly greater predicted CHD risk compared with unaffected subjects. We also found phenotype heterogeneity, with ATP III–defined subjects being less insulin resistant but at greater predicted risk of CHD than WHO-defined subjects. However, the degree to which the WHO- or ATP III–defined syndrome actually predicts risk for incident type 2 diabetes or CVD is only just becoming firmly established. A series of Finnish studies used factor analysis to identify insulin resistance-associated clusters of metabolic risk factors. In one report, the insulin resistance cluster increased the relative risk for incident type 2 diabetes by over fourfold, (12), and in two other studies, increased the relative risk for CVD events by about 30% (11,36). In the Botnia Study, the WHO-defined metabolic syndrome increased risk for CVD events by about threefold (35). In another recent Finnish Study, the metabolic syndrome defined by either ATP III or WHO criteria increased risk of incident CHD death by three- to fourfold (37). In Pima Indians, the metabolic syndrome cluster increased the relative risk for incident diabetes by ~80% (38). Thus, regardless of the definition, evidence is mounting that the metabolic syndrome is a high-risk condition.

It is no surprise that clusters of diabetes or CHD risk factors increase risk for outcomes. An important question remains, however, about the degree to which the metabolic syndrome adds to diabetes or CHD prediction beyond knowledge of standard risk factors. In a recent analysis of Strong Heart Study participants, the ATP III metabolic syndrome predicted incident CVD events, but did not add to CVD prediction once standard CVD risk factors were also considered (39). Whereas some syndrome traits are considered in the Framingham Risk Score (the current standard for CHD risk stratification), other traits are unique to the metabolic syndrome (for instance, triglycerides) and are attributed different degrees of predictive importance than in the Risk Score. As an example, the ATP III criteria weights traits equally in defining the syndrome (one point each for obesity, high triglycerides, etc.), while the Risk Score uses regression coefficients to assign weights to risk factors (28). "Optimal" prediction models for type 2 diabetes developed in the SAHS population also show up to fourfold variation in the strength of syndrome traits predicting incident type 2 diabetes (40). Further work is required to assess whether simple trait counting offers sufficient advantage over more rigorous empiric weighting when considering the metabolic syndrome as a risk factor for type 2 diabetes and CVD, and additional studies assessing the marginal predictive capacity of the syndrome beyond existing risk factors or prediction rules need to be performed.

There are prevention implications of identifying the metabolic syndrome. The ultimate good of identifying affected subjects is to stratify risk, with the hope that specific treatment for the syndrome will confer clinical benefit. For example, if insulin resistance causes the metabolic syndrome, then interventions to improve insulin sensitivity might be uniquely beneficial. In particular, obesity and a sedentary lifestyle are two major modifiable risk factors for insulin resistance. The Diabetes Prevention Program (DPP) demonstrated that an intensive weight loss and physical activity program reduced the relative risk of developing type 2 diabetes by 58% (41). While the metabolic syndrome was not a DPP entry criteria, baseline characteristics suggest that many of the DPP participants had the syndrome (41). Thus, many people with the metabolic syndrome appear likely to gain benefit from DPP-type interventions. In addition to lifestyle modification, use of insulin-sensitizing drugs may be beneficial (41–43); statins and ACE inhibitors also prevent CHD and might prevent diabetes (44,45). However, it is essential to recognize that it is not known whether treatment aimed at the metabolic syndrome per se will reduce risk for adverse outcomes to an equal or greater degree than treatments aimed at individual metabolic traits. In particular, therapies directed specifically at dyslipidemia, hypertension, and hyperglycemia significantly reduce the risk for major adverse outcomes and should be considered as first-line therapy for patients with any of these conditions (16,46, 47). Perhaps the greatest value in recognizing the metabolic syndrome is not that it suggests specific treatment for insulin resistance, but that it identifies persons with an extremely adverse metabolic state warranting intervention for specific traits.

In conclusion, evidence accumulated over the last two decades supports the existence of a risk factor cluster called the metabolic syndrome. In the FOS and SAHS populations, the metabolic syndrome was heterogeneous, very common, and, regardless of the definition, associated with elevated levels of insulin resistance and predicted CHD risk. These findings suggest that the value of identifying the syndrome in the clinical setting is to focus weight control, physical activity, and CHD risk factor interven-

tions on specific high-risk subjects. From a public health perspective, encouraging healthy weight and physical activity behaviors to control the epidemic of obesity will probably be the greatest benefit of the current focus on the metabolic syndrome.

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