Predictors of the Incident Metabolic Syndrome in Adults

The Insulin Resistance Atherosclerosis Study

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OBJECTIVE — To prospectively investigate predictors of the incident metabolic syndrome in nondiabetic adults.

RESEARCH DESIGN AND METHODS — This analysis included 714 white, black, and Hispanic participants in the Insulin Resistance Atherosclerosis Study (IRAS) who were free of the metabolic syndrome at baseline; 139 of these developed the metabolic syndrome in the subsequent 5 years. We examined measures of glucose (fasting and 2 h), insulin (fasting and 2 h, acute insulin response, insulin sensitivity [S_i], and proinsulin), lipids (HDL and triglycerides), blood pressure (systolic and diastolic), waist circumference, and baseline physical activity (total energy expenditure) as predictors of the metabolic syndrome. Logistic regression models were adjusted for age, sex, study site, ethnicity, and impaired glucose tolerance. Signal detection analysis was used to identify the characteristics of the highest risk group.

RESULTS — The best predictors of incident metabolic syndrome were waist circumference (odds ratio [OR] 1.7 [1.3–2.0] per 11 cm), HDL cholesterol (0.6 [0.4–0.7] per 15 mg/dl), and proinsulin (1.7 [1.4–2.0] per 3.3 pmol/l). Signal detection analysis identified waist circumference (>89 cm in women, >102 cm in men) as the optimal predictor.

CONCLUSIONS — These findings suggest that obesity may precede the development of other metabolic syndrome components. Interventions that address obesity and reduce waist circumference may reduce the incidence of the metabolic syndrome in nondiabetic adults.

Diabetes Care 27:788–793, 2004

The term "metabolic syndrome" refers to an apparent clustering of several findings in patients: abdominal obesity, insulin resistance (elevated fasting glucose), hypertension, and dyslipidemia (elevated triglyceride and decreased HDL cholesterol levels) (1). In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III report provided the first definition of the syndrome in national guidelines (2). According to this definition, >20% of adults have the metabolic syndrome (3). While many studies (4) have reported cross-sectional associations between metabolic syndrome components, few have prospectively examined the development of the metabolic syndrome in a cohort.

Prospective studies that use varied definitions of the metabolic syndrome suggest that development of the syndrome may be the result of a combination of factors, including insulin (5,6), obesity (7), and health behaviors (8). Decreased insulin sensitivity is thought to precede the development of the metabolic syndrome (9,10). To date, no published studies have investigated a validated measure of insulin sensitivity, along with a comprehensive set of risk factors, for development of metabolic syndrome in a prospective cohort. The primary aim of this study is to examine the role of insulin sensitivity, insulin secretion, dyslipidemia, hypertension, obesity, and physical activity on the incidence of the metabolic syndrome in nondiabetic adults.

RESEARCH DESIGN AND METHODS

— The Insulin Resistance Atherosclerosis Study (IRAS) is a multicenter, observational, epidemiological study of the relationships between insulin resistance and cardiovascular disease and its known risk factors in different ethnic groups at varying states of glucose tolerance. The design and methods of this study have been described in detail in previous publications (11). Briefly, 1,624 individuals participated in the baseline IRAS examination (56% women), which occurred between October 1992 and April 1994. Sampling strategies were used to identify sufficient numbers of individuals in different ethnic, age, sex, and glucose tolerance groups to allow an efficient study of relationships among and within these groups. Individuals taking insulin were excluded. IRAS was approved by the institutional review boards of all clinical centers and the coordinating center, and informed consent was obtained for all participants. Participants were followed for an average of 5.2 years (range 4.5–6.6).

Clinical measurements and procedures

The IRAS baseline clinical examination consisted of two 4-h visits scheduled about 1 week apart (12). Before each visit, participants were asked to refrain from alcohol and heavy exercise for 24 h, from food for 12 h, and from smoking on the day of the examination. The first visit included a 75-g oral glucose tolerance test; blood was collected for fasting and 2-h

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Received for publication 13 October 2003 and accepted in revised form 16 December 2003.
Abbreviations: IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; NCEP, National Cholesterol Education Program; NGT, normal glucose tolerance.

glucose samples. S_i, a validated measure of insulin resistance (13), was assessed by the frequently sampled intravenous glucose tolerance test with minimal model analyses (14). First-phase insulin secretion, expressed as the acute insulin response, was defined as the mean increment in the plasma insulin concentration above basal in the first 8 min after the administration of glucose.

Blood pressure was measured three times using a standard mercury sphygmomanometer at each visit as part of the baseline and follow-up examination. The average of the last two measurements for each visit was used to characterize the blood pressure at both baseline and follow-up. Weight and height were measured in duplicate and recorded to the nearest 0.1 kg and 0.5 cm, respectively. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured on bare skin during mid-respiration at the natural indentation between the 10th rib and the iliac crest to the nearest 0.5 cm. Classification was based on the average of two duplicate measures. A structured interview was used to collect 1-year recall of physical activity (total energy expenditure), and these methods are described in detail elsewhere (15). Race and ethnicity were self-reported.

Laboratory procedures

Plasma glucose was measured with the glucose oxidase technique on an automated autoanalyzer (Yellow Springs Instruments). Insulin was measured using the dextran-charcoal radioimmunoassay (16). Glucose tolerance status was classified according to World Health Organization criteria as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes (17). Fasting serum–intact proinsulin was determined from samples that had been stored at −70°C for an average of 3.3 years using highly specific immunoradiometric assays (18,19). Plasma lipid concentrations were determined from fasting plasma samples at the central IRAS laboratory (Medlantic Research Institute, Washington, DC) using the Lipid Research Clinics methodology. Follow-up examinations of this cohort were conducted using the same protocol used at baseline.

Definition of the metabolic syndrome

As detailed in the NCEP Adult Treatment Panel III report (2), the metabolic syndrome is defined as three or more of the following characteristics: *1*) abdominal obesity: waist circumference >102 cm in men and >88 cm in women, *2*) hypertriglyceridemia: ≥150 mg/dl (≥1.69 mmol/l), *3*) low HDL cholesterol: <40 mg/dl (<1.04 mmol/l) in men and <50 mg/dl (<1.29 mmol/l) in women, *4*) high blood pressure: ≥130 mmHg systolic or ≥85 mmHg diastolic, and *5*) high fasting glucose: ≥110 mg/dl (≥6.1 mmol/l). Participants who used antihypertensive or antidiabetic (insulin or oral agents) medication were defined as having high blood pressure or high fasting glucose, respectively.

Exclusions

The IRAS population was comprised of 1,624 study subjects (44% with NGT, 23% with IGT, and 33% with type 2 diabetes at baseline). Diabetic participants were excluded from this analysis. Of the 718 participants with NGT, 20% (n = 145) were excluded due to prevalent metabolic syndrome. There were 369 participants with IGT, 47% (n = 173) were excluded due to prevalent metabolic syndrome. There were 55 additional exclusions (49 NGT and 6 IGT) due to loss at follow-up. There were 714 participants included in our analyses.

Statistical analysis

Descriptive summary statistics were generated for the study population using means (and SEs) for continuous variables and proportions for dichotomous variables. The association of predictors and incident metabolic syndrome was modeled using logistic regression in an unadjusted model and in a model including potential confounders: age, sex, ethnicity, and study site. Additional models were adjusted for IGT status. The model adjusted for potential confounders was deemed to be the appropriate test of whether the predictor was independently associated with risk of incident metabolic syndrome. We did not pursue multivariate modeling given the high degree of correlation between the tested predictor variables.

There were no significant sex or ethnicity interactions, and thus analyses were pooled for sex and ethnicity. Statistical significance is denoted by $P < 0.001$ because of the large number of statistical tests. All analyses were conducted using the SAS system (SAS, Cary, NC).

Signal detection (20) was additionally used to identify predictors among nondiabetic adults, with a stopping rule of $P < 0.001$. Participants are stratified by sex in this analysis because waist circumference and HDL cholesterol cut points vary according to sex. Signal detection overcomes the problem of multiple collinearity among predictor variables (20) and allows exploratory testing of higher order interactions. We examined each predictor variable: fasting and 2-h glucose, fasting and 2-h insulin, acute insulin response, S_i, proinsulin, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, waist circumference, and total energy expenditure at 1-unit increments. IGT status was entered as a binary variable. Signal detection determines the optimal cut point across all increments of a variable and across all variables for maximizing both sensitivity and specificity for detecting incident metabolic syndrome.

RESULTS — Table 1 shows demographic and metabolic characteristics for the population free of metabolic syndrome at baseline by sex. The population was evenly divided in having none, one, and two metabolic syndrome components at baseline. Approximately one in five nondiabetic IRAS participants developed the metabolic syndrome over 5 years.

The unadjusted and age-, sex-, study site–, and ethnicity-adjusted odds ratios (ORs) between each predictor (per SD change) and incident metabolic syndrome for adults are displayed in Table 2. Additional adjustment for IGT status is also shown. IGT status as a binary variable was a significant predictor of incident metabolic syndrome. Waist circumference, fasting glucose, and proinsulin were associated with a significantly increased risk of the metabolic syndrome. Higher HDL cholesterol and insulin sensitivity (S_i) protected against developing the metabolic syndrome. After adjustment for IGT status, waist circumference and proinsulin remained significant predictors; HDL continued to be a significant negative predictor.

Signal detection identified predictors that distinguished individuals who were likely to develop the metabolic syndrome

Table 1—*Baseline demographic, anthropometric, and metabolic characteristics of participants without the metabolic syndrome at baseline, by sex*

Baseline variable	Total	Women	Men
n	714	396	318
Age	54.4 ± 8.5	54.3 ± 8.5	54.5 ± 8.5
Ethnicity (non-Hispanic white/black/Hispanic)	40.3/28.9/30.8	37.6/30.1/32.3	43.7/27.4/28.9
Metabolic syndrome components			
Waist circumference (cm)	87.4 ± 11.0	83.4 ± 11.2	92.4 ± 8.5
Triglycerides (mg/dl)	116.1 ± 70.5	106.4 ± 58.6	128.2 ± 81.4
HDL cholesterol (mg/dl)	49.5 ± 15.3	54.7 ± 15.1	43.0 ± 13.0
Systolic blood pressure (mmHg)	119.8 ± 16.0	119.0 ± 16.6	120.8 ± 15.1
Diastolic blood pressure (mmHg)	76.9 ± 9.0	75.6 ± 8.7	78.6 ± 9.2
Fasting glucose (mg/dl)	96.7 ± 10.4	94.7 ± 10.2	99.2 ± 10.0
Fasting insulin (μU/ml)	14.2 ± 15.4	14.0 ± 14.5	14.4 ± 16.4
Proinsulin (pmol/l)	4.9 ± 3.3	4.4 ± 3.0	5.6 ± 3.6
Insulin sensitivity (S_i) ($10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	2.5 ± 2.1	2.6 ± 2.2	2.4 ± 2.1
Acute insulin response ($pmol \cdot ml^{-1} \cdot min^{-1}$)	493.6 ± 471.4	473.0 ± 427.6	519.0 ± 519.6
2-h insulin (μU/ml)	83.2 ± 72.9	81.9 ± 67.3	84.7 ± 79.3
2-h glucose (mg/dl)	119.0 ± 32.1	119.3 ± 31.4	118.6 ± 32.9
Total energy expenditure ($kcal \cdot kg^{-1} \cdot year^{-1}$)	14,826 ± 2,709	14,396 ± 2,243	15,358 ± 3,115
Proportion with IGT	26.6	28.0	24.8
Proportion with one metabolic syndrome component at baseline	34.6	33.6	35.9
Proportion with two metabolic syndrome components at baseline	34.7	34.3	35.2
Proportion that develops incident metabolic syndrome	19.5	20.9	17.1

Data are means ± SD unless noted otherwise.

from those who were not, with a stopping rule $P < 0.001$. The results for women are shown in Fig. 1. Three subgroups are identified among women, with the proportion of individuals who developed the metabolic syndrome ranging from 9 to 61%. At the first level, waist circumference was identified as the optimal predictor, with a cut point of 89 cm ($\chi^2 = 60$). Among the women with larger waists, HDL levels provided additional discrimination, with an optimal cut point of 44 mg/dl. Sixty-one percent of the subgroup with waist circumference >89 cm and HDL cholesterol <44 mg/dl developed the metabolic syndrome.

Figure 2 shows signal detection analysis in men. The optimal predictor was waist circumference, with a cut point of 102 cm ($\chi^2 = 38$). This cut point identified the highest risk group, with a 46% incidence of metabolic syndrome over 5 years; no other variables provided additional discrimination in this group. The 2-h glucose, with a cut point of 160 mg/dl, was identified as an additional predictor in the group with waist circumference <102 cm.

Individual components of the metabolic syndrome at baseline were tested as binary univariate predictors of incident metabolic syndrome among nondiabetic men and women. Table 3 shows that waist circumference is the best predictor at the NCEP-defined levels.

CONCLUSIONS — These findings are the first reported from a prospective study examining direct measures of insulin sensitivity, glucose metabolism, physical activity, and individual components of the syndrome as predictors of metabolic syndrome. These findings underscore the importance of obesity as a significant predictor of incident metabolic syndrome and can be used to identify at-risk individuals.

Univariate analysis

Among nondiabetic IRAS subjects, waist circumference, HDL cholesterol, fasting glucose, proinsulin, insulin sensitivity, 2-h insulin, 2-h glucose, and IGT were all significant predictors in univariate models. These factors are all highly correlated and preclude inclusion into a multivariate model for determination of the most highly associated predictor. Based on strength of association, significance, and clinical utility, waist circumference, HDL cholesterol, and fasting glucose may be identified as useful predictors in this univariate analysis.

IGT

Adjustment for IGT (Table 2) attenuated several associations and may represent overadjustment. After adjustment for IGT, waist circumference, HDL cholesterol, and proinsulin remained significant at the $P < 0.001$ level.

Signal detection analyses

Men and women were stratified in these analyses because HDL cholesterol and waist circumference cut points are sex specific. IGT status was entered as a predictor variable and was not identified as a useful predictor. Signal detection analysis identified waist circumference as the best predictor in both men and women. Interestingly, the optimal cut point chosen for waist circumference was identical to that chosen by NCEP for men (Fig. 1) and was 1 cm higher for women (Fig. 2). Since waist circumference was the optimum variable to predict those who were likely to develop the metabolic syndrome, it is not surprising that this component was the most significant in the binary univariate analysis (Table 3). Entering BMI as an additional variable into the signal detec-

Table 2—*Unadjusted and adjusted predictors for incident metabolic syndrome per SD*

Variable (SD)	Unadjusted	Adjusted*	Adjusted for IGT†
Age (8.5 years)	0.9 (0.8–1.1)	—	—
Sex	0.8 (0.6–1.2)	—	—
Study site			
Los Angeles	0.8 (0.5–1.4)	—	—
Oakland	1.3 (0.8–2.2)	—	—
San Antonio	1.3 (0.8–2.2)	—	—
Ethnicity			
Black	0.8 (0.5–1.3)	—	—
Hispanic	1.0 (0.6–1.5)	—	—
Metabolic syndrome components			
Waist circumference (11.0 cm)	**1.5 (1.3–1.9)**	**1.8 (1.4–2.2)**	**1.7 (1.3–2.0)**
Triglycerides (70.5 mg/dl)	1.3 (1.1–1.5)	1.3 (1.1–1.6)	1.3 (1.1–1.5)
HDL cholesterol (15.3 mg/dl)	**0.7 (0.5–0.8)**	**0.6 (0.4–0.7)**	**0.6 (0.4–0.7)**
Systolic blood pressure (16.0 mmHg)	1.2 (1.0–1.4)	1.3 (1.0–1.6)	1.3 (1.0–1.6)
Diastolic blood pressure (9.0 mmHg)	1.1 (0.9–1.3)	1.2 (1.0–1.4)	1.1 (0.9–1.4)
Fasting glucose (10.4 mg/dl)	**1.4 (1.2–1.7)**	**1.5 (1.2–1.8)**	1.3 (1.1–1.6)
Fasting insulin (15.4 μU/ml)	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.2 (1.0–1.5)
Proinsulin (3.3 pmol/l)	**1.7 (1.4–2.0)**	**1.8 (1.5–2.2)**	**1.7 (1.4–2.0)**
Insulin sensitivity (S_i) ($2.1 \cdot 10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	**0.6 (0.5–0.8)**	**0.5 (0.4–0.7)**	0.6 (0.5–0.8)
Acute insulin response (471.4 pmol $\cdot$ $ml^{-1} \cdot min^{-1}$)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	1.0 (0.8–1.3)
2-h insulin (72.9 μU/ml)	**1.3 (1.1–1.6)**	**1.4 (1.2–1.6)**	1.0 (0.8–1.3)
2-h glucose (32.1 mg/dl)	**1.5 (1.2–1.8)**	**1.6 (1.3–1.9)**	1.2 (0.8–1.6)
Total energy expenditure (2,709 kcal $\cdot$ $kg^{-1} \cdot year^{-1}$)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)
IGT (yes/no)	**2.6 (1.8–3.8)**	**3.0 (2.0–4.4)**	—

Data are OR (95% CI). $N = 714$, and n with incident metabolic syndrome = 139. *Models adjusted for age, sex, study site, and ethnicity; †models adjusted for age, sex, study site, ethnicity, and IGT status. Bold data indicate statistical significance ($P < 0.001$).

tion analysis did not alter the conclusions (results not shown). Thus, waist circumference was a better predictor of incident metabolic syndrome than BMI in our statistical analyses, similar to the results of others (21,22).

For women, the second discriminatory variable identified was HDL cholesterol, with a cut point of 44 mg/dl. This level is lower than the NCEP-defined cut point of 50 mg/dl for women and served to distinguish a high-risk group of women among those with large waists. Among men with smaller waists, 2-h glucose of 160 mg/dl was identified as the next optimal predictor. This cut point is higher than that used to define IGT (140–199 mg/dl). These findings warrant further in-

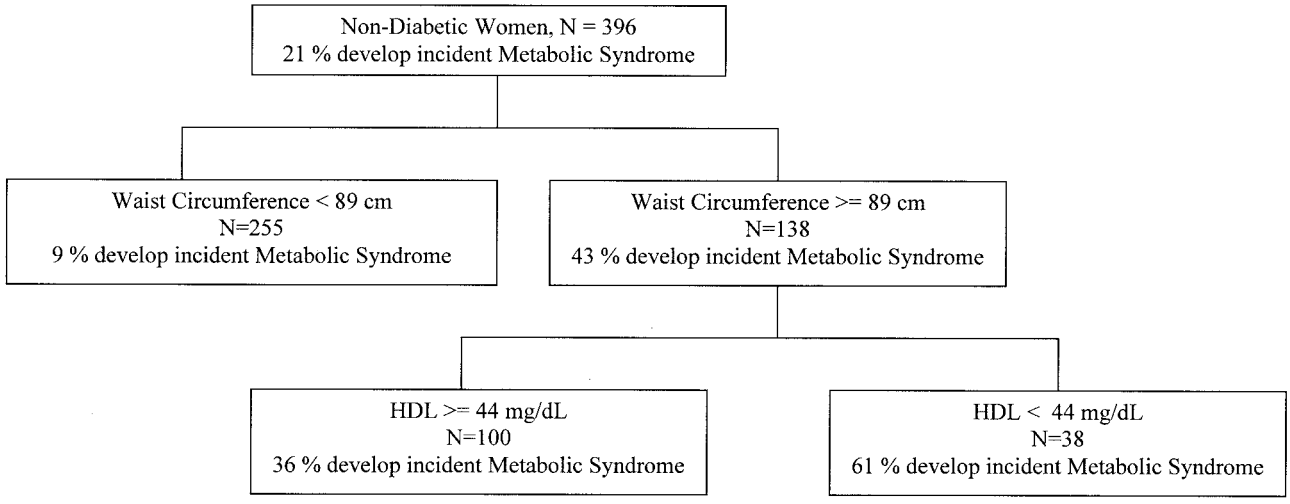

Figure 1—*Signal detection analysis: women. Variables entered were fasting insulin, 2-h insulin, acute insulin response, S_i, proinsulin, HDL, triglycerides, waist circumference, fasting glucose, 2-h glucose, systolic blood pressure, diastolic blood pressure, total energy expenditure, IGT status, age, ethnicity, and clinic.*

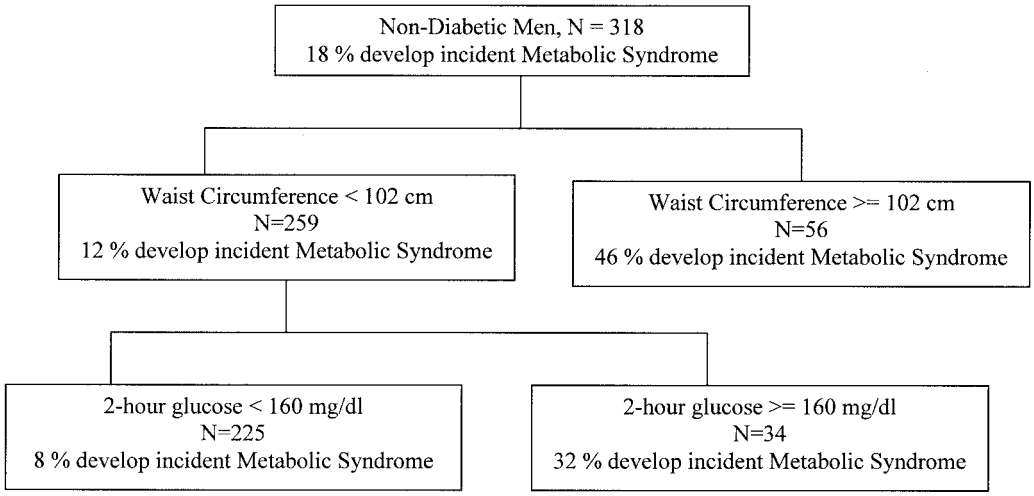

Figure 2—*Signal detection analysis: men. Variables entered were fasting insulin, 2-h insulin, acute insulin response, S_i, proinsulin, HDL, triglycerides, waist circumference, fasting glucose, 2-h glucose, systolic blood pressure, diastolic blood pressure, total energy expenditure, IGT status, age, ethnicity, and clinic.*

vestigation in other populations to determine the discriminatory power of currently utilized cut points for HDL cholesterol and IGT.

Physical activity

Other prospective cohort studies (23,24) have identified baseline physical activity as a predictor of the metabolic syndrome. Baseline physical activity was not a predictor in the IRAS cohort. Our measure of physical activity was based on self-reported participation in activities and was not an objective measure of fitness, and this may have affected its precision as a predictor. Physical activity is likely important in the development of metabolic syndrome to the extent that it influences obesity.

Obesity, insulin resistance, and the metabolic syndrome

Insulin resistance is thought to result from either an inherited genetic defect or obesity (25). Insulin resistance subsequently leads to elevations in triglyceride and glucose levels and in systolic and diastolic blood pressure (26) and to reduced HDL cholesterol levels (5). Our study revealed that obesity was a better predictor of incident metabolic syndrome than directly measured insulin sensitivity. A prospective population-based cohort study in France (27) also identified obesity as a central feature of the syndrome, even after accounting for the contribution of baseline IGT. Obesity and insulin resistance are closely linked (28,29). While not definitive, our findings suggest that obesity may precede the development of insulin resistance. Further prospective research would be valuable in discerning the temporal relationship of these factors in the development of the metabolic syndrome.

Limitations

The IRAS study was not population based. The use of a population-based sample would provide greater support for generalizability (26). Also, some of the possible predictors that are examined in this analysis are themselves criteria for the diagnosis of the metabolic syndrome. This would put a premium on metabolic syndrome components as predictors, even if other measures were actually better clinical predictors.

Strengths

This study also has several strengths. The main advantage of this study was the inclusion of directly measured insulin sensitivity (S_i) in the analysis and its comparison with other measures as a predictor of the metabolic syndrome. The identification of waist circumference as the optimal predictor in signal detection analysis may indicate greater precision in its measurement rather than etiologic precedence. Metabolic syndrome status was defined based on national criteria. All predictors were assessed using a validated and standardized methodology across a range of ethnic groups.

Clinical implications

From a clinical perspective, the modest association observed in this study does not support the routine measurement of proinsulin and S_i. Lack of precision in these measures may influence their quality as predictors. Signal detection analysis was used to weight all predictors and prediction levels equally in evaluating their utility. This analysis confirmed the superiority of routine measures, such as waist circumference, in risk stratification. These findings support the thesis that obesity is a significant predictor of inci-

Table 3—*Individual baseline metabolic syndrome components as predictors of incident metabolic syndrome*

	OR (95% CI)
Blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic)	1.1 (0.7–1.6)
Glucose (≥110 mg/dl)	1.6 (0.9–2.8)
Triglycerides (≥150 mg/dl)	1.6 (1.0–2.4)
Waist Circumference (≥102 cm for men and ≥88 cm for women)	2.0 (1.3–3.1)
Low HDL cholesterol (≤40 mg/dl for men and ≤50 mg/dl for women)	1.6 (1.1–2.4)

dent metabolic syndrome. Interventions to reduce obesity may significantly impact development of the metabolic syndrome, and this approach should be examined in randomized clinical trials.

Acknowledgments— The authors thank Lori Wallace for her assistance with manuscript preparation.

References

1. Reaven GM: Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med* 44:121–131, 1993
2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III): Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
3. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA* 287:356–359, 2002
4. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB: The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 163: 427–436, 2003
5. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 41: 715–722, 1992
6. Han TS, Williams K, Sattar N, Hunt KJ, Lean ME, Haffner SM: Analysis of obesity and hyperinsulinemia in the development of metabolic syndrome: San Antonio Heart Study. *Obes Res* 10:923–931, 2002
7. Liese AD, Mayer-Davis EJ, Tyroler HA, Davis CE, Keil U, Duncan BB, Heiss G: Development of the multiple metabolic syndrome in the ARIC cohort: joint contribution of insulin, BMI, and WHR: Atherosclerosis Risk in Communities. *Ann Epidemiol* 7:407–416, 1997
8. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA: Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. *Diabetes Care* 25:1612–1618, 2002
9. Kendall DM, Harmel AP: The metabolic syndrome, type 2 diabetes, and cardiovascular disease: understanding the role of insulin resistance. *Am J Manag Care* 8: S635–S653, 2002
10. Reusch JE: Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. *Am J Cardiol* 90: 19G–26G, 2002
11. Wagenknecht LE, Mayer EJ, Rewers M, Haffner S, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF, Bergman RN, Hamman R: The Insulin Resistance Atherosclerosis Study (IRAS) objectives, design, and recruitment results. *Ann Epidemiol* 5:464–472, 1995
12. Haffner SM, D'Agostino R, Saad MF, Rewers M, Mykkanen L, Selby J, Howard G, Savage PJ, Hamman RF, Wagenknecht LE, Bergman RN: Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. *Diabetes* 45:742–748, 1996
13. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, Sands RE, Pei D, Savage PJ, Bergman RN: A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance: Insulin Resistance Atherosclerosis Study. *Diabetes* 43:1114–1121, 1994
14. Bergman RN, Prager R, Volund A, Olefsky JM: Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest* 79:790–800, 1987
15. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN: Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 279:669–674, 1998
16. Herbert V, Lau KS, Gottlieb CW, Bleicher SJ: Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab* 25:1375–1384, 1965
17. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
18. Sobey WJ, Beer SF, Carrington CA, Clark PM, Frank BH, Gray IP, Luzio SD, Owens DR, Schneider AE, Siddle K, et al.: Sensitive and specific two-site immunoradiometric assays for human insulin, proinsulin, 65–66 split and 32–33 split proinsulins. *Biochem J* 260:535–541, 1989
19. Haffner SM, D'Agostino R, Mykkanen L, Hales CN, Savage PJ, Bergman RN, O'Leary D, Rewers M, Selby J, Tracy R, Saad MF: Proinsulin and insulin concentrations in relation to carotid wall thickness: Insulin Resistance Atherosclerosis Study. *Stroke* 29:1498–1503, 1998
20. Kiernan M, Kraemer HC, Winkleby MA, King AC, Taylor CB: Do logistic regression and signal detection identify different subgroups at risk? Implications for the design of tailored interventions. *Psychol Methods* 6:35–48, 2001
21. Wei M, Gaskill SP, Haffner SM, Stern MP: Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared with body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans: a 7-year prospective study. *Obes Res* 5:16–23, 1997
22. Janssen I, Katzmarzyk PT, Ross R: Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. *Arch Intern Med* 162:2074–2079, 2002
23. Laaksonen DE, Lakka HM, Lynch J, Lakka TA, Niskanen L, Rauramaa R, Salonen JT, Kauhanen J: Cardiorespiratory fitness and vigorous leisure-time physical activity modify the association of small size at birth with the metabolic syndrome. *Diabetes Care* 26:2156–2164, 2003
24. Carnethon MR, Hill JO, Loria CM, Savage PJ, Liu K: Risk factors for developing the metabolic syndrome in young adults: the CARDIA study (Abstract). *Circulation* 108 (Suppl. IV):728, 2003
25. Liese AD, Mayer-Davis EJ, Haffner SM: Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* 20:157–172, 1998
26. Goff DC Jr, Zaccaro DJ, Haffner SM, Saad MF: Insulin sensitivity and the risk of incident hypertension: insights from the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 26:805–809, 2003
27. Maison P, Byrne CD, Hales CN, Day NE, Wareham NJ: Do different dimensions of the metabolic syndrome change together over time? Evidence supporting obesity as the central feature. *Diabetes Care* 24: 1758–1763, 2001
28. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
29. Anderson PJ, Critchley JA, Chan JC, Cockram CS, Lee ZS, Thomas GN, Tomlinson B: Factor analysis of the metabolic syndrome: obesity vs insulin resistance as the central abnormality. *Int J Obes Relat Metab Disord* 25:1782–1788, 2001