Insulin Resistance as Estimated by Homeostasis Model Assessment Predicts Incident Symptomatic Cardiovascular Disease in Caucasian Subjects From the General Population

The Bruneck Study

Enzo Bonora, md, phd[1]
Stefan Kiechl, md[2]
Johann Willeit, md[2]
Friedrich Oberhollenzer, md[3]
Georg Egger, md[3]
James B. Meigs, md, mph[4]
Riccardo C. Bonadonna, md[1]
Michele Muggeo, md[1]

OBJECTIVE — The purpose of this study was to evaluate whether insulin resistance is associated to cardiovascular disease (CVD) and to understand whether this association can be explained by traditional and novel CVD risk factors associated with this metabolic disorder.

RESEARCH DESIGN AND METHODS — We examined a sample representative of the population of Bruneck, Italy ($n = 919$; aged 40–79 years). Insulin-resistant subjects were those with a score in the top quartile of the homeostasis model assessment (HOMA) for insulin resistance (HOMA-IR). Risk factors correlated with insulin resistance included BMI, A1C, HDL cholesterol, triglycerides, blood pressure, high-sensitivity C-reactive protein (hsCRP), fibrinogen, oxidized LDL, vascular cell adhesion molecule-1 (VCAM-1), and adiponectin. Subjects without CVD at baseline were followed up for 15 years for incident CVD, a composite end point including fatal and nonfatal myocardial infarction and stroke, transient ischemic attack, and any revascularization procedure.

RESULTS — During follow-up, 118 subjects experienced a first symptomatic CVD event. Levels of HOMA-IR were higher at baseline among subjects who developed CVD (2.8) compared with those remaining free of CVD (2.5) ($P < 0.05$). Levels of HOMA-IR also were significantly correlated ($P < 0.05$) with most CVD risk factors we evaluated. In Cox proportional hazard models, insulin-resistant subjects had an age-, sex-, and smoking-adjusted 2.1-fold increased risk (95% CI 1.3–3.1) of incident symptomatic CVD relative to non–insulin-resistant subjects. After sequential adjustment for physical activity and classic risk factors (A1C, LDL cholesterol, and hypertension) as well as BMI, HDL cholesterol, triglycerides, and novel risk factors, including fibrinogen, oxidized LDL, hsCRP, VCAM-1, and adiponectin, the association between HOMA-IR and incident CVD remained significant and virtually unchanged (hazard ratio 2.2 [95% CI 1.4–3.6], $P < 0.001$).

CONCLUSIONS — HOMA-estimated insulin resistance is associated with subsequent symptomatic CVD in the general population independently of all classic and several nontraditional risk factors. These data suggest that insulin resistance may be an important target to reduce CVD risk.

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Insulin resistance is a pathogenic factor for type 2 diabetes (1,2) and is associated with diverse cardiovascular disease (CVD) risk states, including obesity, essential hypertension, hypertriglyceridemia, and low HDL cholesterol (3). A significant proportion of apparently healthy subjects also are insulin resistant (4,5). In aggregate, insulin resistance and related conditions are very common, affecting as many as 30–40% of subjects living in affluent countries. Insulin resistance is also a common finding in developing countries. Throughout the world hundreds of millions of people and perhaps even >1 billion people are estimated to have insulin resistance (6).

In recent years the question as to whether insulin resistance is involved in the pathogenesis of CVD has persisted. This question was originated by the observation that subjects with coronary, carotid, or femoral artery atherosclerosis are insulin resistant compared with subjects without CVD, after matching or adjusting for classic risk factors (7–9). Its validity was supported by the findings that insulin possesses a variety of antiatherogenic effects, which might be blunted by insulin resistance (10–16), and that insulin resistance is related to several nontraditional CVD risk factors, including markers of coagulation, systemic inflammation, subclinical vascular disease, oxidative stress, or dysregulated adipokine signaling (17–20). Findings from prospective studies testing the association of insulin resistance with CVD independently of classic risk factors have been inconsistent (21–31). In addition, no longitudinal study to extensively evaluate the potential con-

From the [1]Division of Endocrinology and Metabolic Diseases, University of Verona Medical School, Verona, Italy; the [2]Department of Neurology, University of Innsbruck Medical School, Innsbruck, Austria; the [3]Division of Internal Medicine, Hospital of Bruneck, Bruneck, Italy; and the [4]Harvard Medical School and General Medicine Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Address correspondence and reprint requests to Prof. Enzo Bonora, Endocrinologia e Malattie del Metabolismo, Ospedale Maggiore, Piazzale Stefani, 1, 37126 Verona, Italy. E-mail: enzobonora@virgilio.it.

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Abbreviations: CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; HOMA, homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; TIA, transient ischemic attack; VCAM-1, vascular adhesion molecule-1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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founding role of novel CVD risk factors has been done. In other words, the association between insulin resistance and CVD, if observed, might be attenuated or abolished after adjustment for novel, insulin resistance–related risk factors.

The effect of ameliorating insulin resistance on CVD outcomes has been tested in only one intervention trial (32). However, although pioglitazone reduced the risk for CVD events in a post hoc subgroup analysis, the trial was conducted among diabetic patients and the suggested benefit of insulin sensitization may have been related to the observed reduction of risk factors (hyperglycemia, dyslipidemia, and hypertension) known to improve with pioglitazone therapy. Thus, the role of insulin resistance in the pathogenesis of CVD remains an open question.

With these issues in mind, in the present study we evaluated whether insulin resistance was associated with new cases of symptomatic CVD independently of traditional and nontraditional risk factors known to cluster with this metabolic disorder in a large sample from the general population of Bruneck, Italy.

RESEARCH DESIGN AND METHODS

The Bruneck Study is a long-term prospective population-based survey of atherosclerosis and its risk factors. It is being conducted in Bruneck, a small town of ~13,500 people, located in Northeastern Italy, close to the Austrian border. As reported previously (33), a baseline evaluation was performed between July and November 1990. Among the 1,000 randomly selected men and women of the 4,793 Caucasians subjects aged 40–79 years, 936 volunteered after the purposes and modalities of the study had been carefully presented. As 17 subjects had incomplete data collection, the sample we used for most statistical analyses included 919 subjects. Insulin measurements were performed in 888 subjects because 2 subjects were receiving insulin treatment, and 29 subjects had no serum available for the measurement of insulin. After exclusion of 49 subjects with preexisting CVD, 839 subjects (416 men and 423 women) remained for the current analysis. The main clinical features of the study population and the subset with insulin measurements available have been reported in previous publications (1,4,17,33–35).

Reevaluations were performed every 5 years, i.e., in 1995, 2000, and 2005. In this period 210 of the 839 subjects died. Follow-up was 100% complete for clinical end points.

The protocol was approved by the ethics committee of the University of Verona. All subjects gave an informed consent.

Clinical data

The following data were collected with a standardized questionnaire: cigarette smoking, alcohol consumption, physical activity, socioeconomic status, previous diseases, and drug prescriptions. BMI, waist circumference, and blood pressure were assessed with standard techniques. Overweight was defined by a BMI from 25 to 29.9 kg/m^2 and obesity by a BMI ≥30 kg/m^2. Hypertension was diagnosed when systolic blood pressure was ≥140 mmHg, diastolic blood pressure was ≥90 mmHg, or antihypertensive treatment was ongoing. At baseline, all subjects underwent a standard oral glucose tolerance test. Details on the methodology have been reported previously (1,4,17,33–35).

Laboratory data

In the morning after an overnight fast, venous blood was sampled for the measurement of A1C, as well as the plasma concentration of glucose and the serum concentrations of total and HDL cholesterol, triglycerides, insulin, adiponectin, high-sensitivity C-reactive protein (hsCRP), fibrinogen, oxidized LDL, and vascular adhesion molecule-1 (VCAM-1). LDL cholesterol was calculated by the formula of Friedewald. Details on analytical procedures have been reported previously (1,4,17,33–35). Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes were diagnosed according to current criteria.

Assessment of insulin resistance

The degree of insulin resistance at baseline was estimated by the homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) (36). In a recent article, we reported on the good reliability of the HOMA for estimating insulin resistance (37). Subjects in the top quartile of HOMA-IR distribution values were considered to be insulin resistant.

Assessment of CVD

The present report focuses on symptomatic CVD, an aggregate end point that included cardiovascular death, nonfatal myocardial infarction and stroke, transient ischemic attack (TIA), and coronary, carotid, or lower limb revascularization. Myocardial infarction was deemed confirmed when World Health Organization criteria for definite disease status were met (38). Ischemic stroke and TIA were classified according to the criteria of the National Survey of Stroke (39). Vascular mortality included deaths due to myocardial infarction and stroke and sudden cardiac deaths. All of these events or procedures were ascertained by examining the medical records of the local general practitioners and confirmed by reviewing the files of Bruneck Hospital. Cardiovascular deaths were identified by reviewing death certificates. Actual event dates were used, and only the first event was considered in this analysis. Major advantages of the Bruneck Study cohort are that virtually all subjects living in the area of Bruneck are referred to the local hospital and that the network existing between the local hospital and the general practitioners allows retrieval of virtually all medical information on people living in the area.

Statistical analysis

Statistical analyses were performed with SPSS-X and BMDP software. Skewed variables were $\log_e$-transformed to improve the approximation to a Gaussian distribution. Nonparametric tests yielded very similar results (data not presented). Reported *P* values are two-sided.

Overall, missing values for the variables adiponectin, hsCRP, oxidized LDL, and VCAM-1 were rare (<5%) and occurred randomly. They were replaced by estimates derived from the "regression procedure" of the SPSS missing value approach.

The correlations of demographic and behavioral variables, as well as laboratory parameters with $\log_e$-transformed insulin resistance (HOMA-IR) were expressed by standard correlation coefficients. Partial correlation coefficients were corrected for sex, age, smoking, and BMI.

Cox proportional hazard models were used to assess whether baseline insulin resistance was an independent predictor of incident CVD. For this purpose, HOMA-IR was modeled as a categorical variable, and subjects were stratified into those belonging to the top quartile (insulin-resistant subjects) versus those belonging to the other three quartiles (non–insulin-resistant subjects). Five nested models were run: the first one included sex, age, smoking, and HOMA-IR; the second model included model 1 variables, physical activity, and the three

Table 1—*Clinical features of subjects in the cohort at baseline*

	CVD negative at follow-up	CVD positive at follow-up
n	721	118
Male sex (%)	47.6	61.9*
Age (years)	57.2 ± 11.2	65.8 ± 9.8*
Smokers (%)	24.1	30.5*
Physical activity (score)	4.4 ± 1.5	4.3 ± 1.6
BMI (kg/m^2)	24.9 ± 3.7	25.1 ± 4.3
Waist (cm)	87 ± 10	89 ± 10
Fasting glucose (mmol/l)	5.50 ± 0.92	5.89 ± 1.67*
A1C (%)	5.5 ± 0.6	5.8 ± 0.9*
Fasting insulin (pmol/l)	75 (49–111)	78 (40–127)
HOMA-IR	2.5 (1.7–3.9)	2.8 (1.4–4.8)*
LDL cholesterol (mmol/l)	3.52 ± 0.97	3.72 ± 0.91*
HDL cholesterol (mmol/l)	1.47 ± 0.36	1.43 ± 0.37
Triglycerides (mmol/l)	1.22 (0.90–1.78)	1.33 (1.08–1.82)
Systolic blood pressure (mmHg)	144 ± 21	155 ± 24*
Diastolic blood pressure (mmHg)	88 ± 10	92 ± 10*
hsCRP (mg/l)	1.4 (0.8–2.8)	2.0 (1.1–4.2)*
Fibrinogen (g/l)	2.56 (2.21–2.92)	2.71 (2.35–3.03)*
Oxidized LDL (units/l)	30.4 (22.4–36.9)	33.0 (27.9–41.9)*
VCAM-1 (ng/ml)	605 (488–808)	669 (553–817)*
Adiponectin (μg/ml)	10.9 (7.6–15.6)	11.1 (7.4–17.5)

Data are means ± SD or median (interquartile range). $n = 839$. *$P < 0.05$.

most classic risk factors (hyperglycemia, here represented by A1C, LDL cholesterol, and hypertension); the third model included model 2 variables and traditional risk factors strongly related to insulin resistance (BMI, HDL cholesterol, and triglycerides); the fourth model included model 3 variables as well as novel risk factors related to insulin resistance, including fibrinogen (prothrombotic state), oxidized LDL (oxidative stress), hsCRP (inflammation), and VCAM-1 (endothelial dysfunction); and the fifth model included model 4 variables as well as adiponectin. In the principal analyses, smoking, hypertension, and HOMA-IR were modeled as categorical variables and the others as continuous variables. Proportional hazard assumptions were satisfied in all models.

RESULTS — At baseline, the prevalences of diabetes, IFG, and IGT were 6.8, 8.6, and 9.2%, respectively; those of overweight and obesity were 27.5 and 8.6, respectively; and that of hypertension was 61.9%. Table 1 displays baseline clinical features of subjects with and without CVD during follow-up. Those who developed CVD had a higher risk profile at baseline. After adjustments for sex, age, smoking, and BMI, $\log_e$-transformed HOMA-IR was significantly correlated to A1C, LDL cholesterol and HDL cholesterol, triglycerides, hsCRP, fibrinogen, oxidized LDL, VCAM-1, and adiponectin (Table 2).

During the 15 years of follow-up, 118 subjects experienced one or more symptomatic CVD events. In particular, we observed 55 cases of nonfatal and fatal myocardial infarction and 58 cases of fatal and nonfatal stroke and TIA. Forty-four subjects underwent coronary, carotid, or lower limb revascularization.

Cox models revealed that insulin-resistant subjects had an increased risk of incident symptomatic CVD compared with non–insulin-resistant subjects (Table 3). This result was found in the model including only sex, age, and smoking; in the model also including physical activity and classic risk factors (A1C, LDL cholesterol, and hypertension); and in the model also including BMI, HDL cholesterol, and triglycerides. Moreover, when the models also included nontraditional risk factors (fibrinogen, oxidized LDL, hsCRP, VCAM-1, and adiponectin), the association between HOMA-IR and CVD remained significant and virtually unchanged (Table 3). With model 5, which also included nontraditional risk factors, the hazard ratios (HRs) for CVD in the different HOMA-IR quartiles were 1.0 (quartile 1, reference), 0.9 ([95% CI 0.5–1.5], quartile 2), 0.9 ([0.5–1.6], quartile 3), and 2.1 ([1.1–3.9], quartile 4) (P for trend = 0.005). Therefore, there was no dose-response relation but a clear binary relation. Accordingly, when HOMA-IR was used as a continuous variable, no significant association was found with HOMA-IR (in model 5 per 1 unit change in HOMA-IR the HR was 1.3 [0.9–1.7], NS).

Results did not change when we used systolic blood pressure instead of hypertension (model 5, HR 2.4 [95% CI 1.5–3.8], $P < 0.001$) or number of cigarettes/day instead of smoking (model 5, 2.5 [1.5–4.0], $P < 0.001$) or when waist circumference replaced BMI (model 5, 2.4 [1.5–3.8], $P < 0.001$) or the presence/absence of IFG/IGT/diabetes replaced A1C (model 5, 2.5 [1.5–4.0], $P < 0.001$).

Table 2—*Simple and multiple-adjusted (partial) correlations of $\log_e$-transformed HOMA-IR with selected variables*

	Simple	Multiple adjusted
BMI	0.44 (0.001)	—
Waist	0.31 (<0.001)	0.07 (0.048)
A1C	0.26 (<0.001)	0.24 (<0.001)
LDL cholesterol	0.09 (0.012)	0.07 (0.037)
HDL cholesterol	−0.29 (<0.001)	−0.21 (<0.001)
Triglycerides	0.41 (<0.001)	0.38 (<0.001)
Systolic blood pressure	0.22 (<0.001)	0.07 (0.063)
Diastolic blood pressure	0.23 (<0.001)	0.04 (0.256)
hsCRP	0.19 (<0.001)	0.09 (0.012)
Fibrinogen	0.21 (<0.001)	0.12 (<0.001)
Oxidized LDL	0.09 (0.012)	0.08 (0.032)
VCAM-1	0.09 (0.009)	0.09 (0.011)
Adiponectin	−0.18 (<0.001)	−0.16 (<0.001)

Data are correlation coefficient (P value) for simple correlations and partial correlation coefficient (P value) for multiple-adjusted correlations. Multiple adjustment included sex, age, smoking, and BMI. $n = 839$.

Table 3—*Cox proportional HR for CVD in subjects of top quartile versus combined other quartiles of HOMA-IR after adjusting for different sets of potential confounding factors*

	n	Model 1	Model 2	Model 3	Model 4	Model 5
All subjects	839	2.1 (1.4–3.1)*	2.0 (1.3–3.1)†	2.2 (1.4–3.4)*	2.2 (1.4–3.5)*	2.2 (1.4–3.6)*
Men	416	2.1 (1.2–3.7)†	1.8 (1.0–3.8)‡	2.3 (1.2–4.3)†	2.6 (1.3–5.0)†	2.6 (1.3–5.0)†
Women	423	2.0 (1.1–3.7)‡	2.5 (1.3–4.9)†	2.4 (1.1–5.0)‡	2.1 (1.0–4.5)‡	2.1 (1.0–4.5)‡
NFG/NGT	661	2.2 (1.2–3.8)†	2.1 (1.2–3.7)†	2.4 (1.3–4.3)†	2.4 (1.3–4.4)†	2.5 (1.4–4.6)†
IFG/IGT/diabetes	178	2.0 (1.0–4.1)	1.8 (0.8–4.1)	1.9 (0.8–4.5)	2.2 (0.9–5.6)	2.2 (0.9–5.5)
No diabetes	782	1.9 (1.2–3.0)†	1.8 (1.2–3.0)†	2.1 (1.3–3.4)†	2.2 (1.3–3.6)†	2.2 (1.3–3.7)†
Diabetes	57	5.3 (1.0–28.2)‡	5.7 (0.9–37.1)	10.0 (0.9–113)	12.8 (1.0–162)‡	17.2 (1.2–245)‡

Data are HR (95% CI). Model 1: sex, age, and smoking; model 2: model 1 + A1C, LDL cholesterol, hypertension, and physical activity; model 3: model 2 + BMI, triglycerides, and HDL cholesterol; model 4: model 3 + fibrinogen, hsCRP, oxizided LDL, and VCAM-1; model 5: model 4 + adiponectin. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$. NFG, normal fasting glucose; NGT, normal glucose tolerance.

When subjects were stratified according to sex, results were confirmed separately in men and women (Table 3). Results were also confirmed separately in those with normal fasting glucose and normal glucose after an oral glucose tolerance test and in those with abnormal glucose regulation (IFG, IGT, or diabetes), as well as in those without and with type 2 diabetes (Table 3). Moreover, the introduction of an interaction term between insulin resistance (HOMA-IR quartile 4) and abnormal glucose regulation (IFG/IGT/diabetes) in a model including these variables yielded similar results, and the interaction term was not significant (model 5, $P = 0.63$).

Results were similar when subjects developing TIA or undergoing revascularization where excluded and when the analysis was restricted to those with fatal and nonfatal myocardial infarction or stroke (model 5, HR 2.2 [95% CI 1.3–3.9], $P = 0.006$). In subjects with insulin resistance the 15-year risks of CVD were 17.5 and 35%, according to the absence or presence of diabetes, respectively ($P = 0.02$ for difference).

When we used insulin rather than HOMA-IR results were quite similar. The HR for CVD in subjects belonging to the top versus the other three quartiles of fasting plasma insulin was 2.0 ([95% CI 1.2–3.2], $P < 0.005$) in model 5. When insulin was modeled as a continuous variable, no association was found with CVD (model 5, per 1 unit change of insulin level, 1.3 [0.99–1.02], $P = 0.5$).

CONCLUSIONS — The main finding of this study is that insulin resistance, as estimated by a simple method based on the measurement of plasma glucose and serum insulin in a single fasting blood sample, was associated with incident symptomatic CVD in a cohort extracted from a population with a low prevalence of diabetes and obesity. The association of insulin resistance with CVD was independent of classic risk factors (including hyperglycemia, hypertension, high LDL cholesterol, smoking, and physical activity) and of other components of the metabolic syndrome (obesity, hypertriglyceridemia, and low HDL cholesterol). Most importantly and originally, the association remained significant and virtually unchanged after accounting for novel risk factors related to insulin resistance, including adiponectin and biomarkers indicating a prothrombotic state (high fibrinogen), increased oxidative stress (high circulating oxidized LDL), endothelial dysfunction (high VCAM-1), and chronic mild inflammation (increased hsCRP).

In previous articles, it was reported that several nontraditional risk factors are related to insulin resistance (17–20). In the present article, we confirm and extend these observations. Nontraditional risk factors might represent further links (or intermediate phenotypes) between insulin resistance and CVD. Accordingly, in vitro and in vivo data suggest that insulin reduces platelet aggregation (10) and fibrinogen synthesis (12), possesses anti-inflammatory and antioxidant properties (13,14), and favorably influences the endothelial function and the physiology of the vascular wall (11,15,16). If we assume that insulin resistance is not confined to glucose metabolism but encompasses many, if not all, biological effects of the hormone, these effects of insulin would be blunted in insulin-resistant states. Insulin resistance, therefore, might be viewed as a common denominator and perhaps a cofactor of several metabolic and nonmetabolic disorders representing cardiovascular risk factors. This mechanistic interpretation is strongly supported by studies reporting that an improvement in insulin resistance yields a correction of diverse metabolic abnormalities. This has been observed with lifestyle changes (40,41), as well as with chronic treatment with drugs such as metformin (42) and, to a greater extent, glitazones (43). Interestingly, metformin was the only pharmacological agent achieving a significant prevention of CVD in the UK Prospective Diabetes Study (UKPDS) (44), and glitazones have been shown to reduce carotid intima-media thickness (45) and to prevent coronary restenosis after angioplasty (46) and perhaps reduce risk for CVD in type 2 diabetes (32).

In this article, we report the novel observation that, although it is statistically and perhaps causally related to diverse novel metabolic and nonmetabolic abnormalities, insulin resistance remains independently associated with incident CVD even after accounting for them. The probable interpretation of this finding is that insulin resistance contributes to the development of CVD by pathophysiological mechanisms that are, at least in part, distinct from those that we tried to gauge in the present study. For instance, we did not measure plasminogen activator inhibitor-1. Fibrinolytic abnormalities might be a major link between insulin resistance and CVD (47). Other intermediates in the link might be free fatty acids, which are higher in subjects with insulin resistance (48), impair endothelial function (49), and predict CVD (50). A further intermediate abnormality might be proinsulin, which is generally increased in insulin-resistant states (51) and is related to CVD (52).

Further, we recognize that a single assessment of a given biochemical or clinical parameter might be insufficient to fully describe its association with insulin resistance and CVD and that more accu-

rate assessments of risk factor (e.g., long-term blood pressure monitoring instead of three spot measurements) or the choice of other parameters reflecting endothelial dysfunction, oxidative stress, or chronic inflammation may better identify their possible role as intermediates between insulin resistance and CVD. Therefore, the hypothesis that insulin resistance might also lead to CVD through its deleterious impact on glucose and lipid metabolism, blood pressure, coagulation abnormalities, inflammation, oxidant stress, and endothelial dysfunction cannot be definitely ruled out.

The present results on the association between insulin resistance and CVD agree with data generated by using our same methodology for estimating insulin resistance (i.e., HOMA) in large samples from the general populations of the U.S. (23,26,31), Finland (22), and Sweden (25). They also are consistent with reports in which insulin sensitivity was more directly assessed with the glucose clamp (29) and the insulin suppression test (21). Of note, our findings extend and strengthen these observations and, for the first time, point out that the association between insulin resistance and CVD is also confirmed when one allows for a greater number of potential confounders, including adiponectin and biomarkers of thrombophilia, inflammation, oxidant stress, and endothelial dysfunction.

The increased cardiovascular risk in subjects with insulin resistance was observed separately in those with and without diabetes. In the latter, however, the HRs increased across the various models and the 95% CIs were broad. This finding is reasonably attributable to the small number of events and sample size relative to the number of variables in the model. The increased risk in diabetic subjects with higher HOMA-IR scores is consistent with results we have found in a study focusing on a large number of patients (24) and in diabetic subjects recruited in the Veterans Affairs HDL Intervention Trial (VA-HIT) (26). Also they are consistent with data generated by insulin tolerance testing in a large sample of Japanese type 2 diabetic patients (28).

In two studies carried out in nondiabetic American Indians (27) and in diabetic Caucasians (30), HOMA-IR was not a predictor of CVD. These discrepancies with all other studies, including ours, might be attributed to differences in the study population, in the statistical methods (in these studies HOMA-IR was modeled as a continuous variable), and to the imperfect estimate of insulin resistance by HOMA. In other words, in some situations HOMA might underestimate the true association between insulin resistance and CVD. In our experience, however, the variability of clamp-measured insulin resistance explained by HOMA-IR was 65% (37). On the other hand, from the clinical perspective, HOMA-IR has the potential to be useful, whereas glucose clamp or other more direct methods are not suitable.

In the discussion of future applications in clinical routine, a suggestion from our study is that insulin resistance might reasonably be included among the metabolic parameters that the physician should evaluate to quantify the overall cardiovascular risk. However, before giving this measure a strong recommendation, further studies are required to confirm our findings and to prove that adding HOMA-IR (or other surrogate measures of insulin resistance) to clinical testing indeed improves prediction accuracy. Moreover, before translation of our results to clinical practice, a standardization of insulin assay and, therefore, HOMA-IR is warranted.

In a mechanistic interpretation of our results, insulin resistance might be reasonably considered among targets for a specific intervention, and the population might be strongly recommended to adopt a lifestyle capable of ameliorating insulin sensitivity. For instance, physical exercise, which was proved to successfully improve insulin sensitivity (53), should be encouraged. In this regard, it might be hypothesized that the lower CVD risk observed in subjects who are less sedentary or who exercise regularly (54) could be attributed also to their higher insulin sensitivity.

In summary, in a general population sample, insulin resistance conferred a greater risk for CVD independently of diverse potential confounders, including traditional and novel risk factors. The identification of intermediate abnormalities linking insulin resistance to CVD deserves further studies. Improvement of insulin sensitivity might be an additional goal in prevention of cardiovascular risk.

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