Insulin Resistance and Risk of Cardiovascular Disease in Postmenopausal Women

A Cohort Study From the Women’s Health Initiative

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Background—Insulin resistance is associated with diabetes mellitus, but it is uncertain whether it improves cardiovascular disease (CVD) risk prediction beyond traditional cardiovascular risk factors.

Methods and Results—We identified 15,288 women from the Women’s Health Initiative Biomarkers studies with no history of CVD, atrial fibrillation, or diabetes mellitus at baseline (1993–1998). We assessed the prognostic value of adding fasting serum insulin, HOMA-IR (homeostasis model assessment–insulin resistance), serum triglyceride-to-serum-high-density lipoprotein-cholesterol ratio TG/HDL-C, or impaired fasting glucose (serum glucose ≥110 mg/dL) to traditional risk factors in separate Cox multivariable analyses and assessed risk discrimination and reclassification. The study end point was major CVD events (nonfatal and fatal coronary heart disease and ischemic stroke) within 10 years, which occurred in 894 (5.8%) women. Insulin resistance was associated with CVD risk after adjusting for age and race/ethnicity with hazard ratios (95% confidence interval [CI]) per doubling in insulin of 1.21 (CI, 1.12–1.31), in HOMA-IR of 1.19 (CI, 1.11–1.28), in TG/HDL-C of 1.35 (CI, 1.26–1.45), and for impaired fasting glucose of 1.31 (CI, 1.05–1.64). Although insulin, HOMA-IR, and TG/HDL-C remained associated with increased CVD risk after adjusting for most CVD risk factors, none remained significant after adjusting for HDL-C: hazard ratios for insulin, 1.06 (CI, 0.98–1.16); for HOMA-IR, 1.06 (CI, 0.98–1.15); for TG/HDL-C, 1.11 (CI, 0.99–1.25); and for glucose, 1.20 (CI, 0.96–1.50). Insulin resistance measures did not improve CVD risk discrimination and reclassification.

Conclusions—Measures of insulin resistance were no longer associated with CVD risk after adjustment for high-density lipoprotein-cholesterol and did not provide independent prognostic information in postmenopausal women without diabetes mellitus.

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Key Words: coronary heart disease ■ insulin resistance ■ ischemic stroke ■ women
Individuals with insulin resistance require increasing levels of insulin to maintain normal glucose levels and are likely to progress to type 2 diabetes mellitus. Insulin resistance is often measured by using the homeostasis model assessment—insulin resistance (HOMA-IR) equation, which is a function of the product of fasting insulin and glucose levels. Fasting insulin levels are the major indicator of insulin resistance and are increased by obesity and decreased with higher degree of physical activity. Despite the potential advantages of measures of insulin resistance, the prognostic value of such measurements has not been extensively evaluated. Estimation of insulin resistance using either levels of insulin, HOMA-IR, glucose, or the ratio of triglycerides and high-density lipoprotein-cholesterol (TG/HDL-C) could potentially improve on cardiovascular risk stratification.

We hypothesized that among postmenopausal women without existing CVD or diabetes mellitus, measures of insulin resistance (eg, serum insulin and HOMA-IR) would improve CVD risk predictions based solely on traditional CVD risk factors. Secondarily, we hypothesized that in a clinical setting, insulin level may be a more easily interpretable measure of insulin resistance and that levels of physical activity and body mass index (BMI) might modify the predictive value of insulin resistance as a risk marker.

Methods

Study Population

The Women’s Health Initiative (WHI, 1993–2005) study and its Extension Study (2005–2010) recruited a large, multiethnic cohort of postmenopausal women aged 50 to 79 years at baseline between 1993 and 1998. The WHI included 3 clinical trial cohorts (ie, women enrolled in either or both a low-fat diet intervention or 1 of 2 trials of menopausal hormone therapies, many of whom also participated in a trial of calcium–vitamin D supplementation) and an observational study cohort. Biomarker data, including fasting insulin levels, were measured in 2 clinical trial subcohorts: the SNP Health Association Resource cohort (SHARE; n=11,967) and the European American Hormone Trial subcohort (EA HT; n=10,161). The SHARE CVD biomarkers study comprised African American and Hispanic participants from either the clinical trials or observational study cohorts, whereas the EA HT CVD biomarkers study primarily comprised white women from the menopausal hormone therapy trials. The scientific rationale, study design, eligibility criteria, and baseline characteristics of patients enrolled in these studies have been reported. The same clinical inclusion and exclusion criteria were applied to the SHARE and EA HT subcohorts. Data collection procedures were similar in the entire WHI; thus, variables are defined and measured similarly in the clinical subcohorts. The WHI studies were approved by an institutional review committee at each participating center, and all participants gave written informed consent.

For the present study, we included all women with available measures of insulin resistance: insulin, glucose, triglycerides, and high-density lipoprotein-cholesterol (HDL-C). Consistent with the recent ACC/AHA atherosclerotic cardiovascular disease (ASCVD) risk assessment guideline, we excluded women with a previous history of myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass surgery, heart failure, or atrial fibrillation at entry. We also excluded women with diabetes mellitus at baseline, defined as either self-reported medical history of diabetes mellitus, or treatment with glucose-lowering agents, or a fasting plasma glucose level ≥126 mg/dL (≥7.0 mmol/L). Further, we excluded women who provided data only at baseline and women who were underweight (BMI<18.5 kg/m²), the latter because of insufficient numbers for reasonable comparisons. We could not determine whether women who were missing BMI were underweight, so all women with missing BMI were excluded from the eligible cohort. From this eligible cohort, we further excluded women with missing data on pertinent variables (age, smoking, total cholesterol, systolic blood pressure, treatment with antihypertensive agents, race/ethnicity, and hormone use).

Primary End Point

The primary end point was time to first major CVD event defined as nonfatal myocardial infarction, fatal coronary heart disease (CHD), and nonfatal and fatal ischemic stroke within 10 years of enrollment in accordance with the ASCVD risk model. These outcomes were identified by means of annual mailed questionnaires (semiannual for clinical trials, response rates >95%). Physicians blinded to exposure data adjudicated all self-reported events locally, with subsequent central adjudication by use of medical records and standard criteria. Nonfatal myocardial infarction was defined using standardized criteria for electrocardiographic changes, elevated cardiac enzymes, or both. Ischemic stroke was defined as rapid onset of persistent neurological deficit lasting >24 hours and attributed to occlusion of cerebral or precerebral arteries with infarction without any other cause; only nonfatal stroke events requiring hospitalization were included. Fatal CVD was confirmed by documentation in hospital, autopsy reports, or listed as the cause of death on death certificates with evidence of previous CVD. The participants were followed until first CVD diagnosis, death from any cause, completion of 10 years of follow-up, or loss to follow-up before 10 years (last visit used as last date of follow-up with no determination of the primary end point after this point).

Risk Factors

Each study participant had a baseline clinic visit during which she completed self-administered questionnaires on medical history, smoking, diet, physical activity, and other lifestyle-related factors and had blood pressure, weight, and height measured. Additionally, all women from the biomarkers studies had blood samples drawn after a 12-hour fast. All analyses in the study population were done on serum by the University of Minnesota Medical Center laboratory.
Insulin Resistance

Insulin was measured using the sandwich immunoassay method (Roche Diagnostics) on Roche Elecsys 2010 Analyzer, and glucose was measured using the Gluco-quant Glucose/Hexokinase Reagent (Roche) on Roche Modular P Chemistry Analyzer. We defined impaired fasting glucose as glucose levels between ≥110 and <126 mg/dL (≥6.1 to <6.7 mmol/L) and calculated HOMA-IR as insulin levels (pmol/L)xglucose levels (mg/dL)/(6.945x405), which is equivalent to insulin levels (μU/mL)xglucose (mmol/L)/22.5.6

Statistical Analyses

Characterizing Associations With CVD

We constructed several plots with nonparametric smoothers to display the relationship between measures of insulin resistance, and BMI and physical activity. Women with missing data on physical activity were excluded from these analyses (n excluded =20). The smoothed fits were created using a generalized additive model. We summarized the incidences of CVD using Kaplan–Meier curves, stratified by categories of insulin levels, HOMA-IR, TG/HDL-C, and glucose. We separately assessed the contribution of each measure of insulin resistance to the traditional cardiovascular risk factors (age, smoking status [current or not], treatment with antihypertensive agents [current or not], systolic blood pressure, total cholesterol, HDL-C, and race/ethnicity) using Cox proportional hazards models, adjusting incrementally for these risk factors to assess the pattern of how the hazard ratios (HRs) changed depending on the traditional risk factors included in the models.16 The 4 models fit for each measure of insulin resistance adjusted for (1) age and race/ethnicity; (2) all risk factors except HDL-C; (3) all risk factors; and (4) age, race/ethnicity, and HDL-C. Because levels of insulin, HOMA-IR, and TG/HDL-C were not normally distributed, we transformed insulin, HOMA-IR, and TG/HDL-C on the logarithmic scale using a base of 2 in all analyses that used the measures as continuous variables. All correlations were assessed using Pearson correlations. The models were stratified by Hormone Trial study arm and hysterectomy history and adjusted for hormone use at baseline because stratification allowed us to control for hormone therapy and hysterectomy, which are potential confounders. Specifically, we modeled 6 strata and fitted a single Cox model that allowed the baseline hazard function to vary across the 6 strata. The HRs estimated from this model were thus adjusted for the study arm and hysterectomy status. The proportional hazards assumption was assessed by visual examination of Schoenfeld residual plots. Additional analyses investigated whether the associations were consistent across race/ethnicity, BMI, and physical activity levels (n excluded from the latter analysis =20) through the use of interaction terms.

Assessing Discriminative Ability of Insulin Measures Beyond Traditional Risk Factors

In addition to the HRs, we also present the corresponding c-indices to compare discriminative ability across models.17 We made use of additional measures of model discrimination derived from Cox proportional hazards models. The integrated discrimination improvement (IDI) estimates the net change in sensitivity and specificity, and the net reclassification improvement (NRI) estimates the net correct upwards and downwards reclassification. For calculation of the NRI, we used the 10-year risk categories of very low (≤5%), low (5 to <7.5%), and elevated (≥7.5%) risk corresponding to the thresholds for treatment with statins in the most recent AHA/ACC guidelines.1 According to the guidelines, treatment with moderate-to-high-intensity statin treatment is a class IA recommendation in individuals with a 10-year CVD risk of ≥7.5% and only recommended in selected individuals with a 10-year CVD risk ≤5%. Confidence intervals for the c-indices, IDI, and NRI were calculated using 1000 bootstrap iterations. We considered a measure of insulin resistance useful if we observed an increment of 0.05 in c-indices or correct reclassification of individuals according to the levels (NRI).18 More information on the c-index, NRI, and IDI statistics for time-to-event data can be found in Pencina et al.19,20

Subanalyses

The main end point was a composite of CHD and ischemic stroke, and we therefore conducted analyses for the 2 separate outcomes in sensitivity analyses, that is, first CHD event and first ischemic stroke. In main analyses, we excluded 306 women with missing data on pertinent variables. We therefore repeated all analyses using imputed data using predictive mean matching to perform multiple imputations for the pertinent variables with missing data.

Most analyses were performed with SAS software, Version 9.3, (SAS Institute, Inc., Cary, North Carolina). R 3.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for c-indices and figures.

Results

Biomarker data were available for 22 128 WHI participants, 6840 of whom met exclusion criteria, primarily baseline CVD and diabetes mellitus (Figure I in the Data Supplement), yielding a final sample of 15 288 postmenopausal women. The median age of the analytic cohort was 64 years (25th–75th percentiles 58–69 years).

Insulin levels and HOMA-IR levels were strongly correlated with one another (r=0.99), and ≤5% of women had elevated levels of insulin without elevated HOMA-IR or vice versa. In contrast, glucose levels were more weakly correlated with insulin levels (r=0.41), HOMA-IR (r=0.54), and TG/HDL-C (r=0.22). Insulin resistance (insulin ≥42 pmol/L) was more common among younger, obese, and black women (Table). Additionally, more women with insulin resistance had hypertension, reported lower physical activity, and had higher glucose levels and more deleterious lipid profiles, with lower HDL-C, as well as higher levels of triglycerides and low-density lipoprotein-cholesterol. The levels of insulin, HOMA-IR, TG/HDL-C, and glucose decreased with increasing level of physical activity and increased with increasing BMI category (Figure II in the Data Supplement).

Associations With CVD

Over a mean follow-up of 9.2 years (standard deviation 1.9 years), there were 894 first CVD events (5.8%) and an incidence rate of 6.4 events/1000 person-years, including 585 CHD events (28 fatal) and 313 ischemic strokes (12 fatal); 4 women had a CHD event and an ischemic stroke on the same day and were counted as having one major CVD event. Women with insulin resistance had higher incidence of CVD irrespective of measure (Figure 1), and each measure of insulin resistance was significantly associated with risk of CVD after adjusting for age and race/ethnicity (Figure 2). Even though insulin levels, HOMA-IR, and TG/HDL-C were significantly associated with increased risk of CVD after adjusting for the majority of cardiovascular risk factors, none of these measures remained significantly associated with CVD risk after adjusting for HDL-C level (Figure 2).

Measures of insulin resistance were also correlated with both physical activity and BMI levels; however, there were no significant statistical interactions between insulin resistance and either BMI or physical activity (P for interactions >0.1) for CVD. Similarly, race/ethnicity did not modify the results (P for interaction >0.05 in all analyses).

Assessing Discriminative Ability of Insulin Measures Ability Beyond Traditional Risk Factors

The prognostic model including all traditional CVD risk factors had a c-index of 0.710, which was essentially unchanged...
by the addition of any of the insulin resistance measures (Figure 3). In simpler models with fewer variables, insulin levels, HOMA-IR, and TG/HDL-C added some degree of discriminative ability. Addition of glucose levels to any of the models did not increase the c-index substantially. Insulin levels, HOMA-IR, and TG/HDL-C still added prognostic information, albeit weak, after adjusting for all traditional risk factors, except HDL-C. However, none of the measures added significant discriminative ability to a model including only age, race/ethnicity, and HDL-C (c-index=0.669): the changes in c-indices were between 0.001 and 0.002, with all 95% confidence intervals (CI) contained in the interval (–0.001 to 0.005).

Measures of reclassification (NRI) for the full model were small in magnitude and not significant. For insulin levels, NRI was 0.004 (CI −0.012 to 0.023), with 79 women being appropriately reclassified (6 women with events, 73 women without events) and 83 being inappropriately reclassified (2 women with events, 81 women without events). For HOMA-IR, the NRI was 0.002 (CI −0.015 to 0.019) with 63 appropriate reclassifications (4 with events, 59 without events) and 67 inappropriate reclassifications (2 with events, 65 without events). For TG/HDL-C, the NRI was 0.012 (CI 0.000–0.041) with 217 appropriate reclassifications (18 with events, 199 without events) and 221 inappropriate reclassifications (6 with events, 215 without events). Finally, for glucose, NRI was −0.003 (CI −0.023 to 0.008) with 80 appropriate (3 with events, 77 without events) and 86 inappropriate reclassifications (6 with events, 80 without events).

The IDIs were correspondingly small, and none were statistically significant: IDI was 0.000 for insulin levels, 0.000 for HOMA-IR, 0.000 for TG/HDL-C, and 0.000 for glucose, with all of the CIs contained in the interval (−0.001 to 0.001).

### Sensitivity Analyses and Other Analyses

In analyses examining the associations between insulin resistance and risk of CHD and ischemic stroke separately, we...
found that our results were primarily driven by CHD risk (Figure III in the Data Supplement).

In analyses using multiple imputations for missing data on pertinent variables (n=306), the population comprised 15,594 women. In accordance with our main results, none of the measures were statistically significantly associated with risk of CVD in the fully adjusted analyses, nor did the insulin resistance measures improve the c-statistics of the model: the difference in c-statistics for all 4 measures of insulin resistance were <0.001 (Table I in the Data Supplement).

Discussion

In this large cohort study, measures of insulin resistance were significantly associated with increased risk of CVD after resistance measures improve the c-statistics of the model: the difference in c-statistics for all 4 measures of insulin resistance were <0.001 (Table I in the Data Supplement).

Figure 1. Kaplan–Meier CVD-free survival curves according to normal/excessive absolute levels of insulin (A), HOMA-IR (B), glucose (C), and TG/HDL (D). Excessive levels of insulin (n=8721), HOMA-IR (n=8876), and TG-HDL-C (n=6129) defined as the 75th percentiles among normal weight women in the Women’s Health Initiative (WHI) and ≥110 mg/dL for impaired fasting glucose (n=1107). CVD indicates cardiovascular disease; HOMA-IR, homeostasis model assessment-insulin resistance; and TG/HDL-C, triglycerides-to-high-density lipoprotein-cholesterol ratio.

Figure 2. HRs for development of cardiovascular disease (CVD) for insulin, HOMA-IR, and TG/HDL, based on a model using log base 2 transformation for each variable. The HRs for the log-transformed measures can be interpreted as the increase in CVD risk associated with a 2-fold increase in the predictor variable (insulin, HOMA-IR, TG/HDL-C). The HR for glucose is based on the categories of impaired fasting glucose (>110 mg/dL) or not. The HR and CI in the TG/HDL-C models adjusting for HDL-C are colored blue to indicate that the interpretation of these HRs are not intuitive as HDL-C is part of the model. *Risk factors: age, race/ethnicity, smoking, total cholesterol, HDL-C, systolic blood pressure, and treatment with antihypertensive agents. BMI indicates body mass index; CI, 95% confidence interval; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; and TG/HDL-C, triglycerides-to-high-density lipoprotein-cholesterol ratio.
adjusting for age and race/ethnicity, yet measures of insulin resistance did not provide additional prognostic information beyond that conveyed by traditional cardiovascular risk factors. In particular, measures of insulin resistance appeared to add little prognostic information once HDL-C levels were considered. Most prior studies have also found that insulin resistance is associated with weakly to moderately increased risk of CVD, yet the results of fully adjusted analyses have been inconsistent. Most prior studies were smaller than the present one and had shorter follow-up periods.

Complex metabolic pathways leading to development of CVD include several measures that are linked to one another pathophysiologically and highly correlated statistically. In such settings, most of the prognostic information may be captured by one measure, such that the remaining factors in the pathway do not provide additional prognostic information. For instance, obesity is clearly important in development of CVD; yet obesity provides little additional prognostic information once hypertension, lipid abnormalities, and diabetes mellitus are taken into account. Similarly, we find that although measures of insulin resistance are associated with CVD risk when considered alone, these associations are greatly attenuated after accounting for traditional risk factors, particularly HDL-C. Statistical measures of association, discrimination, and risk classification accuracy assess risk prediction and do not necessarily address the possible causal role of insulin resistance in the development of CVD. Other types of studies might help to disentangle the effects of insulin resistance and factors correlated with it; Mendelian randomization studies may be useful in assessing causality, and interventions that directly target insulin resistance could be tested to determine whether they reduce the incidence of CVD.

Insulin resistance seems to be mechanistically important in CVD development and is associated with impaired fasting glucose, hypertension, inflammation, dyslipidemia, hypertriglyceridemia, and endothelial dysfunction, all of which augment cardiovascular risk. Insulin resistance is associated with decreased levels of HDL-C and hypertriglyceridemia. Despite recent findings suggesting that HDL-C per se may not be causally related to CHD, it is a key risk factor because of its strong association with CHD and the widespread availability of a standardized assay. The associations between HDL-C and CHD risk may not be causal because it may be confounded by apolipoprotein and atherogenic lipoprotein concentrations, or modified by the presence of insulin resistance. It may be a reliable marker of a harmful risk profile, for example, physical inactivity, poor diet, smoking, and insulin resistance. From a practical standpoint, HDL-C is relatively stable with less intrapatient variability than insulin levels, and assays for HDL-C levels are widely available and standardized, whereas assays for insulin are neither widely available nor well standardized. Finally, measurement of HDL-C is standard for CVD risk assessment because it is used to calculate both low-density lipoprotein-cholesterol and non-HDL-C. For all of these reasons, existing measures of insulin resistance are currently less useful for clinical application. Because insulin levels and HOMA-IR are highly correlated with one another (r=0.99), it is not surprising that they had essentially identical associations with CVD in women without diabetes mellitus. As such, insulin levels may be simpler to interpret than HOMA-IR, and further, most variation in HOMA-IR is as a result of variation in insulin levels, not glucose levels, particularly among women without diabetes mellitus. The limited value of fasting glucose in postmenopausal women without diabetes mellitus or prior CVD was further evident from the wide confidence intervals in Figure 2.

The reference model had a c-index of 0.71, which corresponds to the c-statistics of the Framingham risk model, which had c-statistics of 0.63 to 0.79 when validated in
various cohorts. This validation is comparable to the results of the present study, in which we used the variables from the ASCVD model because the risk factors in the ASCVD model are identical to the Framingham risk score aside from race/ethnicity as an additional variable.

**Strengths and Limitations**

This large, multiethnic study is unique in terms of its prospectively collected data with CHD and stroke as end points that have been adjudicated in the original trials, the long follow-up, and available fasting measures of insulin levels, glucose levels, and lipids for over 15,000 postmenopausal women without CVD or diabetes. Nevertheless, there are several important limitations to this study. First, the WHI included only postmenopausal women; thus, our results may not be generalizable to younger women or to men. Further research is therefore warranted to evaluate whether insulin resistance has a role in CVD risk prediction in populations other than postmenopausal women. Second, we excluded strokes that could not be classified as ischemic or hemorrhagic, resulting in possible omission of maximum 71 ischemic strokes from the analyses. Third, menopausal hormone therapy increases HDL-C and triglycerides and decreases fasting insulin levels, which should be taken into account when interpreting the results. Nonetheless, a study from the WHI suggested that the changes induced by hormone therapy were not associated with future risk of CHD. Finally, although the IDI is less affected by the strength of the baseline model than the c-index, the IDI is less stable and might overestimate the discriminative ability of the predictor in populations with an event rate <5%. Despite the ongoing debate about the NRI and IDI, there is general consensus in the literature that model discrimination is best measured with NRI and IDI in conjunction with the c-index.

By design, this study omitted women with frank diabetes mellitus, which may have led us to underestimate the prognostic value of measures of insulin resistance. Diabetes mellitus is known to be a strong adverse prognostic factor, and because treatment with statins and aggressive treatment of additional cardiovascular risk factors is highly recommended for all individuals with diabetes mellitus, we felt that clinical decision about initiation of statins or use of blood pressure lowering drugs would not be altered by calculated risk scores. Furthermore, measures of insulin resistance might have been altered by drug treatment of women with clinically evident diabetes mellitus. The findings of this study apply only to women without diabetes mellitus.

In conclusion, insulin levels, HOMA-IR, glucose, and the ratio of triglycerides to HDL-C were associated with increased risk of CVD in postmenopausal women in analyses that adjusted only for age and race/ethnicity. However, none of these measures of insulin resistance provided additional prognostic information beyond that of traditional cardiovascular risk factors, in particular beyond HDL-C. Although insulin resistance may be important in the pathophysiology of atherosclerosis, the information provided by measures of insulin resistance appeared to be captured by the traditional cardiovascular risk factors in healthy, postmenopausal women.

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**Disclosures**

R. H. Mackey has received speaker honoraria from the National Lipid Association for educational (nonpromotional) activities. The other authors report no conflicts.

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/8/3/309

Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2015/05/05/CIRCOUTCOMES.114.001563.DC1
SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLE 1: C-statistics and improvement in c-statistics without and with imputations

SUPPLEMENTAL FIGURE 1: Flow-chart

SUPPLEMENTAL FIGURE 2: The estimates of the group means of A) fasting insulin, B) HOMA-IR, C) TG/HDL and D) fasting glucose according to physical activity levels and stratified by BMI-categories.

SUPPLEMENTAL FIGURE 3: HRs of A) coronary heart disease and B) ischemic stroke per two-fold increase in insulin, HOMA-IR and TG/HDL (based on a model using a log base 2 transformation), and for impaired fasting glucose (yes/no) with stepwise adjustment for traditional cardiovascular risk factors.

SUPPLEMENTAL ACKNOWLEDGEMENTS: Acknowledgement of the Women’s Health Initiative (WHI) investigators
## SUPPLEMENTAL TABLE 1: C-statistics and improvement in c-statistics without and with imputations

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*Risk factors: Age, race/ethnicity, smoking, total cholesterol, HDL-C, systolic blood pressure, treatment with antihypertensive agents

HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides
SUPPLEMENTAL FIGURE 1, FLOW-CHART

SHARe CVD Biomarkers Study  
n=11,967

EA HT Biomarkers Study  
n=10,161

Biomarker studies  
n=22,128

Eligible cohort  
n=16,102

Met exclusion criteria (n=6,534):
- History of MI, heart failure, stroke, Afib or coronary revascularization (n=1,885)
- Could not exclude history of MI (n=11), heart failure (n=1,364), stroke (n=5), atrial fibrillation (n=464) or coronary revascularization (n=421)
- No data on diabetes status (n=29)
- History of diabetes or fasting-glucose > 126 mg/dL (n=3,101)
- Underweight (BMI<18.5 kg/m²; n=115)
- No data on BMI or BMI>70 kg/m² (n=162)
- No follow-up data (n=13)
- No data on insulin (n=686), glucose (n=2), triglycerides (n=3) or HDL-cholesterol (n=4)

Missing data on pertinent variables (n=306): hypertension (n=101), smoking (n=206) and hormone use (n=12)

Analytic cohort  
n=15,288
Supplemental Figure 2. The estimates of the group means of A) fasting insulin, B) HOMA-IR, C) TG/HDL and D) fasting glucose according to physical activity levels and stratified by BMI-categories. The shaded gray region around the line gives the 95% confidence band, the standard error, for the mean. The red dotted lines represent the cut-offs: the 75th percentiles among normal weight women in the WHI for insulin (42 pmol/L), HOMA-IR (1.37), and TG/HDL-C (2.48), and ≥110 mg/dL for impaired fasting glucose.
SUPPLEMENTAL FIGURE 3

A) Coronary heart disease

Model adjusted for: HR (95% CI)

**Insulin**
- Age + race/ethnicity: 1.26 (1.15-1.38)
- All risk factors* except HDL-C: 1.20 (1.09-1.32)
- All risk factors*: 1.06 (0.96-1.18)
- Age + race/ethnicity + HDL-C: 1.10 (1.00-1.22)

**HOMA–IR**
- Age + race/ethnicity: 1.23 (1.13-1.34)
- All risk factors* except HDL-C: 1.17 (1.07-1.28)
- All risk factors*: 1.04 (0.95-1.15)
- Age + race/ethnicity + HDL-C: 1.09 (0.99-1.19)

**Glucose**
- Age + race/ethnicity: 1.28 (0.97-1.68)
- All risk factors* except HDL-C: 1.12 (0.85-1.47)
- All risk factors*: 1.05 (0.80-1.39)
- Age + race/ethnicity + HDL-C: 1.16 (0.88-1.53)

**TG/HDL-C**
- Age + race/ethnicity: 1.40 (1.29-1.53)
- All risk factors* except HDL-C: 1.28 (1.17-1.40)
- All risk factors*: 0.96 (0.82-1.13)
- Age + race/ethnicity + HDL-C: 1.19 (1.03-1.36)

B) Ischemic stroke

Model adjusted for: HR (95% CI)

**Insulin**
- Age + race/ethnicity: 1.11 (0.98-1.26)
- All risk factors* except HDL-C: 1.06 (0.93-1.21)
- All risk factors*: 0.94 (0.81-1.08)
- Age + race/ethnicity + HDL-C: 0.97 (0.85-1.12)

**HOMA–IR**
- Age + race/ethnicity: 1.11 (0.99-1.25)
- All risk factors* except HDL-C: 1.06 (0.94-1.20)
- All risk factors*: 0.95 (0.83-1.08)
- Age + race/ethnicity + HDL-C: 0.99 (0.87-1.12)

**Glucose**
- Age + race/ethnicity: 1.22 (0.84-1.78)
- All risk factors* except HDL-C: 1.12 (0.77-1.63)
- All risk factors*: 1.05 (0.72-1.53)
- Age + race/ethnicity + HDL-C: 1.13 (0.77-1.65)

**TG/HDL-C**
- Age + race/ethnicity: 1.27 (1.13-1.43)
- All risk factors* except HDL-C: 1.20 (1.06-1.35)
- All risk factors*: 0.87 (0.70-1.08)
- Age + race/ethnicity + HDL-C: 1.01 (0.83-1.22)
SUPPLEMENTAL FIGURE 3. HRs of A) coronary heart disease and B) ischemic stroke per two-fold increase in insulin, HOMA-IR and TG/HDL (based on a model using a log base 2 transformation), and for impaired fasting glucose (yes/no) with stepwise adjustment for traditional cardiovascular risk factors. The HR and 95%CI in the TG/HDL-C models adjusting for HDL-C are colored blue to indicate that the interpretation of these HRs are not intuitive as HDL-C is part of the model.

*Risk factors: Age, race/ethnicity, smoking, total cholesterol, HDL-C, systolic blood pressure, treatment with antihypertensive agents
BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; HR, hazard ratio; TG/HDL-C, triglycerides/high-density lipoprotein-cholesterol
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*For a list of all the investigators who have contributed to WHI science, please visit:*

https://cleo.whi.org/researchers/SitePages/Write%20a%20Paper.aspx