# Identification of Subjects with Insulin Resistance and β-Cell Dysfunction Using Alternative Definitions of the Metabolic Syndrome

**Anthony J.G. Hanley,[1,2] Lynne E. Wagenknecht,[3] Ralph B. D'Agostino, Jr.,[3] Bernard Zinman,[2] and Steven M. Haffner[1]**

**Recently, the metabolic syndrome (MetS) has attracted much attention as a risk cluster for cardiovascular disease. Although it is believed that individuals with the MetS have insulin resistance (IR), there are few data using direct measures of IR such as glucose clamps or frequently sampled intravenous glucose tolerance tests (FSIGTTs). We examined associations of MetS with FSIGTT-derived measures of insulin sensitivity and secretion among nondiabetic subjects in the Insulin Resistance Atherosclerosis Study. Two sets of MetS criteria were evaluated: those from the 1999 World Health Organization (WHO) and the 2001 National Cholesterol Education Program (NCEP). Both WHO and NCEP MetS definitions were significantly associated with risk of being in the lowest quartile of directly measured insulin sensitivity ($P < 0.0001$ for all subjects as well as within ethnic subgroups). However, the associations with WHO-MetS were stronger for all subjects combined (WHO: odds ratio [OR] = 10.2; 95% CI 7.5–13.9; NCEP: OR = 4.6; 3.4–6.2) and in separate analyses of non-Hispanic whites, blacks, and Hispanics. WHO and NCEP MetS definitions were also significantly associated with risk of being in the lowest quartile of insulin sensitivity–adjusted acute insulin response (AIR) and disposition index (DI; all $P < 0.01$), although the associations were generally weaker than those for insulin sensitivity and there was no difference between the two definitions in all subjects combined (low AIR, WHO: OR = 1.7, 1.2–2.4; NCEP: OR = 1.7, 1.2–2.5). There were, however, a number of ethnic differences, including a stronger association of NCEP-MetS with low AIR among blacks. WHO-MetS was significantly more sensitive than NCEP-MetS in detecting low insulin sensitivity (65.4 vs. 45.6%, respectively; $P < 0.0001$), with no significant differences in specificity between the definitions (84.4 vs. 84.6%; $P = 0.91$), although WHO-MetS had a larger area under the receiver operating characteristic curve (75% vs. 65%; $P < 0.0001$). In conclusion, although both the WHO and NCEP MetS criteria identify nondiabetic individuals with low insulin sensitivity, the associations were notably stronger using the WHO definition. The definitions are generally less useful for identifying those with low AIR or DI, although NCEP-MetS seems to differentiate black subjects with insulin secretion defects. *Diabetes* 52:2740–2747, 2003**

Both type 2 diabetes and cardiovascular disease (CVD) are characterized and predicted by a number of highly intercorrelated metabolic disorders, including abdominal adiposity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension (1,2). This cluster of factors has been variably referred to as syndrome X, the insulin resistance syndrome, and the metabolic syndrome (MetS), with the last term recently adopted by the World Health Organization (WHO) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP) (3,4). Several definitions and multivariate statistical approaches have been proposed to distinguish this high-risk premorbid state (5,6), although none has achieved wide acceptance in the literature. WHO and NCEP have each recently presented criteria for the definition of the MetS (2,3), and it has been reported that the prevalence of the syndrome is high in the general population under these definitions (7–9).

It is generally believed that individuals with MetS have insulin resistance (IR), a notion based on the results of studies that have documented IR in subjects with individual components of the syndrome, such as dyslipidemia and abdominal adiposity (10,11). In addition, in several studies, factor analysis has been used to document underlying (latent) traits or clusters of these disorders in large groups of subjects (5,12–14). In many of these studies, surrogate measures of IR were used, and these measures often loaded on more than one of the underlying factors (5). A limited number of studies have documented prospective associations of WHO- and/or NCEP-defined MetS with outcomes that are related to IR, including type 2 diabetes and CVD (15–20). Few studies, however, have examined associations between MetS and direct measures of IR such as euglycemic-hyperinsulinemic clamps or the frequently sampled intravenous glucose tolerance test (FSIGTT).

From the [1]Division of Clinical Epidemiology, University of Texas Health Sciences Center, San Antonio, Texas; the [2]Leadership Sinai Centre for Diabetes, Mt. Sinai, Hospital, Toronto, Ontario, Canada; and the [3]Department of Public Health Sciences, Wake Forest University School of Medicine, Winston Salem, North Carolina.

Address correspondence and reprint requests to Dr. Steven Haffner, Division of Clinical Epidemiology, University of Texas Health Science Center at San Antonio, Mail Code 7873, 7703 Floyd Curl Dr., San Antonio, TX 78229-3900. E-mail: haffner@uthscsa.edu.

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AIR, acute insulin response; AROC, area under the receiver operating characteristic; CVD, cardiovascular disease; DI, disposition index; FSIGTT, frequently sampled intravenous glucose tolerance test; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; IRAS, Insulin Resistance Atherosclerosis Study; IS, insulin secretion; MetS, metabolic syndrome; NGT, normal glucose tolerance.

TABLE 1
Characteristics of nondiabetic IRAS participants during baseline examination (1992–1994) by sex and ethnicity

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Variable | Non-Hispanic whites | Blacks | Hispanics | Non-Hispanic whites | Blacks | Hispanics |
| *n* | 195 | 113 | 144 | 220 | 156 | 207 |
| Age (years) | 55.4 ± 8.4 | 54.8 ± 8.8 | 53.8 ± 8.9 | 56.3 ± 8.4 | 53.9 ± 8.4 | 53.8 ± 7.9 |
| BMI (kg/m$^2$) | 27.1 ± 3.9 | 28.1 ± 4.6 | 28.3 ± 5.4 | 28.0 ± 6.1 | 30.3 ± 6.6 | 29.1 ± 6.4 |
| Waist-to-hip ratio | 0.92 ± 0.06 | 0.90 ± 0.05 | 0.95 ± 0.05 | 0.80 ± 0.06 | 0.80 ± 0.07 | 0.82 ± 0.06 |
| Waist circumference (cm) | 94.7 ± 10.0 | 93.8 ± 9.8 | 96.1 ± 11.2 | 85.1 ± 12.9 | 89.1 ± 15.0 | 87.4 ± 13.1 |
| Fasting glucose (mg/dl) | 100.8 ± 9.5 | 101.2 ± 9.5 | 99.3 ± 9.8 | 95.3 ± 10.8 | 100.0 ± 11.9 | 95.2 ± 9.5 |
| 2-h glucose (mg/dl) | 120.7 ± 30.9 | 125.6 ± 33.6 | 123.9 ± 37.5 | 125.1 ± 35.3 | 126.1 ± 33.6 | 126.6 ± 33.0 |
| Fasting insulin (μU/ml) | 11 (8–16) | 13 (9–20) | 15 (10–21.5) | 11 (8–16) | 13.5 (9–19) | 14.5 (9–21) |
| LDL cholesterol (mg/dl) | 141.8 ± 35.0 | 145.4 ± 36.6 | 138.1 ± 34.2 | 140.3 ± 32.8 | 147.4 ± 32.3 | 137.4 ± 36.3 |
| HDL cholesterol (mg/dl) | 41.1 ± 12.3 | 45.5 ± 14.3 | 38.7 ± 12.5 | 52.4 ± 15.4 | 56.2 ± 15.5 | 46.8 ± 13.2 |
| Triglyceride (mg/dl) | 124 (86–183) | 98 (81.5–139.5) | 139 (92–223) | 111.5 (75–150) | 76 (61–115) | 121 (88–177) |
| Systolic BP (mmHg) | 121.4 ± 15.1 | 126.6 ± 15.7 | 121.7 ± 15.9 | 121.5 ± 18.6 | 124.9 ± 15.6 | 119.2 ± 17.6 |
| Diastolic BP (mmHg) | 78.2 ± 8.6 | 79.7 ± 9.9 | 80.3 ± 9.0 | 75.0 ± 9.6 | 77.8 ± 9.0 | 76.6 ± 8.5 |
| Albumin/creatinine ratio (mg/g) | 5.3 (3.7–10.9) | 5.3 (3.1–8.7) | 5.7 (4.2–10.4) | 8.6 (4.8–14.1) | 7.4 (3.9–14.7) | 7.3 (4.8–11.7) |
| $S_i \times 10^{-4}$ (min$^{-1}$ · μU$^{-1}$ · ml$^{-1}$) | 1.9 (1.1–3.3) | 1.4 (0.9–2.5) | 1.2 (0.6–2.8) | 1.9 (1.2–3.5) | 1.4 (0.9–2.5) | 1.4 (0.8–2.6) |
| AIR (pmol · ml$^{-1}$ · min$^{-1}$) | 283.4 (143.5–518.2) | 509.3 (197.8–823.4) | 495.7 (282.0–939.6) | 269.4 (138.3–499.3) | 454.9 (192.2–748.9) | 397.7 (219.4–645.8) |
| IGT/IFG (%) | 37 | 39 | 39 | 40 | 41 | 39 |

Data are means ± SD, medians (interquartile range), or proportions. BP, blood pressure.

The objective of this study was to assess, among nondiabetic subjects, the physiological characteristics of WHO- and NCEP-defined MetS in a well-characterized multiethnic cohort of U.S. adults participating in the Insulin Resistance Atherosclerosis Study (IRAS). This study offers a unique opportunity to address these objectives, in that the dataset contains information on directly measured insulin sensitivity and insulin secretion (IS) determined during the FSIGTT.

## RESEARCH DESIGN AND METHODS

**Study subjects.** The IRAS is a multicenter, observational, epidemiologic study of the relationships among IR, CVD and its known risk factors in different ethnic groups, and varying states of glucose tolerance. The design and methods of this study have been described in detail in previous publications (21,22). Briefly, the study was conducted at four clinical centers. At centers in Oakland and Los Angeles, CA, non-Hispanic whites and blacks were recruited from Kaiser Permanente, a nonprofit health maintenance organization. Centers in San Antonio, TX, and San Luis Valley, CO, recruited non-Hispanic whites and Hispanics from two ongoing population-based studies (the San Antonio Heart Study and the San Luis Valley Diabetes Study) (21). A total of 1,625 individuals participated in the baseline IRAS examination (56% women), which occurred between October 1992 and April 1994. The IRAS protocol was approved by local institutional review committees, and all participants provided written informed consent. The present report includes information on 1,035 nondiabetic individuals who participated in the baseline examination and for whom information was available on metabolic variables of interest (Table 1).

**Clinical measurements and procedures.** The IRAS protocol required two visits, 1 week apart, of ~4 h each. Subjects were asked before each visit to fast for 12 h, to abstain from heavy exercise and alcohol for 24 h, and to refrain from smoking the morning of the examination. During the first visit, a 75-g oral glucose tolerance test was administered, with glucose tolerance status classified using WHO criteria (23). During the second visit, insulin sensitivity and insulin secretion were determined using an FSIGTT, with two modifications to the original protocol (24). First, an injection of regular insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance (25). Second, a reduced sampling protocol (with 12 rather than 30 samples) was employed for efficiency given the large number of participants (26). Insulin sensitivity, expressed as the insulin sensitivity index ($S_i$), and first-phase insulin secretion, expressed as the acute insulin response (AIR), were calculated using mathematical modeling methods (MINMOD version 3.0) (27). The repeatability of both $S_i$ and AIR have been demonstrated in a subsample of the IRAS cohort (28). The estimate of $S_i$ from this modified protocol has been validated against gold standard measures of IR from the hyperinsulinemic-euglycemic clamp technique (29). AIR has been validated by others using gold standard measures of IS from the hyperglycemic clamp technique (30). Disposition index (DI), an integrated measure of the ability of the β-cells to compensate for background insulin resistance, was defined as the product of $S_i$ and AIR (31,32). Because some individuals had AIR ≤0 and/or $S_i = 0$, DI was calculated as $(S_i + 1) \times (\text{AIR} + 451)$ to ensure that this index was calculated using positive numbers.

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight/height$^2$ (kg/m$^2$) and was used as an estimate of overall adiposity. Waist circumference, a validated estimate of visceral adiposity (33), was measured to the nearest 0.5 cm using a steel tape. Duplicate measures were made following a standardized protocol, and averages were used in the analysis. Resting blood pressure (systolic and fifth-phase diastolic) was recorded with a standard mercury sphygmomanometer after a 5-min rest. The average of the second and third measurements was used. Ethnicity was assessed by self-report.

**Laboratory procedures.** Glucose concentration was determined using standard methods as described previously (21). Insulin levels were measured using the dextran-charcoal radioimmunoassay (34), which has a 19% external coefficient of variation. This assay displays a high degree of cross-reactivity with proinsulin. Plasma lipid and lipoprotein concentrations were determined from fasting plasma samples at the central IRAS laboratory (Medlantic Research Institute, Washington, DC), using the Lipid Research Clinics method. Urinary albumin and creatinine concentrations were assessed in a random morning spot urine sample using procedures described previously (35).

**Definition of MetS.** MetS was defined using criteria proposed by the WHO and the NCEP-ATP III. Under the WHO criteria (1999 revision), MetS in subjects with glucose intolerance (either impaired fasting glucose [IFG] or

TABLE 2
Prevalence of WHO- and NCEP-defined MetS and syndrome components among nondiabetic IRAS participants, by ethnicity and glucose tolerance status

| | All subjects | | Non-Hispanic whites | | Blacks | | Hispanics | |
|---|---|---|---|---|---|---|---|---|
| Variable | NFG/NGT | IFG/IGT | NFG/NGT | IFG/IGT | NFG/NGT | IFG/IGT | NFG/NGT | IFG/IGT |
| WHO Mets | 17.1 | 60.6 | 11.7 | 57.2 | 13.0 | 56.5 | 26.5§ | 67.7 |
| Central/total obesity | 45.6 | 72.5 | 43.4 | 71.7 | 38.5 | 67.6 | 53.5* | 77.2 |
| Raised arterial pressure | 26.6 | 42.2 | 23.8 | 36.5 | 36.0 | 55.6 | 22.8† | 38.2† |
| High Tg and/or low HDL | 36.6 | 50.5 | 37.5 | 51.6 | 21.1 | 29.6 | 47.0§ | 65.9§ |
| Microalbuminuria | 6.2 | 5.5 | 8.6 | 4.4 | 4.4 | 10.2 | 4.7 | 2.9 |
| NCEP MetS | 15.2 | 45.2 | 14.1 | 42.8 | 6.8 | 42.6 | 22.8§ | 50.0 |
| Abdominal obesity | 22.2 | 44.7 | 18.8 | 42.8 | 23.6 | 48.2 | 25.1 | 44.1 |
| Elevated triglycerides | 25.3 | 38.3 | 27.7 | 36.3 | 13.7 | 19.4 | 31.2‡ | 55.6§ |
| Reduced HDL | 46.2 | 56.1 | 44.9 | 55.7 | 29.8 | 40.7 | 60.0§ | 68.9§ |
| Elevated BP | 39.6 | 57.3 | 37.5 | 50.9 | 49.7 | 70.4 | 34.4† | 54.4† |
| Fasting hyperglycemia | 0.0 | 39.5 | 0.0 | 36.5 | 0.0 | 52.8 | 0.0 | 32.4† |

Data are %. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$; §$P < 0.0001$; $P$ values reflect overall differences across ethnic groups, by glucose tolerance status. NFG, normal fasting glucose; Tg, triglyceride.

impaired glucose tolerance [IGT]) was defined as the presence of two or more of the following risk factors: arterial blood pressure ≥140/90 mmHg; triglycerides ≥150 mg/dl and/or HDL cholesterol <35 mg/dl (men) or <39 mg/dl (women); waist-to-hip ratio >0.9 (men) or >0.85 women and/or BMI >30 kg/m$^2$; and albumin/creatinine ratio (≥30 mg/g) (3). MetS in subjects with normal glucose tolerance (NGT) was defined as the presence of two or more of the above-listed risk factors, in addition to IR, which was defined in the present study as the highest quartile of fasting insulin concentration in this glucose tolerance category (36).

Under the NCEP-ATP III criteria, MetS was defined as the presence of three or more of the following risk factors: abdominal obesity (waist circumference >102 cm [men] or >88 cm [women]), triglycerides ≥150 mg/dl, HDL cholesterol <40 mg/dl (men) or <50 mg/dl (women), blood pressure ≥130/≥85 mmHg, and fasting glucose ≥110 mg/dl (4). For both WHO and NCEP definitions, subjects who were taking antihypertensive medication were considered to have hypertension.

**Statistical analyses.** Means and SDs, medians and interquartile ranges, or proportions were presented stratified by sex and glucose tolerance status. Associations of $S_i$, AIR, and DI with variables used in MetS definitions were assessed using Spearman correlation analysis. Logistic regression analysis was used to determine the association between WHO and NCEP MetS definitions and risk of IR and β-cell dysfunction in nondiabetic subjects. In these analyses, IR was defined as the lowest quartile of directly measured $S_i$ during the FSIGTT, whereas β-cell dysfunction was defined as the lowest quartile of AIR or, alternatively, the lowest quartile of DI. AIR models were adjusted for $S_i$. In addition, we calculated the sensitivity and specificity of the definitions in detecting IR and β-cell dysfunction, with differences between the definitions assessed using McNemar's test. Furthermore, the areas under the receiver operating characteristic (AROC) curves for each definition were calculated. The area under an ROC curve is a measure of how well a variable is able to predict the outcome of interest. Finally, the AROCs for each model were formally compared using the DeLong algorithm (37).

## RESULTS

Characteristics of IRAS subjects by sex and ethnicity are presented in Table 1. Black men and women tended to have higher concentrations of HDL cholesterol and elevated levels of blood pressure. Hispanic men and women had higher triglyceride concentrations, whereas non-Hispanic whites were the most insulin sensitive and had the lowest AIR. Overall, WHO-MetS was more common than NCEP-MetS (34.1 vs. 26.9%; $P < 0.001$), and WHO-MetS was more prevalent in ethnic and glucose tolerance subgroups, with the exception of non-Hispanic whites subjects with NGT (Table 2). The prevalence of MetS and its individual components was higher in subjects with IFG or IGT. There were also notable ethnic differences in the prevalence of individual components of the syndrome, with increased hypertension and fasting hyperglycemia among blacks, increase in obesity among Hispanics, and lower prevalences of lipid abnormalities among blacks (Table 2).

$S_i$ showed strong inverse correlations with fasting insulin and measures of adiposity ($r = -0.54$ to $0.68$; $P < 0.0001$); more moderate but significant inverse associations with fasting glucose, triglyceride, and systolic blood pressure; and a positive correlation with HDL (Table 3). AIR was positively associated with insulin and adiposity ($r = 0.14–0.24$; $P < 0.0001$) and inversely correlated with fasting glucose and HDL ($r = -0.26$ to $-0.13$, respectively; $P < 0.0001$). DI was inversely correlated with the majority of MetS variables, including insulin, glucose, adiposity, triglyceride, and systolic blood pressure ($P < 0.0001$; Table 3). The magnitude and direction of these coefficients were similar in separate analyses of men and women (data not shown).

Approximately 18% of subjects who met neither WHO nor NCEP MetS definitions were insulin resistant, defined as being in the lowest quartile of $S_i$. Prevalence of IR was notably higher among those who met the criteria for either WHO-MetS alone or both the WHO and NCEP MetS definitions (68 and 74%, respectively) versus those who met only the NCEP MetS definition (32%; Fig. 1*A*). There

TABLE 3
Spearman correlation analysis of associations of $S_i$, AIR, and DI with MetS variables* among nondiabetic IRAS participants

| Variable | $S_i$ | AIR ($r$) | DI ($r$) |
|---|---|---|---|
| Fasting insulin | −0.68‖ | 0.24‖ | −0.41‖ |
| Fasting glucose | −0.33‖ | −0.26‖ | −0.47‖ |
| BMI | −0.54‖ | 0.14‖ | −0.35‖ |
| Waist circumference | −0.54‖ | 0.14‖ | −0.37‖ |
| Waist-to-hip ratio | −0.33‖ | 0.12§ | −0.21‖ |
| Tg | −0.30‖ | 0.03 | −0.24‖ |
| HDL | 0.29‖ | −0.13‖ | 0.16‖ |
| Systolic BP | −0.25‖ | −0.09‡ | −0.29‖ |
| Diastolic BP | −0.01 | −0.02 | −0.02 |
| Albumin/creatinine ratio | −0.08†‡ | 0.02 | −0.07† |

*Similar magnitude and direction of coefficients in separate analyses of men and women. †$P < 0.05$; ‡$P < 0.01$; §$P < 0.001$; ‖$P < 0.0001$.

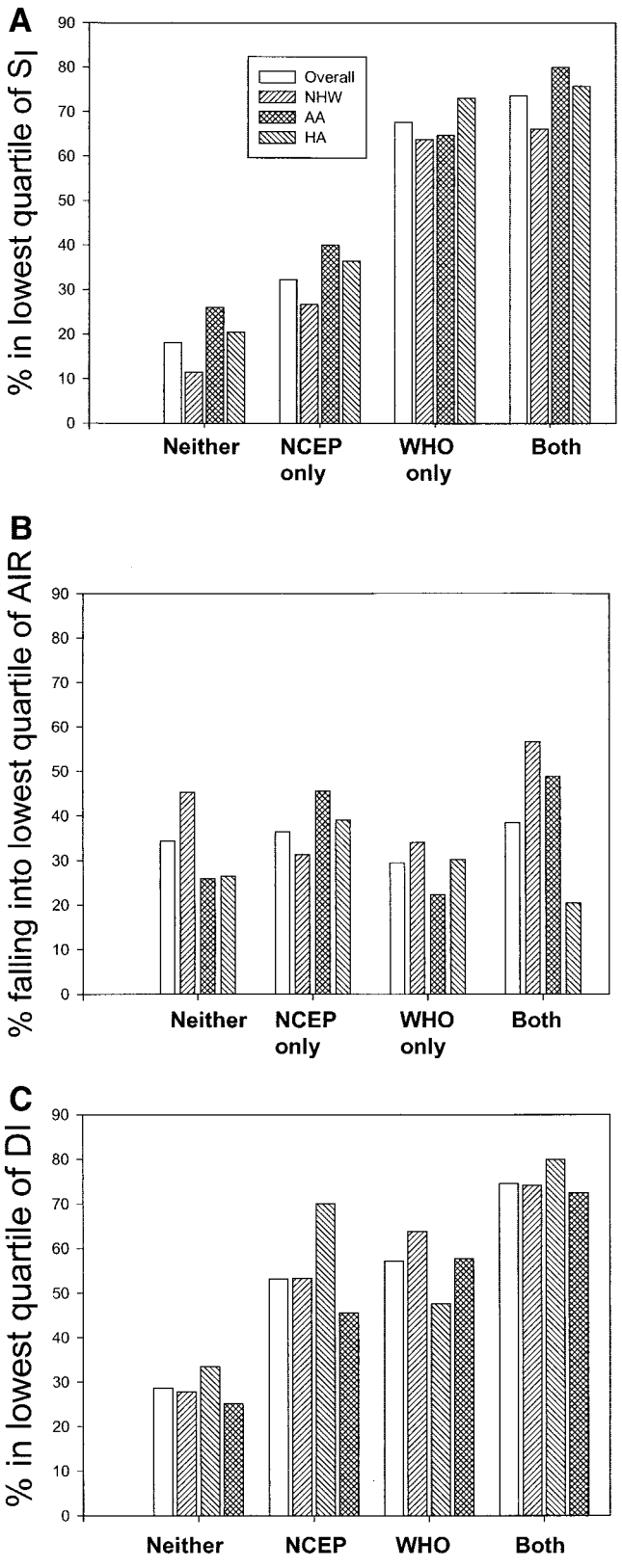


**FIG. 1. Proportion of nondiabetic IRAS subjects who fall into the lowest quartile of $S_i$ (*A*), AIR (*B*), and DI (*C*) according to WHO and NCEP MetS definitions.**

was no such pattern for β-cell dysfunction, defined as being in the lowest quartile of AIR (Fig. 1*B*). Approximately 29% of subjects who met neither WHO nor NCEP MetS definitions were in the lowest quartile of DI, in contrast to 75% who met both (Fig. 1*C*). There was little difference between WHO-MetS alone and NCEP-MetS alone in the proportion of subjects with low DI.

Both WHO and NCEP MetS definitions were significantly associated with risk of being in the lowest quartile of directly measured insulin sensitivity ($S_i$; $P < 0.0001$ for all subjects as well as within ethnic subgroups; Table 4). However, the associations with WHO-MetS were stronger for all subjects combined (WHO: odds ratio [OR] = 10.2, 95% CI 7.5–13.9; NCEP: OR = 4.6, 3.4–6.2) and in separate analyses of non-Hispanic whites, blacks, and Hispanics. WHO and NCEP MetS definitions were also significantly associated with risk of being in the lowest quartile of $S_i$-adjusted AIR (both $P < 0.01$), although the associations were weaker than those for $S_i$ and there was no difference between the two definitions in all subjects combined (WHO: OR = 1.7, 1.2–2.4; NCEP: OR = 1.7, 1.2–2.5). There were, however, a number of ethnic differences, including a stronger association of NCEP-MetS with low AIR among blacks (WHO: OR = 2.2, 1.1–4.5; NCEP: OR = 4.6, 2.2–9.9). Risk of being in the lowest quartile of DI was also significantly elevated in those who met WHO or NCEP MetS definitions (WHO: OR = 4.6, 3.5–6.1; NCEP: OR = 4.4, 3.2–6.0), with, again, a stronger association among blacks for the NCEP definition (WHO: OR = 3.3, 1.9–5.9; NCEP: OR = 6.3, 3.0–13.1). There were no statistically significant interactions by sex in the associations of either MetS definition with risk of being in the lowest quartile of $S_i$, AIR, or DI, with the exception of the NCEP definition for DI, which had a significantly stronger association among women.

WHO-MetS was significantly more sensitive than NCEP-MetS in detecting IR (65.4 vs. 45.6%, respectively; $P < 0.0001$; Table 5). Although there were no significant differences in specificity between the definitions (84.4 vs. 84.6%; $P = 0.91$), the WHO-MetS AROC was significantly greater than that for NCEP-MetS (75 vs. 65%; $P < 0.0001$). These results were similar in separate analyses by ethnicity. WHO-MetS was significantly more sensitive (52.9 vs. 42.6% for WHO and NCEP; $P < 0.001$) and NCEP-MetS significantly more specific (80.4 vs. 85.6%; $P < 0.001$) in identifying subjects with reduced DI, although there was no significant AROC difference between the definitions (67 vs. 64%; $P = 0.09$). This pattern was generally consistent by ethnicity, although there was some subgroup variation in the significance of the differences (Table 5). Finally, there were no significant differences between the definitions in the prediction of low AIR (AROC comparison, all subjects combined, 50 vs. 52%; $P = 0.21$).

We repeated these analyses combining all subjects in the database (NGT, IGT, and diabetes). The associations of the MetS definitions with $S_i$, AIR, and DI were stronger compared with the results from nondiabetic subjects, as would be expected given the high prevalence of CVD risk factors among individuals with diabetes. However, the overall conclusions were not markedly different from analyses restricted to nondiabetic subjects, i.e., the WHO definition was more strongly associated with IR, and both definitions were associated with poor IS, with no differences in the magnitude of the associations between the two (data not shown).

TABLE 4
Associations between WHO- and NCEP-defined MetS risk of being in the lowest quartile of $S_I$, AIR, and DI from the FSIGTT among nondiabetic IRAS participants, by ethnicity*

| | WHO definition | | NCEP definition | |
|---|---|---|---|---|
| Dependent variable | OR† | 95% CI | OR† | 95% CI |
| $S_I$, quartile 1 | | | | |
| All subjects | 10.2 | 7.5–13.9‖ | 4.6 | 3.4–6.2‖ |
| Non-Hispanic white | 12.4 | 7.3–20.9‖ | 4.6 | 2.8–7.6‖ |
| Black | 7.4 | 4.0–13.7‖ | 5.3 | 2.6–10.5‖ |
| Hispanic | 10.4 | 6.2–17.3‖ | 4.4 | 2.7–7.1‖ |
| AIR, quartile 1 (adjusted for $S_i$) | | | | |
| All subjects | 1.7 | 1.2–2.4§ | 1.7 | 1.2–2.5§ |
| Non-Hispanic white | 1.8 | 1.1–3.0‡ | 1.5 | 0.9–2.5 |
| Black | 2.2 | 1.1–4.5‡ | 4.6 | 2.2–9.9‖ |
| Hispanic | 1.6 | 0.8–3.0 | 1.3 | 0.7–2.3 |
| DI, quartile 1 | | | | |
| All subjects | 4.6 | 3.5–6.1‖ | 4.4 | 3.2–6.0‖ |
| Non-Hispanic white | 5.2 | 3.2–8.4‖ | 4.1 | 2.5–6.7‖ |
| Black | 3.3 | 1.9–5.9‖ | 6.3 | 3.0–13.1‖ |
| Hispanic | 5.4 | 3.4–8.6‖ | 4.2 | 2.6–6.8‖ |

*Similar results in analyses adjusted for age and sex; no statistically significant effect modification by sex in the associations of either MetS definition with risk of being in the lowest quartile of $S_i$, AIR, or DI, with the exception of the NCEP definition for DI, which had a significantly stronger association among women. †ORs are from separate models and refer to the risk of being in the lowest quartile of $S_i$, AIR, or DI in those with MetS compared with those without MetS (OR = 1 in the latter group). ‡$P < 0.05$; §$P < 0.01$; ‖$P < 0.0001$.

## DISCUSSION

In the present study, we found that both the WHO and the NCEP definitions of MetS clearly differentiated nondiabetic subjects with IR, although the magnitude of the associations was higher for WHO-MetS. In addition, both definitions also identified subjects with IS abnormalities, but the associations were weaker and there were a number of differences by ethnicity. The prevalence of MetS was high in this cohort using either WHO or NCEP criteria. The WHO definition identified more people across catego-

TABLE 5
Sensitivity and specificity for WHO- and NCEP-defined MetS in identifying subjects in the lowest quartile of $S_i$ and DI from the FSIGTT among nondiabetic IRAS participants, by ethnicity

| | | WHO definition | | NCEP definition | |
|---|---|---|---|---|---|
| Dependent variable | | % | 95% CI | % | 95% CI |
| $S_I$, quartile 1 | | | | | |
| All subjects | Se | 65.4 | 60.3–70.2 | 45.6 | 40.5–50.8§ |
| | Sp | 84.4 | 81.3–87.2 | 84.6 | 81.5–87.3 |
| | AROC | 74.9 | | 65.0§ | |
| Non-Hispanic white | Se | 66.4 | 57.0–74.8 | 45.8 | 36.5–55.3‡ |
| | Sp | 86.2 | 81.8–89.9 | 84.2 | 79.8–88.3 |
| | AROC | 76.3 | | 65.1‡ | |
| Black | Se | 54.6 | 44.7–64.2 | 36.4 | 27.3–46.2‡ |
| | Sp | 86.0 | 79.6–91.0 | 90.2 | 84.5–94.3 |
| | AROC | 70.3 | | 63.3* | |
| Hispanic | Se | 78.1 | 64.2–78.6 | 51.7 | 43.7–59.6§ |
| | Sp | 80.3 | 74.1–85.6 | 80.3 | 74.1–85.6 |
| | AROC | 76.1 | | 66.0§ | |
| DI, quartile 1 | | | | | |
| All subjects | Se | 52.9 | 48.1–57.7 | 42.6 | 37.9–47.3§ |
| | Sp | 80.4 | 76.9–83.6 | 85.6 | 82.4–88.4† |
| | AROC | 66.6 | | 64.1 | |
| Non-Hispanic white | Se | 47.5 | 39.8–55.3 | 38.8 | 31.4–46.5* |
| | Sp | 85.2 | 80.1–89.4 | 86.6 | 81.6–90.6 |
| | AROC | 66.4 | | 62.6 | |
| Black | Se | 44.4 | 35.3–53.9 | 36.1 | 27.5–45.5 |
| | Sp | 80.6 | 73.3–86.6 | 91.8 | 86.2–95.6† |
| | AROC | 62.5 | | 64.0 | |
| Hispanic | Se | 64.9 | 56.9–72.2 | 51.4 | 43.3–59.3† |
| | Sp | 74.5 | 67.8–80.4 | 79.9 | 73.6–85.2 |
| | AROC | 69.7 | | 65.6 | |

AROC comparison, low AIR ($S_i$ adjusted), 50.1 vs. 52.0%, $P = 0.21$. Se, sensitivity; Sp, specificity. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$; §$P < 0.0001$ vs. the WHO definition.

ries of ethnicity and glucose tolerance status, with particularly elevated prevalence among Hispanic men and women.

The clustering of risk factors for diabetes and CVD has been recognized for many years, and the existence of a syndrome that includes obesity, dyslipidemia, hypertension, and hyperglycemia is now widely accepted (5,6). There is much less agreement regarding the central or primary disorder underlying this syndrome. Many investigators have suggested that IR may be playing this role, a notion that is supported by the results of studies from a number of areas, including animal models (38,39), detailed metabolic studies of humans (10,11), multivariate statistical analyses of large epidemiologic databases (including principal components and factor analyses) (5,12–14), and prospective cohort studies (40–42). A limited number of studies have reported that MetS (by WHO and/or NCEP criteria) is associated with prevalent and incident diabetes and CVD (15–19), diseases in which IR is a well-known (in the case of diabetes) or suspected (in the case of CVD) causative factor. Few data are available, however, on the metabolic characterization of alternative definitions of the MetS using direct measures of IR. In the present study, both WHO and NCEP definitions of MetS were strongly associated with IR in nondiabetic individuals. Specifically, subjects with NCEP- and WHO-defined MetS had 5- and 10-fold increased risks (respectively) of being in the lowest quartile of directly measured insulin sensitivity, a finding that was consistent across ethnic subgroups. This observation provides strong support for the notion that individuals with MetS are insulin resistant and that this disorder may be at the core of the cluster of metabolic abnormalities that characterizes the syndrome. The stronger associations (higher OR, Se, and AROC) with IR for the WHO versus the NCEP-MetS definition likely reflects that a measure of IR (in this case, fasting insulin concentration) is a component of the WHO definition among nondiabetic individuals. Controversy exists in the literature regarding the prevalence of IR among black subjects, including notable inconsistencies in the reported proportion of black subjects who have diabetes and are insulin sensitive (43,44). In the present study, both the WHO and the NCEP MetS definitions were significantly associated with directly measured insulin sensitivity among black participants.

The MetS definitions also seemed to be able to differentiate subjects with pancreatic β-cell dysfunction. Specifically, WHO- and NCEP-MetS were significantly associated with risk of being in the lowest quartiles of both $S_i$-adjusted AIR and DI. Although the magnitudes of the associations were weaker than those for $S_i$, there were a number of notable ethnic differences, including a stronger association of NCEP-MetS with low AIR and low DI among blacks. This observation is significant in light of the well-documented prospective association between β-cell dysfunction and risk of diabetes, an association that is independent of directly measured insulin sensitivity (45,46). The biological mechanism underlying the association between MetS and β-cell dysfunction may be related to the fact that a number of MetS components, including elevated abdominal obesity and triglyceride concentration and reduced HDL levels, are strongly correlated with elevated circulating concentrations of free fatty acids (47), chronic elevations of which are known to be associated with lipotoxic damage to the pancreatic β-cells (48). This hypothesis is consistent with results from a previous study using IRAS data, in which it was reported that elevated waist circumference was significantly associated with reduced DI (49). The notably strong association of NCEP-MetS with reduced IS among blacks suggests the possibility that NCEP-MetS may be an especially useful predictor of diabetes in this ethnic group.

The demonstration that both WHO- and NCEP-MetS identify subjects with IR and (to a lesser degree) β-cell dysfunction has important clinical and public health implications. That the definitions capture these two important, independent domains of type 2 diabetes pathogenesis (in addition to indicating risk for CVD) suggests that they will be especially useful in identifying high-risk subjects for this disease. It has been demonstrated in a number of large clinical trials that intervening with lifestyle change or medication among high-risk individuals before the onset of type 2 diabetes is efficacious in delaying or preventing the onset of disease (50–52). Furthermore, IR is emerging as an important risk factor for CVD, an association that seems to be independent of traditional CVD risk factors (39,40). Defining MetS thus will be important in identifying individuals who are at risk for several common and burdensome chronic diseases. Although the association with IR was lower for NCEP- versus WHO-MetS, the NCEP definition still indicated a fivefold increased risk of IR. In addition, NCEP-MetS had a similar magnitude of association and was more specific (although less sensitive) in identifying subjects with IS abnormalities. The NCEP criteria do not require oral glucose tolerance testing or measures of insulin or microalbuminuria and thus are simpler to define in general clinical settings.

Ford et al. (7) reported a high prevalence of NCEP-MetS using data from the Third National Health and Nutrition Examination Survey, a nationally representative multiethnic sample of US adults, with especially elevated prevalence among Mexican Americans. We have confirmed this high prevalence and variation by ethnicity in the IRAS cohort and have extended this work by examining MetS within categories of glucose homeostasis determined using oral glucose tolerance testing. The prevalence of MetS was higher in the current article compared with rates reported by Ford et al. because of the older age of the subjects and the IRAS recruiting objective, which was to enroll equal numbers of subjects with NGT, IGT, and diabetes (21). Also consistent with Ford et al. was our observation of ethnic variation in prevalence of the different components used to define the syndrome. In particular, lipid abnormalities were less common and hypertension more common among black subjects.

Previous studies comparing WHO- versus NCEP-defined MetS have reported higher prevalence rates of WHO-NCEP (8,9,16), an observation consistent with the results of the present study. One possible explanation for the higher prevalence of WHO-MetS in the current study, even among nondiabetic subjects, relates to the older age and high proportion of subjects with IFG and/or IGT in the IRAS cohort. Our prevalence results should be interpreted cau-

tiously, however, given that IRAS was not a population-based study (21).

In conclusion, although both the WHO and NCEP MetS criteria were significantly associated with low $S_i$ in nondiabetic subjects, the associations were notably stronger using the WHO definition. The definitions were generally less useful for identifying those with low AIR or DI, although NCEP-MetS seems to differentiate black subjects with IS defects. Despite these differences, MetS, using either the WHO or the NCEP definition, was common in three large US ethnic groups and identified nondiabetic subjects with defects in both insulin sensitivity and IS. Given the documented association of these disorders with diabetes and CVD, individuals with MetS are ideal candidates for aggressive lifestyle and/or pharmacologic intervention.

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