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Cardiovascular Disease: A Population-Based Study**

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Insulin Resistance, the Metabolic Syndrome, and Risk of Incident Cardiovascular Disease

A Population-Based Study

Jørgen Jeppesen, MD, DMSc,* Tine W. Hansen, MD, PhD,†‡ Susanne Rasmussen, MD, PhD,†
Hans Ibsen, MD, DMSc,* Christian Torp-Pedersen, MD, DMSc,‡ Sten Madsbad, MD, DMSc§
Glostrup, Copenhagen, and Hvidovre, Denmark

- Objectives** The goal was to clarify if insulin resistance (IR) would predict cardiovascular disease (CVD) independent of the metabolic syndrome (MetSyn).
- Background** Although the cause of MetSyn is not well defined, IR has been proposed to be an important cause. Only a small number of population-based studies have sought to clarify if IR predicts CVD independent of MetSyn.
- Methods** This was a prospective Danish population-based study of 2,493 men and women, age 41 to 72 years, without major CVD at baseline. We defined MetSyn according to both the International Diabetes Foundation (IDF) and the National Cholesterol Education Program (NCEP) criteria, and we quantified IR by the homeostasis model assessment (HOMA-IR). Prevalence of MetSyn was 21% according to IDF criteria and 16% according to NCEP criteria. Accordingly, we defined IDF-HOMA-IR as belonging to the highest 21% of the HOMA-IR distribution, and NCEP-HOMA-IR as belonging to the highest 16% of the HOMA-IR distribution.
- Results** Over a median follow-up of 9.4 years, the incidence of CV end points (CV death, nonfatal ischemic heart disease, and nonfatal stroke) amounted to 233 cases. In proportional hazard models, adjusting for age, gender, smoking, and low-density lipoprotein cholesterol, and with IDF-HOMA-IR and IDF-MetSyn included in the same model, the relative risk of an end point was 1.67 (95% confidence interval [CI] 1.22 to 2.29) for IDF-HOMA-IR and 1.16 (95% CI 0.84 to 1.60) for IDF-MetSyn. The corresponding figures for NCEP-HOMA-IR and NCEP-MetSyn included in the same model were 1.49 (95% CI 1.07 to 2.07) and 1.56 (95% CI 1.12 to 2.17).
- Conclusions** In this Danish study, both HOMA-IR and NCEP-MetSyn were independent predictors of incident CVD. (J Am Coll Cardiol 2007;49:2112–9) © 2007 by the American College of Cardiology Foundation

Although others had proposed similar concepts before 1988 (1,2), the Reaven (3) Banting lecture from that year, introducing the concept of syndrome X as a fundamental factor in the pathogenesis and clinical course of what are often referred to as the diseases of Western civilization—type 2 diabetes, hypertension, and atherosclerotic cardiovascular disease (CVD)—received much attention. Reaven's syndrome X originally consisted of resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hyperglycemia, an increased concentration of very-low-density lipoprotein triglyceride, a decreased concentration of high-

density lipoprotein cholesterol (HDL-C), and high blood pressure. Reaven (3) proposed that insulin resistance (IR) with compensatory hyperinsulinemia was the culprit in syndrome X.

Reaven's work inspired much research interest in the area (1,2,4). Reaven (3) did not offer specific criteria for having syndrome X, and he did not include obesity or visceral obesity as a criterion. Later, others, including leading organizations and associations working in primary and secondary prevention of CVD, added measures of visceral obesity and offered specific criteria to define the metabolic syndrome (MetSyn) (1,4,5). Recently, however, the importance of the MetSyn as a risk factor of CVD and the role of IR as a cause of the MetSyn has become an issue for discussion (1).

The purpose of the present study was to present an analysis of data from a large Danish population-based study dealing with some of the latest issues regarding the MetSyn and risk of CVD. We were particularly interested in clarifying if IR would predict incident CVD independent of

From the *Department of Medicine, Glostrup University Hospital, Glostrup, Denmark; †Research Center for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark; ‡Department of Cardiology, Bispebjerg University Hospital, Copenhagen, Denmark; and the §Department of Endocrinology and Internal Medicine, Hvidovre University Hospital, Hvidovre, Denmark. Supported by the Danish Heart Foundation (grant no. 01-2-9-9A-22914), the Danish Medical Association Research Fund/Volten, and the Danish Pharmaceutical Association.

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the MetSyn, and how 2 different definitions of the MetSyn would affect the risk of CVD associated with the MetSyn and IR. We used the homeostasis model assessment (HOMA) to assess IR (6,7), and we defined the MetSyn according to both the International Diabetes Foundation (IDF) criteria (5) and the National Cholesterol Education Program (NCEP) criteria (4).

Methods

Study population. In 1982 to 1984, a random sample of 4,581 men and women from the southwestern part of Copenhagen County were invited to participate in the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA-1) health survey (8). According to the MONICA protocol, participants were selected to represent an equal number of men and women age 30, 40, 50, and 60 years. Eventually, 3,785 (83.0%) participated. In 1993 to 1994, the MONICA participants were asked if they would be willing to participate in a new study. Since the first examination, 428 subjects had died and 23 had moved or could not be reached. Of the remaining 3,785 subjects, 2,656 (70.2%) were willing to participate in a new study protocol. The study was performed in the Research Center for Prevention and Health in Glostrup. All subjects completed a questionnaire about current and prior diseases, use of medication, and presence and absence of CVD risk factors. For the present study, 163 subjects with a previous diagnosis of myocardial infarction or stroke or taking digoxin or nitrates were excluded, leaving 2,493 men and women to be studied. The study was conducted in accordance with the Second Helsinki Declaration and approved by the Ethics Committee for Copenhagen County. Written informed consent was obtained from all of the subjects.

Classification of metabolic status. For this study, we defined the MetSyn according to both the IDF (4,5) and the NCEP (4) criteria. Regarding the NCEP criteria, we used the latest version (4). According to the IDF criteria with specific reference to a European population (4,5), the MetSyn was based on the existence of a waist circumference ≥ 80 cm in women and ≥ 94 cm in men and 2 or more of the following components: 1) a fasting triglyceride concentration ≥ 1.7 mmol/l; 2) an HDL-C concentration < 1.29 mmol/l in women and < 1.03 mmol/l in men; 3) a blood pressure ≥ 130 mm Hg (systolic) or ≥ 85 mm Hg (diastolic) or use of antihypertensive drugs; and 4) a fasting plasma glucose ≥ 5.6 mmol/l or use of antidiabetic drugs. Based on the IDF criteria, 514 subjects (20.6%) had the MetSyn. According to the NCEP criteria, the MetSyn was based on the existence of 3 or more of the following components: 1) a waist circumference ≥ 88 cm in women and ≥ 102 cm in men; 2) a fasting triglyceride concentration ≥ 1.7 mmol/l; 3) an HDL-C concentration < 1.30 mmol/l in women and < 1.03 mmol/l in men; 4) a blood pressure ≥ 130 mm Hg (systolic) or ≥ 85 mm Hg (diastolic) or use of antihypertensive drugs; and 5) a fasting

plasma glucose ≥ 5.6 mmol/l or use of antidiabetic drugs. Based on the NCEP criteria, 409 subjects (16.4%) had the MetSyn.

Regarding IR, we used HOMA to quantify IR (fasting glucose \times fasting insulin/22.5) (6,7). The HOMA-IR values have been shown to correlate well with values obtained using the “gold standard” clamp technique (7). We entered HOMA-IR both as a categorical variable and as a continuous variable in our analyses. Because the prevalence of the MetSyn was 20.6% according to IDF criteria and 16.4% according to NCEP criteria, we defined IDF-HOMA-IR as belonging (as closely as possible) to the highest 20.6% of the HOMA-IR distribution, and NCEP-HOMA-IR as belonging (as closely as possible) to the highest 16.4% of the HOMA-IR distribution. The reason we did this and did not use the usual definition of IR (highest 25%) (1,4) was that we did not want a priori to start our analyses knowing that around 4% or 9% of the defined insulin-resistant subjects would not be classified as having the MetSyn, depending on which definition of the MetSyn was used. We preferred to study and compare equal proportions in our categorical analyses to provide results that were easy to understand and interpret.

Measurements. Fasting concentrations of lipids, insulin, and glucose were analyzed by standard methods (9,10). Blood pressure was measured in the sitting position after 5 min of rest using a random zero mercury sphygmomanometer. Determinations of body mass index (BMI), waist, hip, waist-to-hip ratio, heart rate, and alcohol intake, as well as subdivisions of the population according to smoking status and low or high level of physical activity, were done as described in detail elsewhere (11).

End points. Complete follow-up regarding death was obtained through information from the Civil Registration System. Information on cardiovascular mortality was obtained from blinded classification of death certificates, and information on hospitalizations was recorded from the Danish National Health Register, which is known to have high sensitivity and predictive value (12). The prespecified end point was the combination of cardiovascular mortality, ischemic heart disease (ICD-8 codes 410 to 414 or ICD-10 codes I20 to I25), and stroke (ICD-8 codes 431, 433, and 434 or ICD-10 codes I61 and I63).

Statistical analysis. All analyses were performed with the Statistical Analysis System, version 9.1 (SAS Institute, Cary, North Carolina). Baseline characteristics, presented as

Abbreviations and Acronyms

BMI	= body mass index
CI	= confidence interval
CVD	= cardiovascular disease
HDL-C	= high-density lipoprotein cholesterol
HOMA	= homeostasis model assessment
HR	= hazard ratio
IDF	= International Diabetes Foundation
IR	= insulin resistance
LDL-C	= low-density lipoprotein cholesterol
MetSyn	= metabolic syndrome
NCEP	= National Cholesterol Education Program

median and 5% to 95% percentiles or as percent, were compared with nonparametric rank sum tests for continuous variables and chi-squared tests for categorical variables. Spearman correlation coefficients analysis was used to assess the relation between IR and the continuously distributed individual components of the MetSyn. Survival was analyzed with Cox proportional hazard models. In the outcome analysis, for participants who experienced multiple events we only considered the first. The assumption of linearity was assessed by demonstrating that inclusion of variables representing quintiles did not improve the model. Interaction was tested with a likelihood ratio test and the proportional hazard assumption was tested by demonstrating no importance of variables multiplied by time as time-dependent variables (13). Population-attributable risk estimates were calculated as described in detail elsewhere (14). All statistical tests were 2-sided and the significance level was chosen as $p < 0.05$.

Results

Baseline characteristics of the participating women and men are summarized in Table 1. In total, 2.6% had fasting

glucose levels ≥ 7.0 mmol/l, and 1.0% had fasting glucose levels ≥ 10.5 mmol/l. The median (range) of HOMA-IR was 6.2 (0.8 to 201.1) U. Based on both IDF and NCEP criteria, the male participants had a higher prevalence of the MetSyn, and they also had higher HOMA-IR values and higher levels of fasting insulin.

Table 2 describes the baseline characteristics of the participants according to definition of the MetSyn and definition of IR. It is seen in Table 2 that the frequency of concordance among those individuals with the MetSyn and IR only amounted to 52.6% and 56.5%, depending on which definition of the MetSyn was used.

Table 3 shows the correlation coefficients between HOMA-IR and the continuously distributed individual components of the MetSyn, including fasting insulin.

The median study duration, from baseline evaluation until follow-up on October 1, 2003, was 9.4 years (5th to 95th percentile interval 4.0 to 10.1 years). In the follow-up period, 233 end points were recorded: 56 cardiovascular deaths, 140 coronary events (including 66 acute myocardial infarctions), and 37 strokes. The incidence of a cardiovascular end point was 14.6% in participants with the

Table 1 Baseline Characteristics of Study Subjects

	Women (n = 1,264)	Men (n = 1,229)	p Value
Demographic variables			
Age (yrs)	51 (41-71)	51 (41-71)	0.51
History of diabetes (%)	1.7	3.6	0.003
Treatment of hypertension (%)	8.5	8.2	0.73
Metabolic syndrome IDF (%)	17.5	23.8	<0.0001
Metabolic syndrome NCEP (%)	14.3	18.6	0.004
Lipid variables (mmol/l)			
Total cholesterol	6.07 (4.51-8.07)	6.08 (4.55-8.09)	0.69
VLDL-C	0.51 (0.27-1.15)	0.61 (0.31-1.47)	<0.0001
LDL-C	3.89 (2.43-5.76)	4.04 (2.64-5.80)	<0.0001
HDL-C	1.54 (1.00-2.37)	1.26 (0.85-1.93)	<0.0001
Total/HDL-C	3.85 (2.42-6.63)	4.82 (2.93-7.78)	<0.0001
Triglycerides	1.09 (0.58-2.52)	1.31 (0.65-3.42)	<0.0001
Metabolic variables			
Glucose (mmol/l)	4.6 (4.0-5.6)	4.9 (4.2-6.5)	<0.0001
Insulin (pmol/l)	28 (5-83)	32 (6-96)	<0.0001
HOMA insulin resistance (U)	5.6 (1.0-19.0)	7.0 (1.4-25.2)	<0.0001
Physical variables			
BMI (kg/m ²)	24.5 (19.6-34.3)	26.0 (21.2-33.0)	<0.0001
Waist (cm)	79 (67-103)	93 (78-113)	<0.0001
Waist/hip ratio	0.81 (0.73-0.92)	0.94 (0.85-1.04)	<0.0001
Hemodynamic variables			
Systolic blood pressure (mm Hg)	124 (100-162)	129 (104-164)	<0.0001
Diastolic blood pressure (mm Hg)	80 (65-98)	83 (67-102)	<0.0001
Lifestyle variables			
Smoking (%)	43.3	49.1	0.0033
Alcohol use (beverages/week)	4 (0-20)	10 (0-39)	<0.0001
High physical activity (%)	16.1	28.3	<0.0001

Data are presented as median and 5% to 95% percentiles or frequency in percentage.

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; HOMA = homeostasis model assessment; IDF = International Diabetes Foundation; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; VLDL-C = very-low-density lipoprotein cholesterol.

Table 2 Baseline Characteristics of Study Subjects According to Definition of Metabolic Syndrome and Insulin Resistance

	Control (n = 1,726)	IDF Metabolic Syndrome (n = 514)	IDF HOMA Insulin Resistance (n = 512)	NCEP Metabolic Syndrome (n = 409)	NCEP HOMA Insulin Resistance (n = 405)
Demographic variables					
Age (yrs)	51 (41-71)	61 (41-71)*	61 (41-71)*	61 (41-71)*	61 (41-71)*
Males (%)	45.0	57.0*	61.9*	55.8*	64.2*
History of diabetes (%)	0.75	6.2*	9.2*	8.1*	11.1*
Treatment of hypertension (%)	5.4	17.0*	15.4*	17.1*	15.7*
Lipid variables (mmol/l)					
Total cholesterol	5.98 (4.45-7.91)	6.48 (4.81-8.61)*	6.26 (4.65-8.42)*	6.47 (4.79-8.66)*	6.22 (4.63-8.38)*
VLDL-C	0.48 (0.27-0.93)	0.98 (0.48-1.74)*	0.83 (0.38-1.64)*	1.00 (0.53-1.74)*	0.87 (0.39-1.66)*
LDL-C	3.90 (2.51-5.70)	4.21 (2.71-6.10)*	4.07 (2.65-5.82)*	4.20 (2.69-6.17)*	4.02 (2.64-5.77)†
HDL-C	1.50 (1.02-2.31)	1.10 (0.79-1.70)*	1.18 (0.82-1.80)*	1.06 (0.79-1.58)*	1.16 (0.81-1.71)*
Total/HDL-C	3.91 (2.48-6.42)	5.83 (3.47-8.80)*	5.30 (3.16-8.57)*	5.98 (3.71-9.17)*	5.40 (3.28-9.00)*
Triglycerides	1.03 (0.58-1.98)	2.12 (1.03-4.70)*	1.83 (0.81-4.54)*	2.19 (1.13-5.24)*	1.89 (0.84-4.78)*
Metabolic variables					
Glucose (mmol/l)	4.6 (4.0-5.3)	5.1 (4.4-8.6)*	5.2 (4.5-10.3)*	5.2 (4.4-10.3)*	5.3 (4.5-10.5)*
Insulin (pmol/l)	23 (5-47)	53 (18-137)*	70 (46-168)*	56 (21-168)*	77 (51-181)*
HOMA insulin resistance (U)	4.7 (1.0-9.9)	12.3 (3.8-43.3)*	16.8 (11.5-47.6)*	13.5 (4.4-49.1)*	18.3 (13.3-53.0)*
Physical variables					
BMI (kg/m ²)	24.2 (19.7-30.7)	29.0 (24.5-37.6)*	29.0 (22.6-37.6)*	29.7 (24.1-38.2)*	29.4 (23.0-37.6)*
Waist (cm)	83 (68-101)	98 (82-117)*	98 (77-117)*	100 (83-119)*	99 (78-117)*
Waist/hip ratio	0.85 (0.74-0.98)	0.95 (0.80-1.07)*	0.94 (0.79-1.07)*	0.95 (0.82-1.07)*	0.95 (0.80-1.07)*
Hemodynamic variables					
Systolic blood pressure (mm Hg)	122 (100-158)	138 (115-172)*	136 (111-171)*	139 (116-173)*	137 (111-169)*
Diastolic blood pressure (mm Hg)	80 (65-97)	89 (72-105)*	87 (70-106)*	89 (74-105)*	88 (70-106)*
Lifestyle variables					
Smoking (%)	47.4	44.0	43.0	44.0	43.7
Alcohol use (beverages/week)	6.0 (0.0-30.0)	7.0 (0.0-37.0)	7.0 (0.0-35.0)	6.0 (0.0-38.0)	6.0 (0.0-36.0)
High physical activity (%)	24.8	16.3*	16.3*	14.6*	15.3*
Metabolic category					
IDF metabolic syndrome (%)	0	100*	56.5*	71.2*	48.2*
IDF HOMA insulin resistance (%)	0	55.9*	100*	47.3*	79.1*
NCEP metabolic syndrome (%)	0	89.5*	60.1*	100*	52.6*
NCEP HOMA insulin resistance (%)	0	60.3*	100*	52.4*	100*

Data are presented as median and 5% to 95% percentiles or frequency (%). IDF-HOMA insulin resistance was defined to represent the highest HOMA values (>11.2 U) selecting study subjects corresponding to basically the same proportion of study subjects classified to have the metabolic syndrome according to IDF criteria. NCEP-HOMA insulin resistance was defined to represent the highest HOMA values (>12.9 U) selecting study subjects corresponding to basically the same proportion of study subjects classified to have the metabolic syndrome according to NCEP criteria. *p < 0.001 compared with control; †p < 0.01. Abbreviations as in Table 1.

MetSyn based on IDF criteria and 16.6% in participants with the MetSyn based on NCEP criteria. Because we found no gender-based difference (p = 0.46) in the

relationships between MetSyn and IR and risk of CVD, we pooled all of the data together in our outcome analysis to increase power.

Table 4 shows the relationship between the MetSyn based on IDF criteria, IDF-HOMA-IR, HOMA-IR as a continuous variable, and risk of CVD, adjusted for age, gender, smoking, and low-density lipoprotein cholesterol (LDL-C). It is seen that, when entered individually in the models, both the MetSyn and IDF-HOMA-IR were significant predictors of a cardiovascular end point. However, when entered with IDF-HOMA-IR in the same model, the MetSyn based on IDF criteria was no longer a significant predictor of CVD. It is also seen in Table 4 that the results were the same when HOMA-IR was entered as a continuous variable.

Table 5 shows the relationship between the MetSyn based on NCEP criteria, NCEP-HOMA-IR, HOMA-IR

Table 3 Spearman Correlation Coefficients Between HOMA-IR and the Continuously Distributed Individual Components of the Metabolic Syndrome

Variables	Women	Men
Triglycerides	0.44	0.46
HDL-C	-0.31	-0.31
Systolic blood pressure	0.27	0.33
Diastolic blood pressure	0.27	0.32
Waist	0.46	0.54
Fasting glucose	0.50	0.51
Fasting insulin	0.99	0.98

p < 0.001.
 HDL-C = high-density lipoprotein cholesterol; HOMA-IR = insulin resistance as assessed by homeostasis model.

Table 4 Relationship Between the Metabolic Syndrome Based on IDF Criteria, HOMA-IR Expressed Both as a Categorical Variable and as a Continuous Variable, and Risk of Cardiovascular Disease With Successive Inclusion of Variables in the Models

	Model 1	Model 2	Model 3	Model 4	Model 5
Metabolic syndrome IDF (n = 514) vs. others	1.46 (1.10-1.94)*			1.16 (0.84-1.60)	1.30 (0.97-1.75)
Categorical HOMA-IR (n = 512) vs. others		1.79 (1.36-2.36)†		1.67 (1.22-2.29)*	
Continuous HOMA-IR per unit increase‡			1.014 (1.007-1.021)†		1.013 (1.005-1.021)*

Data are presented as hazard ratios (95% confidence intervals). Categorical insulin resistance was defined to represent the highest HOMA values (>11.2 U) selecting study subjects corresponding to basically the same proportion of study subjects classified to have the metabolic syndrome. Model 1: metabolic syndrome alone; model 2: categorical HOMA-IR alone; model 3: continuous HOMA-IR per unit increase alone; model 4: metabolic syndrome and categorical HOMA-IR in the same model; model 5: metabolic syndrome and continuous HOMA-IR per unit increase in the same model. All data are adjusted for age, gender, smoking, and LDL-C. *p < 0.01; †p < 0.001; ‡range of continuous HOMA-IR was 0.8 to 201.1 U.

Abbreviations as in Tables 1 and 3.

as a continuous variable, and risk of CVD, adjusted for age, gender, smoking, and LDL-C. When entered individually in the models, both the MetSyn and NCEP-HOMA-IR were significant predictors of risk of a cardiovascular end point. When entered with NCEP-HOMA-IR in the same model, both the MetSyn based on NCEP criteria and NCEP-HOMA-IR were significant predictors of CVD. It is also seen in Table 5 that the results were the same when HOMA-IR was entered as a continuous variable.

Table 6 shows the hazard ratios (HRs) of CVD of the various components in the MetSyn compared with their respective counterparts in multivariate models adjusted for age, gender, smoking, and LDL-C.

Additional analyses. Repeating the analyses excluding subjects with diabetes, based on either history, use of antidiabetic drugs, or fasting glucose ≥ 7.00 mmol/l (n = 73; 2.9%) did not change the results much. When the MetSyn based on IDF criteria and IDF-HOMA-IR were included in the same model and adjusted for age, gender, smoking, and LDL-C, the HRs were 1.16 (95% confidence interval [CI] 0.83 to 1.63; p = 0.39) and 1.56 (95% CI 1.12 to 2.18; p = 0.009), respectively. When the MetSyn based on NCEP criteria and NCEP-HOMA-IR were included in the same model and adjusted for age, gender, smoking, and LDL-C, the HRs were 1.48 (95% CI 1.05 to 2.12; p = 0.027) and 1.39 (95% CI 0.98 to 1.99; p = 0.066), respectively. Finally, when HOMA-IR was entered as a continuous variable with the MetSyn based on either IDF or NCEP criteria in the model described above, HOMA-IR was significantly related to risk of CVD with HRs of 1.025 (95% CI 1.010 to 1.040; p = 0.0013) and 1.020 (95% CI 1.005 to 1.036; p = 0.011), respectively, per unit increase.

We also examined the relationship between IR and the MetSyn and risk of CVD with adjustment for the Framingham risk score (15). The median Framingham risk score value with 5% to 95% percentiles was 7 points (-1 to 12). As seen in Tables 7 and 8, IDF-HOMA-IR, the NCEP definition of the MetSyn, NCEP-HOMA-IR, and HOMA-IR entered as a continuous variable were all significant predictors of incident CVD after adjustment for the Framingham risk score.

We also calculated population-attributable risk estimates (14). Based on a model including age, gender, smoking, and LDL-C and entering the various definitions of the MetSyn and IR individually, the population-attributable risk estimate was 8.7% for the IDF definition of the MetSyn, 13.9% for IDF-HOMA-IR, 12.4% for the NCEP definition of the MetSyn, and 11.8% for NCEP-HOMA-IR. In comparison, age (>60 years), male gender, and smoking accounted for more than 60% of all CVD events in the present study population.

Finally, we found no interactions regarding the MetSyn, gender, age, or its individual components.

Discussion

The present study provided interesting results: 1) IR predicted incident CVD independent of the MetSyn based on either IDF or NCEP criteria; 2) adjusted for IR, the MetSyn based on NCEP criteria was a significant predictor of CVD, whereas the MetSyn based on IDF criteria was not; 3) the MetSyn and IR were significant risk factors of CVD in the nondiabetic population; 4) IR, defined as belonging to the highest 20.6% of the HOMA-IR distribution, predicted incident CVD independent of the Fra-

Table 5 Relationship Between the Metabolic Syndrome Based on NCEP Criteria, HOMA-IR Expressed Both as a Categorical Variable and as a Continuous Variable, and Risk of Cardiovascular Disease With Successive Inclusion of Variables in the Models

	Model 1	Model 2	Model 3	Model 4	Model 5
Metabolic syndrome NCEP (n = 409) vs. others	1.86 (1.39-2.45)*			1.56 (1.12-2.17)†	1.66 (1.22-2.27)†
Categorical HOMA-IR (n = 405) vs. others		1.82 (1.36-2.43)*		1.49 (1.07-2.07)‡	
Continuous HOMA-IR per unit increase§			1.014 (1.007-1.021)*		1.010 (1.001-1.019)‡

Data are presented as hazard ratios (95% confidence intervals). Categorical insulin resistance was defined to represent the highest HOMA values (>12.9 U) selecting study subjects corresponding to basically the same proportion of study subjects classified to have the metabolic syndrome. Model 1: metabolic syndrome alone; model 2: categorical HOMA-IR alone; model 3: continuous HOMA-IR per unit increase alone; model 4: metabolic syndrome and categorical HOMA-IR in the same model; model 5: metabolic syndrome and continuous HOMA-IR per unit increase in the same model. All data are adjusted for age, gender, smoking, and LDL-C. *p < 0.001; †p < 0.01; ‡p < 0.05; §range of continuous HOMA-IR was 0.8 to 201.1 U.

Abbreviations as in Tables 1 and 3.

Table 6 Relationship Between Risks of Cardiovascular Events According to the Individual Components in the Metabolic Syndrome Compared With Their Respective Counterparts Based on Both IDF Criteria and NCEP Criteria

Variables	Hazard Ratio (95% CI)	p Value
Waist, IDF criteria: ≥ 80 cm in women, ≥ 94 cm in men (n = 1,197)	1.14 (0.88–1.49)	0.32
Waist, NCEP criteria: ≥ 88 cm in women, ≥ 102 cm in men (n = 558)	1.27 (0.94–1.71)	0.12
Triglycerides: ≥ 1.7 mmol/l (n = 620)	1.49 (1.13–1.97)	0.0052
HDL-C: < 1.03 mmol/L for men, < 1.29 mmol/l for women (n = 558)	1.12 (0.88–1.63)	0.24
Blood pressure: ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or treatment (n = 1,318)	1.99 (1.47–2.73)	< 0.0001
Glucose intolerance, IDF and new NCEP criteria: ≥ 5.6 mmol/l (n = 216)	1.84 (1.30–2.61)	0.0007
Glucose intolerance, old NCEP criteria: ≥ 6.1 mmol/l (n = 116)	2.26 (1.47–3.49)	0.0002

Data are presented as hazard ratios (95% confidence intervals [CI]). All data are adjusted for age, gender, smoking, and LDL-C. Abbreviations as in Table 1.

mingham risk score with an approximate 1.5-fold increased risk; and 5) the rate of concordance among those individuals with the MetSyn and IR amounted to around 50%.

Recently, the importance of the MetSyn as a risk factor of CVD and the role of IR as a cause of the MetSyn has become an issue for discussion (1). Although several large population-based studies found that subjects with the MetSyn had an increased risk of CVD independent of traditional risk factors (16–22), the value of the MetSyn as a risk factor of CVD has been questioned (1), because it was shown in several population-based studies that risk score programs such as the Framingham risk score provided more information of global risk of CVD than the MetSyn (23–26). However, that analysis could be misleading. Risk score programs include predictors of CVD that are independent of the MetSyn, such as age, gender, and smoking, the leading causes of CVD in the community (25,27). Also, in the present study, old age (> 60 years), male gender, and smoking accounted for more than 60% of all CVD events. In comparison, the MetSyn based on IDF criteria accounted for 8.7% of all CVD events and the MetSyn based on NCEP criteria accounted for 12.4% of all CVD events. In our study, the MetSyn based on NCEP criteria and both IDF-HOMA-IR and NCEP-HOMA-IR predicted incident CVD independent of the Framingham risk score, but the increased risk associated with the NCEP definition, IDF-HOMA-IR, and NCEP-HOMA-IR only corresponded to an increase in Framingham risk score of approximate 2 points, so it is obvious that also in our study

population a risk score program, such as the Framingham risk score, provided more information of global risk of CVD than the MetSyn and IR.

Although IR has been proposed as an important cause of the MetSyn, the present results showed that other causes must be present. Accordingly, the rate of concordance among those individuals with the MetSyn and IR only amounted to around 50%, and the correlation coefficients between HOMA-IR and the continuously distributed components of the MetSyn were not that high either, as seen in Table 3. However, based on the medical literature (2–4), it is reasonable to believe that IR is a major cause of the MetSyn, although the exact percentage of MetSyn cases caused by IR remains to be defined.

Another issue regarding the value of the MetSyn as a risk factor of CVD involves the many different definitions of the syndrome (1,4,5). In the present study, we examined how 2 different definitions of the MetSyn influenced the risk of CVD associated with the MetSyn and IR. We found that the MetSyn based on IDF criteria was no longer a significant predictor of CVD after adjustment for IDF-HOMA-IR or HOMA-IR, whereas both the MetSyn based on NCEP criteria and NCEP-HOMA-IR or HOMA-IR were all significantly related to CVD risk when entered in the same model. Owing to the overlap of subjects between the various groups defined to have the MetSyn and/or IR, it was difficult to formally compare differences between the groups statistically, so the only reasonable

Table 7 Relationship Between the Metabolic Syndrome Based on IDF Criteria, HOMA-IR Expressed Both as a Categorical Variable and as a Continuous Variable, and Risk of Cardiovascular Disease With Adjustment for the Framingham Risk Score

	Model 1	Model 2	Model 3
Framingham 10-yr risk per 1-point increase	1.27 (1.21–1.33)*	1.26 (1.21–1.32)*	1.27 (1.22–1.33)*
Metabolic syndrome IDF (n = 514) vs. others	1.26 (0.95–1.67)		
Categorical HOMA-IR (n = 512) vs. others		1.56 (1.19–2.05)†	
Continuous HOMA-IR per unit increase‡			1.009 (1.001–1.016)§

Data are presented as hazard ratios (95% confidence intervals). Categorical insulin resistance was defined to represent the highest HOMA values (> 11.2 U) selecting study subjects corresponding to basically the same proportion of study subjects classified to have the metabolic syndrome. Model 1: Framingham risk score and metabolic syndrome in the same model; model 2: Framingham risk score and categorical HOMA-IR in the same model; model 3: Framingham risk score and continuous HOMA-IR per unit increase in the same model. * $p < 0.001$; † $p < 0.01$; ‡range of continuous HOMA-IR was 0.8 to 201.1 U; § $p < 0.05$. Abbreviations as in Tables 1 and 3.

Table 8

Relationship Between the Metabolic Syndrome Based on NCEP Criteria, Insulin Resistance as Assessed by Homeostasis Model Assessment, Expressed Both as a Categorical Variable and as a Continuous Variable, and Risk of Cardiovascular Disease With Adjustment for Framingham Risk Score

	Model 1	Model 2	Model 3
Framingham 10-year risk per 1-point increase	1.26 (1.21-1.32)*	1.26 (1.21-1.32)*	1.27 (1.22-1.33)*
Metabolic syndrome NCEP (n = 409) vs. others	1.52 (1.14-2.03)†		
Categorical HOMA-IR (n = 405) vs. others		1.56 (1.17-2.08)†	
Continuous HOMA-IR per unit increase‡			1.009 (1.001-1.016)§

Data are presented as hazard ratios (95% confidence intervals). Categorical insulin resistance was defined to represent the highest HOMA values (>12.9 U) selecting study subjects corresponding to basically the same proportion of study subjects classified to have the metabolic syndrome. Model 1: Framingham risk score and metabolic syndrome in the same model; model 2: Framingham risk score and categorical HOMA-IR in the same model; model 3: Framingham risk score and continuous HOMA-IR per unit increase in the same model. *p < 0.001; †p < 0.01; ‡range of continuous HOMA-IR was 0.8 to 201.1 U; §p < 0.05. Abbreviations as in Tables 1 and 3.

conclusion to draw was that IR predicted CVD events independent of the MetSyn.

So far, several studies have been published focusing on IR and risk of incident CVD (26,28-33). It is a major limitation of the present study that we used a surrogate measure of IR and not a “gold standard” technique to quantify IR. However, there exists only 1 large population-based prospective study that has used “gold standard” techniques to study the relation between IR and risk of incident CVD: the Uppsala Longitudinal Study of Adult Men (USLAM) (33,34). In a cohort of 815 men, age 70 years at baseline, with a follow-up of up to 10 years, IR as determined by the euglycemic clamp technique predicted incident coronary heart disease with adjustment for serum cholesterol, fasting plasma glucose, BMI, and smoking (33). However, in the USLAM cohort, no data were presented regarding the relationship between IR and CVD after adjustment for the components of the MetSyn or the MetSyn itself (33,34). In a small study of healthy subjects, IR as determined by the insulin suppression test (“gold standard” technique) was a strong predictor of CVD independent of all other major risk factors of CVD (32). In the other population-based prospective studies (26,28-31), the method used to quantify IR was the HOMA model (6,7). The results in those studies were mixed, showing significant independent relationships between HOMA-IR and incident CVD in some (28,29) but not all (26,30,31) of the studies after adjustment for traditional risk factors, including the components of the MetSyn or the MetSyn itself.

In conclusion, what is the situation with the MetSyn and IR after the present findings? Regarding the MetSyn as a risk factor of CVD, it is obvious that risk score programs such as the Framingham risk score provides more information about global risk of CVD compared with the MetSyn. However, because the MetSyn based on NCEP criteria in the present study was associated with an around 50% increased risk of CVD adjusted for the Framingham risk score, our results support the view of the NCEP panel (4) that the MetSyn will help with the evaluation of individuals at low or moderate risk by the Framingham risk score who warrant intervention based on the presence of MetSyn.

Regarding IR as the cause of the MetSyn and the associated adverse cardiovascular consequences, the present results indicate that IR may be the cause of around 50% of the MetSyn cases, but the fact that IR was identified as an independent risk factor of CVD adjusted for the MetSyn or the Framingham risk score indicates the IR may indeed be a factor in the pathogenesis of CVD. However, because HOMA-IR values have not yet been standardized for routine use, the clinician will probably continue to use the MetSyn and not consider measures of IR, because the MetSyn is much easier and more practical to apply in the typical clinical setting. Nevertheless, we think that IR is an important concept, because IR, similar to a high LDL-C level, seems to represent a basic pathophysiologic pathway leading to potentially preventable CVD in the community (4). However, we have to acknowledge at this stage that because no large randomized clinical trial has demonstrated that reducing the level of IR improves CVD outcome, the best thing to do to help persons with IR would be to focus on proven interventions, such as lowering LDL-C, blood glucose, and blood pressure, to reduce the risk of CVD in this high-risk population (4).

Reprint requests and correspondence: Dr. Jørgen Jeppesen, Department of Medicine, Glostrup University Hospital, Ndr. Ringvej, DK-2600 Glostrup, Denmark. E-mail: jj@heart.dk.

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Insulin Resistance, the Metabolic Syndrome, and Risk of Incident Cardiovascular Disease: A Population-Based Study

Jørgen Jeppesen, Tine W. Hansen, Susanne Rasmussen, Hans Ibsen, Christian Torp-Pedersen, and Sten Madsbad

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