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A systematic evaluation of the insulin resistance syndrome as an independent risk factor for cardiovascular disease mortality and derivation of a clinical index

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ABSTRACT

Insulin resistance–related risk factor clustering (the insulin resistance syndrome or IRS) may be a cardiovascular disease (CVD) risk factor, but a convincing demonstration of this requires a rigorously derived reference measure and a systematic evaluation of measures and indices that derive from that measure. Using established IRS characteristics, factor analysis in 832 white men, generally healthy at baseline, generated a priori an IRS reference measure. An IRS diagnostic was chosen by evaluating CVD mortality risk in percentiles of the reference measure. An IRS clinical index was derived by (1) identification of readily measured, independent predictors of the IRS reference measure by multiple linear regression; (2) assignment to each predictor of a cut point optimal for discrimination of participants diagnosed with IRS; and (3) selection of a combination of the dichotomized predictors that further optimized IRS discrimination. The reference IRS diagnostic was defined by the top 16.7% of the IRS reference measure and predicted CVD mortality in Cox proportional hazards modeling (hazard ratio, 2.7; 95% confidence interval, 1.5-5.2; $P = .002$). An optimized IRS index was defined by triglycerides of at least 1.6 mmol/L and uric acid of at least 400 μmol/L plus any one of fasting plasma glucose of at least 5.4 mmol/L, diastolic blood pressure of at least 90 mm Hg, or body mass index of at least 27.0 kg/m^2 and predicted CVD mortality (hazard ratio, 2.14 [1.08-4.24]; $P = .02$). Prediction was independent of hypertension, hypercholesterolemia, and smoking. Conventionally derived glucoregulatory insulin resistance and metabolic syndrome were not predictive. The IRS is an independent risk factor for CVD mortality; and an effective, clinically usable index can be derived from readily measured variables.

1. Introduction

The coassociation of obesity, dyslipidemia, hypertension, and hyperglycemia has led to the concept of a "metabolic syndrome" [1-4]. Because each of these features is itself an independent cardiovascular disease (CVD) risk factor, it was hoped that an agreed syndrome definition would enhance individual CVD risk prediction beyond established risk prediction models or the individual components. This hope remains controversial [5-7].

The metabolic syndrome concept was given a mechanistic basis by Reaven's [8] proposal in 1988 that insulin resistance

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can cause elevated plasma very low-density lipoprotein, insulin, and glucose concentrations; decreased high-density lipoprotein (HDL) cholesterol; increased blood pressure; and, included subsequently, increased uric acid [9]. It was hypothesized that this "insulin resistance syndrome" (IRS) could, itself, increase CVD risk. This hypothesis has never been tested, attention having been directed toward the more easily determined metabolic syndrome, which may differ significantly in its behavior and features from the IRS [10]. Nevertheless, if an IRS reference measure could be established, more accessible surrogate IRS indices could be explored.

In the present analysis, we test the hypothesis that the IRS is a risk factor for CVD. We first derive a reference measure using a factor analysis [11,12] incorporating only those variables originally proposed by Reaven to be mechanistically affected by insulin resistance, namely, triglycerides (a surrogate for very low-density lipoprotein), HDL cholesterol, blood pressure, glucose, insulin, and uric acid. Secondly, we evaluate this measure as a covariate of CVD survival time. Finally, we explore IRS diagnostic criteria and establish whether an effective IRS index can be derived using panels of dichotomized, readily measured variables and whether this index is also a significant covariate of CVD survival time.

2. Methods

2.1. Data acquisition

The Heart Disease and Diabetes Risk Indicators in a Screened Cohort (HDDRISC) Study is an open cohort study of metabolic risk in the development of CVD and diabetes [13]. Beginning as a company health program, 1278 participants were recruited of whom 1192 were white men (age range, 26-70 years) and make up the HDDRISC cohort. Recruitment lasted from June 1971 to August 1997, with the last participant visit in January 2000. Ethics committee approval was from the St Mary's Hospital and Cavendish Clinic Research Ethics Committees, and each participant gave written consent. Subjects attended after an overnight fast [12]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured, and fasting bloods were taken. The majority of participants underwent an oral glucose tolerance test (OGTT), sampling at 30, 60, 90, 120, 150, and 180 minutes.

Plasma glucose and insulin, and serum total and HDL cholesterol and triglyceride were measured [13]. Routine hematology (including erythrocyte sedimentation rate) and biochemistry (uric acid, albumin, globulin, bilirubin, and phosphate concentrations and γ-glutamyl transferase, aspartate transaminase, and alkaline phosphatase activities) were performed. Quality control was ensured using pooled stored samples and by participation in national schemes. Long-term continuity of measurement was sustained with replicate assay of previously analyzed frozen samples and comparisons when there was any change in assay methodology (eg, Khan et al [14]).

Deaths from CVD were identified to January 2009 through the National Health Service Information Centre for Health and Social Care. Cardiovascular disease mortality was assigned if myocardial infarction, coronary artery disease or thrombosis, cerebrovascular incident, stroke, peripheral vascular disease, or aortic aneurysm was recorded as a primary cause of death. With the exception of 27 individuals who are no longer traceable, mortality ascertainment for the HDDRISC cohort is complete.

2.2. Data analysis

Fasting plasma glucose (FPG) and fasting plasma insulin (FPI) concentrations were expressed as the mean of 2 fasting measurements. Glucose tolerance and the insulin response to glucose were quantified as the OGTT incremental area under the curve (AUC). The homeostasis model assessment of insulin resistance (HOMA-IR) was the fasting index of glucoregulatory insulin resistance [15]; and the Matsuda index of insulin sensitivity (Matsuda-IS), derived from the OGTT glucose and insulin levels, was the postglucose index [16]. Metabolic syndrome status was assigned to each individual using both the National Cholesterol Education Program (NCEP) [3] and International Diabetes Federation (IDF) [1] criteria. Because waist circumference measurements were not available, cutoffs of body mass index (BMI) of at least 27.0 kg/m^2 and at least 30 kg/m^2 were used in place of the IDF and NCEP waist circumference cutoffs, respectively, as validated using data from a previously described cohort of 1784 white male subjects [17]. All study participants had measurements in the fasting state and comprised the "full cohort," with HOMA-IR providing an index of glucoregulatory insulin resistance. Participants who had also undergone an OGTT comprised the "OGTT cohort," with Matsuda-IS providing an index of glucoregulatory insulin sensitivity.

Statistical analyses were carried out using STATA 8 (Stata, College Station, TX). Excluded from the analysis were participants taking blood pressure–, lipid-, or uric acid–lowering medications or with missing values for any of the 6 IRS measures, evidence of diabetes mellitus, or a history of CVD. For parametric analyses, measures were normalized as appropriate. Kruskal-Wallis test, χ^2 test, Pearson correlation, stepwise multiple linear regression, logistic regression, Cox proportional hazards modeling, with testing of the proportional hazards assumption using Schoenfeld residuals, receiver operating characteristic (ROC) analysis, and factor analysis, as previously described [18], were used as appropriate. Blood pressure was entered into the factor analysis as mean arterial pressure (MAP: [(2 × DBP) + SBP]/3) to avoid the emergence of a single, noninformative factor comprising the highly correlated SBP and DBP measurements [12].

The factor score from a factor analysis of the 6 IRS variables was taken as a single reference IRS measure. Factor analysis, as used previously in this cohort [18], identifies underlying "factors" responsible for coassociations between intercorrelated variables. Each variable is associated with a given factor according to a "loading," which quantifies its importance as a feature of the factor. For a given individual, summing the products of an individual's level for each variable (standardized according to its mean and standard deviation) and the loading of each variable on a particular factor provides a score for that factor for the individual. This "factor score" quantifies the intensity with which the cluster of coassociated variables is expressed in the individual and can be used as a single

variable in further statistical analysis. We expected the 6 IRS measures to appear as features of a single factor. The analysis was, therefore, confirmatory [12].

3. Results

After exclusions, 832 participants contributed data to the full cohort and 543 to the OGTT cohort. Characteristics are shown in Table 1. In general, the 2 cohorts were highly comparable. There was a high prevalence of overweight, with 55% having a BMI of at least 25, 27% a BMI of at least 27, and 7% a BMI of at least 30 kg/m^2.

3.1. Derivation of the IRS reference measure

An IRS reference measure in each cohort was provided by the factor score from factor analysis with entry of the 6 IRS measures: triglycerides, HDL cholesterol, uric acid, and MAP plus, as measures of insulinemia, FPI or OGTT insulin incremental AUC for the full or OGTT cohorts, respectively, and, as measures of glycemia, FPG or OGTT glucose incremental AUC. As expected, factor analyses in the full and OGTT cohorts each returned a single factor. Factor loadings in the full cohort were as follows: triglycerides, 0.57; HDL cholesterol, –0.39; MAP, 0.33; uric acid, 0.42; FPI, 0.38; and FPG, 0.26. The equivalent figures in the OGTT cohort were 0.51, –0.28, 0.32, 0.43, 0.51, and 0.41. The factor score for each participant in each cohort provided the cohort's IRS reference measure. Pearson correlation coefficients were derived between the IRS reference measure (which relates to overall insulin resistance) in each cohort and the cohort measure of glucoregulatory insulin resistance. Correlation coefficients were 0.54 with HOMA-IR in the full cohort and –0.49 with Matsuda-IS in the OGTT cohort (both $P < .001$).

Table 1 – Group characteristics

	Full cohort (N = 832)	OGTT cohort (n = 543)
Age (y)	46.8 (40.7-52.5)	48.1 (42.8-53.8)
BMI (kg/m^2)	25.3 (23.7-27.3)	25.1 (23.6-26.9)
SBP (mm Hg)	120 (110-132)	125 (115-135)
DBP (mm Hg)	79 (70-86)	80 (70-90)
Total cholesterol (mmol/L)	5.35 (4.79-6.11)	5.41 (4.81-6.19)
Triglycerides (mmol/L)	1.15 (0.82-1.64)	1.16 (0.85-1.60)
HDL cholesterol (mmol/L)	1.30 (1.12-1.51)	1.30 (1.14-1.53)
Uric acid (μmol/L)	370 (320-420)	380 (340-430)
Fasting plasma glucose (mmol/L)	5.3 (5.0-5.6)	5.3 (5.0-5.6)
Fasting plasma insulin (mU/L)	9.9 (6.0-15.0)	10.5 (6.0-16.0)
Smoking		
Nonsmoker (%)	71	66
<15 Cigarettes/d (%)	19	21
≥15 Cigarettes/d (%)	10	13
Alcohol		
<28 U/wk (%)	64	58
≥28 U/wk (%)	36	42
Exercise		
No exercise (%)	39	37
Nonaerobic (%)	45	45
Aerobic (%)	16	18

Medians and interquartile ranges are shown for continuous variables and percentages for categorical variables.

3.2. The IRS reference measure as a covariate of CVD survival time

Mean follow-up times for the full and OGTT cohorts were 21.4 and 23.8 years, respectively, with 44 and 42 deaths from CVD, respectively. In Cox proportional hazards modeling, the hazard ratio for the IRS reference measure as a covariate of CVD survival time was 2.00 (95% confidence interval [CI], 1.35-2.96; $P = .001$) for the full cohort and 1.86 (95% CI, 1.28-2.71; $P = .001$) (Table 2) for the OGTT cohort. The glucoregulatory insulin resistance/sensitivity measures, HOMA-IR and Matsuda-IS, were not significant as covariates.

3.3. Derivation of an IRS reference diagnostic

Risk of CVD mortality was explored in successive percentiles of the IRS reference measure in the full cohort. Relative to a hazard ratio of 1.0 in the lowest percentile, hazard ratios in increasing percentiles of the IRS reference measure were as follows:

- Tertiles: 3.2 ($P = .02$) and 4.5 ($P = .002$)
- Quartiles 5.6 ($P = .02$), 5.8 ($P = .02$), 8.4 ($P = .004$)
- Quintiles 2.9 ($P = .1$), 3.6 ($P = .1$), 5.9 ($P = .01$), 7.8 ($P = .006$)
- Sextiles 1.3 ($P = .7$), 4.3 ($P = .06$), 3.3 ($P = .1$), 3.6 ($P = .1$), 7.5 ($P = .008$)

The relatively high risk in the top sextile and the lack of significance in the lower sextiles suggested that a value for the IRS reference measure in the top sextile (ie, the top 16.7%) could be considered as a clinical criterion for an abnormally high intensity of insulin resistance–related risk factor clustering. For the purposes of the present analysis, we have adopted this criterion as diagnostic for the IRS; in other words, the 139 individuals in our study with a value for the IRS reference measure in the top sextile of the IRS reference measure are considered as "having the IRS." In the full cohort, the hazard ratio for CVD mortality for those with the IRS relative to all other participants was 2.74 (95% CI, 1.45-5.17; $P = .002$). The same percentile cutoff applied to the OGTT cohort IRS reference measure gave a hazard ratio for those with the IRS of 2.43 (95% CI, 1.26-4.69; $P = .008$) (Table 2).

3.4. Selection of variables for possible inclusion in a clinical index of the IRS

Variables considered were those known to correlate with glucoregulatory insulin sensitivity and either could be affected by insulin resistance (eg, triglycerides or uric acid) or could affect insulin resistance (eg, BMI or inflammation-related measures) and were readily available (this excluded insulin or OGTT-derived measures). Variables were BMI, FPG, DBP, SBP, total cholesterol, triglycerides, HDL cholesterol, uric acid, γ-glutamyl transferase, aspartate transaminase, alkaline phosphatase, bilirubin, phosphate, albumin, globulin, white blood cell count, erythrocyte sedimentation rate, and hemoglobin. Only albumin in the full cohort did not correlate significantly with the IRS reference measure. In each cohort, these variables

were entered stepwise in multiple linear regression analysis as predictors of the IRS reference measure. Independent predictors of the IRS reference measure that changed the R^2 value for the model by more than 1% were, in order of entry, as follows: full cohort—triglycerides, uric acid, HDL cholesterol, DBP, and FPG; OGTT cohort—triglycerides, uric acid, HDL cholesterol, DBP, and BMI. These analyses, therefore, identified triglycerides, uric acid, HDL cholesterol, DBP, FPG, and BMI as readily measured variables for possible inclusion in an IRS clinical index.

3.5. *Derivation of a clinical index for the IRS reference diagnostic*

There are various approaches to derivation of a clinical index using the selected readily measured variables. To establish, in principle, whether a clinical index could be derived, we identified for each readily measured variable a cutoff that could optimally discriminate reference IRS diagnostic status. We then evaluated combinations of these dichotomized variables that could further optimize discrimination of IRS diagnostic status. This was carried out in the full cohort.

Optimal cutoffs for readily measured variables were determined by examination of the sensitivity/specificity profile following logistic regression discrimination of reference IRS diagnostic status by that variable. The value of the variable corresponding to the predicted positive outcome probability at which the sensitivity and specificity profiles crossed then provided the cutoff. Cutoffs for optimum prediction of the reference IRS diagnostic were as follows: triglycerides of at least 1.57 mmol/L, uric acid of at least 400 μmol/L, HDL cholesterol not exceeding 1.19 mmol/L, DBP of at least 80 mm Hg, FPG of at least 5.4 mmol/L, and BMI of at least 26.24 kg/m^2.

To help identify a combination of these dichotomized variables that could optimally discriminate reference IRS diagnostic status, we referred to the relative contribution to prediction of reference IRS diagnostic status by each of the dichotomized variables in logistic regression analysis. Triglyceride value of at least 1.57 mmol/L was the strongest predictor (t value = 9.8), followed by uric acid of at least 400 μmol/L (6.8), HDL cholesterol not exceeding 1.19 mmol/L (6.8), FPG of at least 5.4 mmol/L (4.4), BMI of at least 26.24 kg/m^2 (3.1), and DBP of at least 80 mm Hg (2.8). A surrogate index would, therefore, most likely include high triglycerides combined with high uric acid or low HDL cholesterol. High FPG, high BMI, or high DBP might then offer further discrimination. Seventeen different combinations were explored, 5 examples of which are shown in Table 3. In terms of the sensitivity, specificity, and the area under the ROC curve (AROC) with which each combination could correctly assign reference IRS diagnostic status, as well as the performance of each combination as a covariate of CVD survival time, there was little difference between a number of the combinations. The combination of high triglycerides and high uric acid plus any one of high FPG, high BMI, or high DBP (combination 4; Table 3) had a slight advantage in its level of significance as a covariate of CVD survival time and is chosen as an example for further discussion.

3.6. *Derivation of a clinically usable index for the IRS reference diagnostic*

To improve ease of use, cut points were rounded to give the following "IRS index": triglycerides of at least 1.6 mmol/L and uric acid of at least 400 μmol/L, plus any one of DBP of at least 80 mm Hg, FPG of at least 5.4 mmol/L, and BMI of at least 27.0 kg/m^2.

Table 2 – Continuous indices of glucoregulatory insulin resistance/sensitivity entered into the model were the HOMA-IR (full cohort) index of insulin resistance or the Matsuda-IS (OGTT cohort) index of insulin sensitivity

	Continuous			
	Glucoregulatory insulin resistance/sensitivity		IRS reference measure	
	Full cohort, HOMA-IR			
	OGTT cohort, Matsuda-IS		IRS variables factor score	
	HR (95% CI)	Significance	HR (95% CI)	Significance
Full cohort	1.12 (0.79-1.61)	.5	2.00 (1.35-2.96)	.001
OGTT cohort	0.76 (0.49-1.24)	.2	1.86 (1.28-2.71)	.001
	Diagnostic			
	Full cohort, HOMA-IR top sextile			
	OGTT cohort, Matsuda-IS top sextile		IRS variables factor score top sextile	
	HR (95% CI)	Significance	HR (95% CI)	Significance
Full cohort	0.73 (0.31-1.72)	.4	2.74 (1.45-5.17)	.002
OGTT cohort	0.70 (0.27-1.78)	.4	2.43 (1.26-4.69)	.008

As a continuous reference measure of the IRS, the factor score from factor analyses of the IRS variables in the full cohort or the OGTT cohort was entered into the model. The diagnostic index for glucoregulatory insulin resistance or the IRS was determined according to the cutoff for the top sextile (or bottom sextile for insulin sensitivity, Matsuda-IS) of each continuous measure. Hazard ratios (95% confidence intervals) from Cox proportional hazards modeling of CVD mortality. HR indicates hazard ratio.

Table 3 – Example combinations of the IRS clinical index variables: triglycerides of at least 1.57 mmol/L, uric acid of at least 400 μmol/L, HDL cholesterol not exceeding 1.17 mmol/L, FPG of at least 5.4 mmol/L, BMI of at least 26.24 kg/m^2, and DBP of at least 80 mm Hg as predictors of reference IRS status in logistic regression analysis in the full cohort (N = 832)

	Prediction of IRS status in logistic regression analysis				Prediction of CVD mortality in Cox modeling	
	No. assigned to positive IRS status	Sensitivity	Specificity	AROC	Hazard ratio (95% CI)	Significance
1. Triglycerides, uric acid, HDL cholesterol	66	43	99	0.77	2.25 (1.00-5.04)	.04
2. Triglycerides, uric acid, HDL cholesterol plus any one of FPG, BMI, or DBP	64	43	99	0.77	2.32 (1.03-5.20)	.04
3. Triglycerides, uric acid plus any one of HDL cholesterol, FPG, BMI, or DBP	119	59	95	0.77	2.10 (1.06-4.16)	.03
4. Triglycerides, uric acid plus any one of FPG, BMI, or DBP	117	59	95	0.76	2.14 (1.08-4.24)	.02
5) Triglycerides, uric acid, plus HDL cholesterol or FPG	92	54	97	0.77	2.21 (1.06-4.59)	.03

Cox proportional hazards modeling of CVD survival time with example combinations as covariates is shown in the right-hand column (positive reference IRS status applied to 139 participants in the cohort and predicted CVD mortality with a hazard ratio of 2.74; 95% CI, 1.45-5.17; $P<0.01$—Table 2).

This predicted IRS diagnostic status with a sensitivity of 56%, a specificity of 96%, and AROC of 0.76 and predicted CVD mortality with a hazard ratio of 2.36 (95% CI, 1.19-4.68; $P = .01$).

To compare this IRS index with established CVD risk factors, *hypertension* was defined as blood pressure of at least 140/90 mm Hg, *hypercholesterolemia* as serum cholesterol of at least 5.2 mmol/L, and *cigarette smoking* as 5 or more cigarettes per day. In the full cohort, on Cox proportional hazards modeling, these predicted CVD survival time with hazard ratios of 2.54 ($P = .005$), 1.83 ($P = .06$), and 1.66 ($P = .2$), respectively. Together, the IRS index and hypertension predicted CVD survival time with hazard ratios of 2.14 (95% CI, 1.07-4.26; $P = .03$) and 2.35 (95% CI, 1.22-4.53; $P = .01$), respectively. Inclusion of hypercholesterolemia or cigarette smoking with the IRS index did not affect prediction by the IRS index.

With the 3 established risk factors plus the IRS index entered in the model together, the IRS index and hypertension predicted CVD survival time with hazard ratios of 1.94 (95% CI, 0.96-3.93; $P = .06$) and 2.20 (95% CI, 1.14-4.27; $P = .02$), respectively. Hypercholesterolemia and smoking were not predictive. In the OGTT cohort, the IRS index was similarly predictive (results not shown). Further investigations suggested that a cutoff of SBP of at least 130 mm Hg instead of DBP of at least 80 mm Hg might improve prediction of CVD survival time without affecting prediction of IRS status. The CVD mortality hazard ratio for an IRS index using SBP in the model incorporating the 3 classic risk factors was 2.07 (95% CI, 1.02-4.19; $P = .04$).

The NCEP and IDF metabolic syndrome in the full cohort was present in 9% and 13% of participants, respectively. On Cox proportional hazards modeling, the NCEP metabolic syndrome hazard ratio for CVD survival time was 2.05 (95% CI, 0.86-4.85; $P = .1$); and for the IDF metabolic syndrome, 1.40 (95% CI, 0.62-3.14; $P = .4$).

4. Discussion

Our analyses constitute an algorithm for testing the hypothesis that the IRS is an independent CVD risk factor and for determining whether the IRS can contribute clinically to CVD risk evaluation. Importantly, on Cox proportional hazards modeling, CVD mortality was predicted by (1) an IRS reference measure based on the coassociation between variables mechanistically influenced by insulin resistance; (2) reference IRS diagnostic status, derived according to CVD risk in successive percentiles of the IRS reference measure; and (3) a clinically usable IRS index, derived from readily measured correlates of the IRS reference measure. Neither glucoregulatory insulin resistance nor 2 versions of the metabolic syndrome were predictive, and the IRS index predicted independently of 3 major risk factors. The IRS can, therefore, enhance CVD risk evaluation.

"Insulin resistance" encompasses insulin's effects on a range of processes, but it has conventionally been quantified exclusively in terms of the sensitivity of glucoregulation to insulin. Only 2 of the IRS variables relate to glucoregulatory insulin resistance that has, accordingly, been a relatively weak predictor of CVD [19-22]. We found only weak correlations between our IRS reference measure and indices of glucoregulatory insulin resistance, neither of which was a significant CVD risk factor.

The metabolic syndrome (NCEP and IDF) did not predict CVD death. Possibly, our use of a BMI surrogate for waist circumference diminished the precision of the indices, as waist circumference is a better predictor of incident CVD [23] and can vary appreciably for a given BMI [24]. At population level, several factors may contribute to divergences between BMI and waist circumference, including sex, socioeconomic status, and comorbidity. Our cohort was highly homogenous in these respects; and in a comparable cohort, there was a very close relationship [17]. Central adiposity rather than insulin resistance may be the major influence on risk factor clustering, and central adiposity–related risk factor clustering might usefully be explored. There will, however, be overlap between this and the IRS. It is important to identify which mechanistic axis any analysis of risk factor clustering is addressing, and we have examined only those variables for which it is well established that insulin resistance has an important influence.

Global risk indices such as the Framingham risk score [25-27] were designed to maximize event prediction by combining strong, independent CVD predictors. To compare an index or measure of a syndrome, be it the metabolic syndrome or the IRS, with a risk score is clearly inappropriate because a syndrome measure should be treated as a risk factor rather than a risk model. The metabolic syndrome, despite predicting CVD, does not improve risk evaluation beyond the Framingham score [25]; but whether the IRS would achieve an improvement has not been studied previously. In our analysis Framingham event probabilities were not predictive of CVD mortality (results not shown), probably reflecting differences between population samples (our high socioeconomic status cohort had a CVD incidence only 55% of the contemporaneous UK national average). Consequently, the IRS offered a marked improvement over the Framingham score.

Our relatively homogeneous cohort had the advantage of minimizing confounding population variation but the disadvantages of being a small cohort with few events. General criteria for the metabolic syndrome [28] have been sought; but it is questionable whether these can be achieved [6], and whether general criteria for the IRS are realistic remains to be established. Our algorithm, or one similar, will need to be explored with larger populations and numbers of cases; different cohorts, especially including women, who differ from men in their risk factor relationships with regional fat distribution [29,30]; different ethnic groups; stroke and coronary artery disease morbidity and mortality; and other measures that might contribute to an IRS clinical index [31].

Although others have found measures of risk factor clustering based on factor analysis [32-37], or the related technique of principal components analysis [38], to consistently and independently predict CVD, the ability of these approaches to discriminate coassociated risk factor variation and provide for a reference measure has not previously been highlighted. Our analysis might be improved by including other measures such as waist circumference or C-reactive protein; but it should be taken primarily as (1) a test of the IRS hypothesis, (2) an illustration of how insulin resistance–related risk factor clustering may be rendered as a continuous measure, and (3) an evaluation of whether, in principle, a clinically useful index of the IRS can be derived. The variables and their cut points that make up our index resemble those for several definitions of the metabolic syndrome, although uric acid, which is currently receiving renewed attention as a risk factor [39,40], played an additional and prominent role. Moreover, in contrast to the metabolic syndrome, our selection of variables, cut points, and combinations of variables for the clinical index was made systematically with reference to a rigorously derived reference measure of the IRS.

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