Insulin Resistance Predicts Mortality in Nondiabetic Individuals in the U.S.

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OBJECTIVE — Insulin resistance is a suspected causative factor in a wide variety of diseases. We aimed to determine whether insulin resistance, estimated by the homeostasis model assessment for insulin resistance (HOMA-IR), is associated with all-cause or disease-specific mortality among nondiabetic persons in the U.S.

RESEARCH DESIGN AND METHODS — We determined the association between HOMA-IR and death certificate–based mortality among 5,511 nondiabetic, adult participants of the third U.S. National Health and Nutrition Examination Survey (1988–1994) during up to 12 years of follow-up, after adjustment for potential confounders (age, sex, BMI, waist-to-hip ratio, alcohol consumption, race/ethnicity, educational attainment, smoking status, physical activity, C-reactive protein, systolic and diastolic blood pressure, plasma total and HDL cholesterol, and triglycerides).

RESULTS — HOMA-IR was significantly associated with all-cause mortality (adjusted hazard ratio 1.16 [95% CI 1.01–1.3], comparing successive quartiles of HOMA-IR in a linear model and 1.64 [1.1–2.5], comparing the top [HOMA-IR >2.8] to the bottom [HOMA-IR ≤1.4] quartile). HOMA-IR was significantly associated with all-cause mortality only in subjects with BMI <25.2 kg/m^2 (the median value) but not in subjects with BMI ≥25.2 kg/m^2. Subjects in the second, third, and fourth quartile of HOMA-IR appeared to have higher cardiovascular mortality than subjects in the lowest quartile of HOMA-IR. HOMA-IR was not associated with cancer-related mortality.

CONCLUSIONS — HOMA-IR is associated with all-cause mortality in the nondiabetic U.S. population but only among persons with normal BMI. HOMA-IR is a readily available measure that can be used in the future to predict mortality in clinical or epidemiological settings.

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Insulin resistance is a condition in which normal amounts of insulin are not adequate to produce the expected biologic response in target tissues, including adipose tissue, muscle, and liver. Insulin resistance has been associated with a wide variety of adverse health outcomes, including type 2 diabetes (1), hypertension (2), cardiovascular disease (1), cerebrovascular disease (3), peripheral vascular disease (4), congestive heart failure (5), nonalcoholic fatty liver disease (6), dyslipidemia (low HDL cholesterol and high triglycerides) (7), and a variety of malignancies (8). Using a mathematical simulation model, Eddy et al. (9) recently estimated that insulin resistance was responsible for 42% of myocardial infarctions in the U.S. and was the most important single cause of coronary artery disease.

Obesity is known to be a strong risk factor for insulin resistance, in particular ectopic as opposed to subcutaneous adiposity (10). In addition, factors unrelated to obesity are important contributors to insulin resistance, such as race, sex, physical activity, and genetic factors, while as-yet-unknown causes of insulin resistance also likely exist.

The homeostasis model assessment for insulin resistance (HOMA-IR) estimates insulin resistance from fasting plasma glucose and serum insulin levels (11). There is good correlation between values of insulin resistance obtained using HOMA-IR and the euglycemic-hyperinsulinemic clamp method (12), the gold-standard test that is too costly and technically demanding to be used in epidemiologic studies or clinical practice. Given the combination of accuracy and ease of testing, HOMA-IR is considered an appropriate method for measurement of insulin resistance in epidemiologic studies (12).

Our aim was to determine the association between HOMA-IR and mortality in nondiabetic people in the U.S. independently of other important predictors of mortality. This finding would be important in incorporating HOMA-IR into future models predicting mortality for clinical or epidemiological purposes, especially since HOMA-IR is readily available.

RESEARCH DESIGN AND METHODS

— Data were derived from the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional study conducted by the National Center for Health Statistics (NCHS) between 1988 and 1994 in order to assess the health and nutritional status of the noninstitutionalized U.S. population (13). Participants completed personal, structured interviews at home and then attended a mobile examination center at 89 locations throughout the U.S. NHANES III utilized a stratified, multistage, probability cluster sampling design to obtain a representative sample of the civilian, noninstitutionalized population. Non-Hispanic blacks, Mexican Americans, and the elderly were deliberately oversampled, in order to allow calculation of more precise estimates of the distribution of variables in these groups.

The NCHS created the NHANES III–linked mortality file by linking NHANES III with the National Death Index (14), a

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computerized database of all certified deaths in the U.S. since 1979. This file links NHANES III participants, aged ≥17 years, with death records from the National Death Index through 31 December 2000. National Death Index records provided data on date and underlying cause of death. Linkage of NHANES III and National Death Index records was performed by probabilistic matching using up to 12 identifying data items (15). A selected sample of death certificates was reviewed manually to validate the accuracy of the process. We studied the associations between HOMA-IR ascertained at baseline in NHANES III between 1988 and 1994 and mortality up to 31 December 2000, determined from the NHANES III–linked mortality file.

NHANES III participants were assigned to morning, afternoon, or evening examinations and were instructed to fast for 10–16 h prior to the morning examination or for 6 h before the afternoon or evening examination. The study was designed such that the participants assigned to the morning examination constituted a nationally representative sample. We limited the current analysis to participants assigned to the morning examination, reasoning that there are systematic differences in serum insulin and plasma glucose levels measured in the morning, afternoon, or evening despite fasting. Of 7,959 participants aged ≥20 years assigned to the morning (10:00 A.M.) phlebotomy and examination, we excluded 129 pregnant women; 483 participants who fasted for <9 or >24 h; and participants with missing data on serum insulin or plasma glucose levels (n = 455), waist circumference, or BMI (n = 250); educational attainment (n = 28); systolic or diastolic blood pressure (n = 169); alcohol consumption (n = 209); and serum cholesterol, HDL cholesterol, triglyceride (n = 94); and serum C-reactive protein (n = 46) levels. We excluded 344 participants with previously diagnosed diabetes and 237 with previously undiagnosed diabetes. Participants were defined as having previously diagnosed diabetes if they reported "ever being told by a doctor that they had diabetes or sugar diabetes other than during pregnancy" or if they were taking insulin or oral hypoglycemic medications. Undiagnosed diabetes was defined as a fasting plasma glucose level ≥126 mg/dl among individuals without diagnosed diabetes. Only four additional participants did not have data linked to the NHANES III mortality file, leaving 5,511 participants in the current analyses.

Determination of HOMA-IR

Fasting plasma glucose was measured using a modified hexokinase enzymatic assay (Cobas Mira Chemistry System; Roche Diagnostic Systems, Montclair, NJ). Fasting serum insulin was measured by radioimmunoassay using a double-antibody batch method (Pharmacia Insulin RIA kit; Pharmacia Diagnostics, Uppsala, Sweden). During the 6 years of the study, the coefficient of variation ranged from 1.6 to 3.7% for the glucose assay and 5.8 to 13.8% for the insulin assay (16). We calculated HOMA-IR as (fasting serum insulin [μU/ml] × fasting plasma glucose [mmol/l])/22.5 (12).

Ascertainment of mortality

Our primary outcome was all-cause mortality. In secondary analyses, we considered whether HOMA-IR was associated with mortality from cardiovascular diseases or cancer, two conditions that have been associated with insulin resistance and that constitute the most important causes of death in the U.S. population. Cardiovascular mortality was defined by the presence of the following ICD-10 codes recorded as the underlying cause of death on death certificates: ischemic heart diseases (I20–I25), atherosclerosis (I70), heart failure (I50), and cerebrovascular diseases (I60–69). Cancer mortality was defined by ICD-10 codes for malignant neoplasms (C00–C97) and in situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior (D00–D48).

Risk variables and potential confounders

We considered variables that may be associated with insulin resistance and/or mortality as potential confounders in multivariate models including age, sex, BMI, waist-to-hip ratio, alcohol consumption (categorized as none or <12 drinks in any year, >0–1 drink/day, >1–2 drinks/day, and >2 drinks/day on average over the preceding 12 months), race-ethnicity (categorized as non-Hispanic white, non-Hispanic black, Mexican American, and "other"), educational attainment (years of school completed), smoking status (never, former, <1 pack/day, ≥1 pack/day), C-reactive protein (categorized as 0–0.3 and >0.3 mg/dl), physical activity (calculated by multiplying each recreational and non-recreational activity by its intensity value and adding up the products for all activity types), systolic and diastolic blood pressure, plasma total and HDL cholesterol, and triglycerides (the last six variables categorized into quartiles as dummy categorical variables).

Statistical analyses

Cox proportional hazards models (17) were used to determine the hazard ratio (HR) for mortality associated with HOMA-IR. HOMA-IR was divided into quartiles (≤1.4, >1.4–2.0, >2.0–2.8, and >2.8) and modeled as a dummy categorical variable (each higher quartile compared with the lowest quartile) or modeled as the difference between successive quartiles. HOMA-IR was also modeled as a linear continuous variable. The proportional hazards assumption was examined using −log plots of survival versus time. The date of the NHANES III baseline examination, which occurred for each participant at some time between 1988 and 1994, was used as time zero. For participants who died before 31 December 2000, person-months of follow-up were calculated from the examination date through the date of death. For participants who were alive as of 31 December 2000, person-months of follow-up were calculated from the examination date through the end of the mortality follow-up period on 31 December 2000. This variable, "describing the person-months of follow-up" is provided by the NCHS as part of the NHANES III mortality files under the name "permth_exm." For analyses of cause-specific mortality, participants who died of other causes were censored at the date of death.

We developed three models that simultaneously adjusted for the following variables in the association between HOMA-IR and mortality:

- Model 1: age and sex.
- Model 2: age, sex, BMI, and waist-to-hip ratio.
- Model 3: age, sex, BMI, waist-to-hip ratio, race/ethnicity, smoking, alcohol consumption, physical activity, education, systolic blood pressure, diastolic blood pressure, total serum cholesterol, serum HDL cholesterol, serum triglycerides, and serum C-reactive protein.

We determined whether the association between HOMA-IR and mortality was different among subgroups defined by BMI,

Table 1—*Baseline characteristics of participants by HOMA-IR quartile

Characteristic	HOMA-IR ≤1.4	>1.4–2.0	>2.0–2.8	>2.8
Age (years)	40.1 ± 0.63	42.6 ± 0.78	43.9 ± 0.65	47.4 ± 0.62
Education (years)	12.9 ± 0.11	12.9 ± 0.14	12.4 ± 0.15	12.0 ± 0.14
BMI (kg/m^2)	22.6 ± 0.13	24.5 ± 0.13	26.8 ± 0.16	31.1 ± 0.28
Waist circumference (cm)	80.5 ± 0.38	86.2 ± 0.39	93.2 ± 0.40	103.8 ± 0.62
Waist-to-hip ratio	0.85 ± 0.003	0.88 ± 0.004	0.92 ± 0.003	0.96 ± 0.003
Serum total cholesterol (mg/dl)	189 ± 1.7	201 ± 1.6	207 ± 1.4	214 ± 1.3
Serum HDL cholesterol (mg/dl)	57.0 ± 0.74	52.8 ± 0.73	48.5 ± 0.57	43.7 ± 0.65
Serum triglycerides (mg/dl)	88 ± 2.3	112 ± 3.3	137 ± 3.1	178 ± 3.5
Systolic blood pressure (mmHg)	112 ± 0.6	115 ± 0.6	119 ± 0.6	124 ± 0.8
Diastolic blood pressure (mmHg)	69.0 ± 0.52	70.9 ± 0.39	73.6 ± 0.44	76.3 ± 0.48
Physical activity intensity (MET)†	132 ± 7.0	128 ± 7.1	108 ± 5.3	96 ± 6.5
Daily coffee intake (cup)	1.44 ± 0.113	1.22 ± 0.100	1.22 ± 0.077	1.22 ± 0.079
Women (%)	58.0 ± 2.2	55.7 ± 2.2	47.6 ± 2.1	48.7 ± 2.1
Ethnicity (%)				
Non-Hispanic white	83.2 ± 1.7	80.7 ± 1.5	78.2 ± 1.4	71.0 ± 2.1
Non-Hispanic black	7.5 ± 0.78	8.1 ± 0.68	10.2 ± 0.81	12.6 ± 1.0
Mexican American	3.8 ± 0.54	3.7 ± 0.43	4.3 ± 0.51	7.3 ± 0.85
Other	5.4 ± 1.1	7.4 ± 1.3	7.3 ± 1.0	9.1 ± 1.8
Cigarette smoking (%)				
Never	45.7 ± 1.9	48.9 ± 2.2	46.9 ± 1.6	42.3 ± 2.4
Former	19.3 ± 1.7	23.1 ± 1.9	27.7 ± 1.6	34.6 ± 2.5
Less than one pack per day	15.3 ± 2.1	10.7 ± 1.5	10.3 ± 1.3	10.6 ± 1.3
One or more packs per day	19.7 ± 1.9	17.3 ± 1.7	15.1 ± 1.4	12.5 ± 1.7
Alcohol consumption (%)				
None to <12 drinks per year	34.5 ± 2.7	40.0 ± 2.4	41.2 ± 1.7	56.2 ± 2.3
≥12 drinks per year–1 drink per day	47.1 ± 2.5	44.6 ± 2.5	44.9 ± 2.1	31.3 ± 2.1
>1–2 drinks per day	11.0 ± 1.3	7.7 ± 1.2	7.7 ± 1.1	8.3 ± 1.4
>2 drinks per day	7.4 ± 1.0	7.7 ± 1.0	6.2 ± 1.1	4.1 ± 0.8
C-reactive protein (%)				
0–0.3 mg/dl	86.7 ± 1.6	79.6 ± 1.5	75.8 ± 2.4	56.4 ± 2.5
>0.3 mg/dl	13.3 ± 1.6	20.4 ± 1.5	24.2 ± 2.4	43.6 ± 2.5

Data are means or proportions ± SE. *Results adjusted for sampling and weighting processes of NHANES III to reflect estimates for the U.S. population. †Sum of the products of activity frequency in the previous month and an intensity rating for nine common activities.

waist-to-hip ratio, or sex by using interaction terms and subgroup analyses.

NHANES III is based upon a complex sampling design that we took into account in statistical analyses using the survey commands of STATA statistical software version 10 and the appropriate weight ("wtpfhsd6," specific for subjects assigned to the morning examination), strata ("sdpstra6"), and primary sampling unit ("sdppsu6") variables as recommended in the NHANES III Analytical Guidelines, such that our results are representative of the U.S. population (18). Taylor series linearization was used for variance estimation. A two-sided *P* value <0.05 was a priori considered to be statistically significant.

RESULTS — Higher HOMA-IR quartiles were associated with greater mean age, BMI, waist circumference, waist-to-hip ratio, plasma total cholesterol, plasma triglycerides, systolic and diastolic blood pressure, and with lower mean plasma HDL cholesterol and physical activity (Table 1). Subjects within higher HOMA-IR quartiles were more likely to have elevated serum C-reactive protein, to be male, to have ethnicity other than non-Hispanic white, and to consume little or no alcohol.

In our analytical cohort of 5,511 participants, 643 deaths occurred during a mean follow-up of 8.5 years, including 237 deaths related to cardiovascular diseases and 170 cancer-related deaths. Increasing HOMA-IR quartile was significantly associated with increasing all-cause mortality after adjustment for all potential confounders listed above (adjusted HR [AHR] 1.25 [95% CI 1.1–1.5], comparing successive quartiles) (Table 2). Subjects in the top quartile of HOMA-IR (>2.8) had significantly greater mortality than subjects in the bottom quartile (HOMA-IR ≤1.4) after adjustment for potential confounders (1.64 [1.1–2.5]). When HOMA-IR was modeled as a linear continuous variable, it was significantly associated with mortality (1.06 [1.02–1.1], for each unit increase in HOMA-IR).

We identified substantial interaction between HOMA-IR and BMI in the association with mortality ($P < 0.05$ for the categorical interaction term). HOMA-IR was significantly associated with mortality among subjects with BMI below the median level (25.2 kg/m^2) but not among subjects with BMI >25.2 kg/m^2 (Table 2). The association between HOMA-IR and mortality was similar in men and women and in people with high or low waist-to-hip ratio.

HOMA-IR was not associated with

Table 2—*The association between HOMA-IR and all-cause mortality*

	Age- and sex-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI)*	Multivariate-adjusted HR (95% CI)†
HOMA-IR			
≤1.4	1	1	1
>1.4–2.0	1.13 (0.8–1.6)	1.19 (0.8–1.7)	1.30 (0.9–1.9)
>2.0–2.8	1.15 (0.8–1.6)	1.30 (0.9–1.9)	1.37 (0.9–2.0)
>2.8	1.31 (0.9–1.9)	1.54 (1.1–2.2)	1.64 (1.1–2.5)
HOMA-IR: comparing successive quartiles	1.09 (1.0–1.2)	1.15 (1.01–1.3)	1.16 (1.01–1.3)
HOMA-IR: comparing subjects with a HOMA-IR difference of 1	1.05 (1.0–1.11)	1.07 (1.02–1.11)	1.06 (1.02–1.1)
Participants with BMI ≤25.3 kg/m^2			
HOMA-IR			
≤1.4	1	1	1
>1.4–2.0	1.15 (0.7–1.8)	1.15 (0.7–1.8)	1.33 (0.8–2.2)
>2.0–2.8	1.47 (0.9–2.4)	1.47 (0.9–2.4)	1.73 (1.1–2.8)
>2.8	1.60 (1.1–2.4)	1.65 (1.1–2.4)	1.86 (1.1–3.0)
HOMA-IR: comparing successive quartiles	1.19 (1.02–1.4)	1.19 (1.04–1.4)	1.25 (1.1–1.5)
HOMA-IR: comparing subjects with a HOMA-IR difference of 1	1.19 (1.02–1.4)	1.20 (1.03–1.40)	1.26 (1.1–1.5)
Participants with BMI >25.3 kg/m^2			
HOMA-IR			
≤1.4	1	1	1
>1.4–2.0	1.18 (0.6–2.3)	1.17 (0.6–2.2)	0.99 (0.5–1.8)
>2.0–2.8	1.03 (0.6–1.9)	1.03 (0.6–1.9)	0.91 (0.5–1.6)
>2.8	1.38 (0.7–2.7)	1.34 (0.7–2.6)	1.13 (0.6–2.2)
HOMA-IR: comparing successive quartiles	1.12 (0.9–1.3)	1.10 (0.9–1.3)	1.07 (0.9–1.3)
HOMA-IR: comparing subjects with a HOMA-IR difference of 1	1.06 (1.0–1.1)	1.06 (1.0–1.1)	1.04 (0.9–1.1)
Men			
HOMA-IR			
≤1.4	1	1	1
>1.4–2.0	1.02 (0.5–1.9)	1.19 (0.6–2.3)	1.25 (0.7–2.3)
>2.0–2.8	1.14 (0.7–1.8)	1.51 (0.9–2.5)	1.77 (1.1–2.7)
>2.8	1.23 (0.7–2.1)	1.72 (1.0–3.0)	1.87 (1.1–3.3)
HOMA-IR: comparing successive quartiles	1.08 (0.9–1.3)	1.20 (1.03–1.4)	1.24 (1.05–1.5)
HOMA-IR: comparing subjects with a HOMA-IR difference of 1	1.04 (0.9–1.1)	1.06 (1.01–1.12)	1.05 (1.0–1.10)
Women			
HOMA-IR			
≤1.4	1	1	1
>1.4–2.0	1.25 (0.8–2.0)	1.28 (0.8–2.0)	1.52 (0.9–2.5)
>2.0–2.8	1.14 (0.7–1.8)	1.16 (0.7–1.9)	1.21 (0.7–2.0)
>2.8	1.41 (0.9–2.2)	1.52 (0.9–2.6)	1.62 (0.9–3.0)
HOMA-IR: comparing successive quartiles	1.10 (1.0–1.2)	1.12 (0.95–1.3)	1.12 (0.93–1.36)
HOMA-IR: comparing subjects with a HOMA-IR difference of 1	1.07 (0.99–1.15)	1.08 (0.99–1.16)	1.08 (0.99–1.2)

*Adjusted for age, sex, insulin resistance, BMI, and waist-to-hip ratio. †Adjusted for age, sex, insulin resistance, BMI, waist-to-hip ratio, race/ethnicity, smoking, alcohol consumption, physical activity, education, systolic blood pressure, diastolic blood pressure, total serum cholesterol, serum HDL cholesterol, serum triglycerides, and serum C-reactive protein.

cancer-related mortality (Table 3). Subjects in the second, third, and fourth quartile of HOMA-IR appeared to have a higher cardiovascular mortality risk than subjects in the lowest quartile of HOMA-IR (Table 3). There did not appear to be a "linear" relationship between HOMA-IR and cardiovascular mortality; rather, the risk appeared uniformly elevated in the three higher quartiles relative to the bottom quartile. When modeled as a linear continuous variable, HOMA-IR was not significantly associated with cardiovascular mortality (AHR 1.06 [95% CI 0.98–1.2]).

We investigated the association between each of the components of HOMA-IR (plasma glucose and serum insulin) and mortality (Table 4). Fasting plasma glucose was not associated with mortality. Higher serum insulin appeared to be associated with mortality, but this association did not reach statistical significance.

CONCLUSIONS — HOMA-IR, a marker of insulin resistance, was independently associated with increased all-

Table 3—*The association between HOMA-IR and cardiovascular or cancer mortality*

	Age- and sex-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI)*	Multivariate-adjusted HR (95% CI)†
Cardiovascular mortality			
HOMA-IR			
≤1.4	1	1	1
>1.4–2.0	3.0 (1.7–5.3)	3.1 (1.8–5.4)	3.7 (2.0–6.9)
>2.0–2.8	2.0 (1.1–3.8)	2.2 (1.2–3.9)	2.6 (1.3–5.2)
>2.8	2.4 (1.4–4.2)	2.5 (1.4–4.3)	3.2 (1.7–5.9)
HOMA-IR: comparing successive quartiles	1.13 (0.98–1.3)	1.15 (0.99–1.3)	1.21 (1.03–1.4)
HOMA-IR: comparing subjects with a HOMA-IR difference of 1	1.06 (0.98–1.2)	1.05 (0.97–1.1)	1.06 (0.98–1.2)
Cancer mortality			
HOMA-IR			
≤1.4	1	1	1
>1.4–2.0	0.59 (0.3–1.05)	0.63 (0.4–1.1)	0.62 (0.3–1.2)
>2.0–2.8	0.88 (0.6–1.4)	1.0 (0.6–1.7)	0.83 (0.5–1.5)
>2.8	0.95 (0.6–1.5)	1.2 (0.7–2.1)	0.90 (0.4–1.8)
HOMA-IR: comparing successive quartiles	1.04 (0.9–1.2)	1.11 (0.9–1.4)	1.01 (0.8–1.3)
HOMA-IR: comparing subjects with a HOMA-IR difference of 1	0.99 (0.9–1.1)	1.01 (0.9–1.2)	0.94 (0.8–1.2)

*Adjusted for age, sex, insulin resistance, BMI, and waist-to-hip ratio. †Adjusted for age, sex, insulin resistance, BMI, waist-to-hip ratio, race/ethnicity, smoking, alcohol consumption, physical activity, education, systolic blood pressure, diastolic blood pressure, total serum cholesterol, serum HDL cholesterol, serum triglycerides, and serum C-reactive protein.

cause mortality in nondiabetic adults after adjusting for measures of obesity, including BMI and waist-to-hip ratio, and other common predictors of mortality that might also be associated with insulin resistance. The association between HOMA-IR and mortality was observed only among people with normal BMI (below the median level of 25.2 kg/m^2) but not among people with a BMI >25.2 kg/m^2.

Insulin resistance estimated by HOMA-IR was previously associated with increased coronary events and all-cause mortality among nondiabetic adults in Malmo, Sweden (19). Insulin resistance was also shown to be predictive of increased mortality in certain high-risk populations, including patients with diabetes (20), congestive heart failure (21), and end-stage renal disease (22). In addition, Balkau et al. (23) showed increased all-cause mortality in nondiabetic European men with hyperglycemia (upper 20% of 2-h glucose level after an oral glucose tolerance test). However, we found no other studies linking insulin resistance estimated by HOMA-IR to all-cause mortality in nondiabetic individuals representative of the U.S. population. There are several studies evaluating the relationship between insulin resistance and cardiovascular disease showing an increased risk of

Table 4—*The association between the components of HOMA-IR (fasting serum insulin and fasting plasma glucose) and all-cause mortality*

	Age- and sex-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI)*	Multivariate-adjusted HR (95% CI)†
Fasting plasma glucose			
≤89	1	1	1
>89–94	0.77 (0.5–1.1)	0.78 (0.5–1.2)	0.76 (0.5–1.2)
>94–100	0.65 (0.4–1.0)	0.66 (0.5–1.0)	0.66 (0.4–1.0)
>100	0.94 (0.6–1.4)	0.96 (0.6–1.4)	0.95 (0.6–1.5)
Fasting plasma glucose: comparing successive quartiles	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)
Linear fasting plasma glucose: comparing subjects with a fasting plasma glucose difference of 1	1.0 (0.99–1.01)	1.0 (0.99–1.01)	1.0 (0.99–1.01)
Fasting serum insulin			
≤6.15	1	1	1
>6.15–8.35	1.01 (0.7–1.4)	1.08 (0.8–1.5)	1.16 (0.8–1.6)
>8.35–11.5	1.19 (0.9–1.6)	1.34 (0.9–2.0)	1.40 (0.9–2.1)
>11.5	1.23 (0.9–1.7)	1.43 (1.0–2.1)	1.48 (0.9–2.2)
Fasting serum insulin: comparing successive quartiles	1.08 (0.98–1.2)	1.14 (1.0–1.3)	1.14 (0.99–1.31)
Linear fasting plasma insulin: comparing subjects with a fasting serum insulin difference of 1	1.01 (0.99–1.03)	1.02 (1.0–1.03)	1.02 (1.0–1.03)

*Adjusted for age, sex, BMI, and waist-to-hip ratio. †Adjusted for age, sex, BMI, waist-to-hip ratio, race/ethnicity, smoking, alcohol consumption, physical activity, education, systolic blood pressure, diastolic blood pressure, total serum cholesterol, serum HDL cholesterol, serum triglycerides, and serum C-reactive protein.

congestive heart failure (5) and major cardiovascular events in both patients with (1) and without (24) a previous history of coronary artery disease.

Insulin resistance is strongly associated with measures of obesity, such as BMI and waist-to-hip ratio. In fact, excess adiposity is considered a major cause of insulin resistance. However, we found that insulin resistance is associated with mortality even after adjusting for BMI and waist-to-hip ratio. Furthermore, a novel and surprising finding of our study was that insulin resistance was independently associated with mortality only among individuals with a normal BMI (below the median level of 25.2 kg/m^2). In these individuals, insulin resistance is presumably caused by factors other than obesity, as defined by elevated BMI. Therefore, our findings suggest that high BMI–related insulin resistance does not confer an independent, excess risk of mortality. On the other hand, low BMI–related insulin resistance is independently associated with mortality. In support of this finding, hyperinsulinemia has been associated with a more marked increase in inflammatory cytokines (specifically interleukin-6) among healthy subjects with normal BMI when compared with diabetic subjects with an overweight BMI (25). Future studies should investigate further the systematic differences between insulin-resistant individuals with high BMI and insulin-resistant individuals with low BMI.

Table 4 suggests that the association between HOMA-IR and mortality that we describe is driven primarily by the association between serum insulin and mortality. There was no association between fasting plasma glucose (the other component of HOMA-IR) and mortality in these nondiabetic subjects. The magnitude of the associations between quartiles of HOMA-IR and mortality was greater than the magnitude of the associations between serum insulin and mortality. This suggests that improved prediction of mortality would be expected by using HOMA-IR rather than just using serum insulin.

In secondary analyses, we identified that HOMA-IR was associated with cardiovascular mortality but not cancer mortality. We did not identify a trend of increasing cardiovascular mortality with increasing HOMA-IR category. Rather, it appeared that subjects in the top three quartiles of insulin resistance had uniformly elevated mortality relative to subjects in the lowest quartile. When modeled as a linear variable, HOMA-IR was not significantly associated with cardiovascular mortality (AHR 1.06 [95% CI 0.98–1.2]). However, the cause of death in our study was identified from death certificates that may be inaccurate and therefore masking any real trends in cardiovascular mortality with increasing HOMA-IR. While ascertainment of cause of death might have been subject to some inaccuracy, vital status and date of death were very accurately ascertained (~99%). Thus, our results on the association between HOMA-IR and all-cause mortality are expected to be accurate and valid and constitute our study's primary outcome. Future studies should explore further the associations between insulin resistance and cause-specific mortality with better ascertainment of the cause of death. At the same time, our study has considerable strengths. HOMA-IR was measured in a large sample representative of the U.S. population. Follow-up duration was adequate and ascertainment of mortality was accurate and performed without relevance to baseline HOMA-IR level.

HOMA-IR is associated with mortality in the U.S. population particularly among individuals with normal BMI. HOMA-IR is a readily available measure that can be used in the future to predict mortality in clinical or epidemiological settings. The distinction between the implications of elevated HOMA-IR in subjects with normal BMI versus elevated BMI deserves further investigation and may shed light on the pathophysiology of insulin resistance and its consequences.

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