# Association Between Insulin Resistance and Cardiovascular Disease Risk Varies According to Glucose Tolerance Status: A Nationwide Prospective Cohort Study

Diabetes Care 2022;45:1863–1872 | https://doi.org/10.2337/dc22-0202

Tiange Wang,[1,2] Mian Li,[1,2] Tianshu Zeng,[3] Ruying Hu,[4] Yu Xu,[1,2] Min Xu,[1,2] Zhiyun Zhao,[1,2] Yuhong Chen,[1,2] Shuangyuan Wang,[1,2] Hong Lin,[1,2] Xuefeng Yu,[5] Gang Chen,[6] Qing Su,[7] Yiming Mu,[8] Lulu Chen,[3] Xulei Tang,[9] Li Yan,[10] Guijun Qin,[11] Qin Wan,[12] Zhengnan Gao,[13] Guixia Wang,[14] Feixia Shen,[15] Zuojie Luo,[16] Yingfen Qin,[16] Li Chen,[17] Yanan Huo,[18] Qiang Li,[19] Zhen Ye,[4] Yinfei Zhang,[20] Chao Liu,[21] Youmin Wang,[22] Shengli Wu,[23] Tao Yang,[24] Huacong Deng,[25] Jiajun Zhao,[26] Lixin Shi,[27] Guang Ning,[1,2] Yufang Bi,[1,2] Weiqing Wang,[1,2] and Jieli Lu[1,2]

## OBJECTIVE

**To investigate whether the association between insulin resistance and cardiovascular disease (CVD) differs by glucose tolerance status.**

## RESEARCH DESIGN AND METHODS

**We analyzed a nationwide sample of 111,576 adults without CVD at baseline, using data from the China Cardiometabolic Disease and Cancer Cohort Study. Insulin resistance was estimated by sex-specific HOMA of insulin resistance (HOMA-IR) quartiles for participants with normal glucose tolerance, prediabetes, or diabetes, separately, and by 1 SD of HOMA-IR for the overall study participants. We used Cox proportional hazards models to examine the association between insulin resistance and incident CVD according to glucose tolerance status and evaluate the CVD risk associated with the combined categories of insulin resistance and obesity in prediabetes and diabetes, as compared with normal glucose tolerance. Models were adjusted for age, sex, education attainment, alcohol drinking, smoking, physical activity, and diet quality.**

## RESULTS

**In participants with normal glucose tolerance, prediabetes, and diabetes defined by three glucose parameters, multivariable-adjusted hazard ratios (95% CIs) for incident CVD associated with the highest versus the lowest quartile of HOMA-IR were 1.03 (0.82–1.30), 1.23 (1.07–1.42), and 1.61 (1.30–2.00), respectively; the corresponding values for CVD per 1-SD increase in HOMA-IR were 1.04 (0.92–1.18), 1.12 (1.06–1.18), and 1.15 (1.09–1.21), respectively ($P$ for interaction = 0.011). Compared with participants with normal glucose tolerance, in participants with prediabetes, the combination of the highest HOMA-IR quartile and obesity showed 17% (95% CI 2–34%) higher risk of CVD, while the combination of the lowest two HOMA-IR quartiles and nonobesity showed 15–17% lower risk of CVD. In participants with diabetes, the upper two HOMA-IR quartiles exhibited 44–77% higher risk of CVD, regardless of obesity status. Consistent findings were observed for glucose tolerance status defined by different combinations of glycemic parameters.**

## CONCLUSIONS

**Glucose intolerance status exacerbated the association between insulin resistance and CVD risk. Compared with adults with normal glucose tolerance, adults with prediabetes who were both insulin resistant and obese exhibited higher risks of CVD, while in adults with diabetes, the CVD risk related to insulin resistance remained, regardless of obesity.**

[1]Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[2]Shanghai National Clinical Research Center for Endocrine and Metabolic Diseases, State Key Laboratory for Endocrine and Metabolic Diseases, State Key Laboratory for Endocrine Tumor, State Key Laboratory for Medical Genomics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[4]Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China
[5]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[6]Fujian Provincial Hospital, Fujian Medical University, Fuzhou, China
[7]Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
[8]Chinese People's Liberation Army General Hospital, Beijing, China
[9]The First Hospital of Lanzhou University, Lanzhou, China
[10]Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
[11]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[12]The Affiliated Hospital of Southwest Medical University, Luzhou, China
[13]Dalian Municipal Central Hospital, Dalian, China

Insulin resistance, characterized by defects in insulin-mediated glucose metabolism regulation in tissues such as the liver, skeletal muscle, and adipose tissue, is one of the earliest manifestations of a constellation of cardiometabolic diseases that include type 2 diabetes and cardiovascular disease (CVD) (1,2). Hyperglycemia occurs when the pancreas fails to supply excess insulin to compensate for the increasing insulin resistance, progressing to prediabetes and diabetes (3). Previous evidence suggests that insulin resistance and its biologic effects in various tissues are more essential factors than hyperglycemia in inducing cardiometabolic complications (2,4), and individuals with insulin resistance, even without diabetes, are predisposed to an increased risk of CVD (5,6). Nevertheless, the close interplay between insulin resistance and hyperglycemia suggests that the two factors may synergistically regulate the development of CVD (2). Thus far, it remains unclear whether and in what pattern the association between insulin resistance and CVD risk varies depending on glucose tolerance status.

In addition, obesity is closely related to insulin resistance; together, they contribute to the risk of multiple cardiometabolic diseases (7). Our previous study demonstrated that in Chinese adults whose β-cell dysfunction was a common metabolic disturbance, the impact of insulin resistance on diabetes was strengthened in those with obesity, suggesting that obesity-modulated insulin resistance might be responsible, at least in part, for the recent diabetes epidemic in the Chinese population (8). Another important question is whether obesity modifies the association between insulin resistance and CVD risk in individuals with glucose intolerance, such as prediabetes and diabetes.

To this end, in a nationwide prospective cohort study, we investigated the association between insulin resistance and incident CVD according to normal glucose tolerance, prediabetes, and diabetes and the joint association of insulin resistance and obesity with the risk of CVD in those with prediabetes and diabetes compared with the risk of CVD in those with normal glucose tolerance. Specifically, taking advantage of comprehensive measures of fasting and postload glucose and glycated hemoglobin $A_{1c}$ ($HbA_{1c}$), we assessed glucose tolerance status by different combinations of glycemic parameters based on the American Diabetes Association (ADA) 2010 criteria.

## RESEARCH DESIGN AND METHODS

### Study Design and Participants

The China Cardiometabolic Disease and Cancer Cohort Study is a nationwide population-based prospective cohort study (8–10). The baseline survey was conducted between 2011 and 2012. Twenty communities were selected according to geographic region (Northeast, North, East, South Central, Northwest, and Southwest China), degree of urbanization (large and midsize cities, county seats, and rural townships), and economic development status (by gross domestic product of each province) in China. From local resident registration systems of the 20 communities, 193,846 men and women aged 40 years or older were recruited to represent the general population. The follow-up visit was conducted between 2014 and 2016, and all participants were invited to attend an in-person follow-up visit. Of 170,240 participants with follow-up data available, we excluded 11,590 participants with CVD at baseline, 12,552 participants taking hypoglycemic pharmacologic therapy, including oral diabetes medications, glucagon-like peptide 1 receptor agonist, and insulin, 15,504 participants with missing data on baseline HOMA of insulin resistance (HOMA-IR) index or glucose tolerance status, and 19,018 participants whose information on ascertainment of incident CVD during follow-up was not available. Finally, 111,576 participants were included in the main analyses. Key characteristics between study participants and participants who were excluded because of missing data were not substantially different (Supplementary Table 1). This study was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China. All study participants provided written informed consent.

### Data Collection

At baseline and follow-up visits, data collection was performed in local community clinics by trained study personnel following standardized protocols. Standardized questionnaires were used to collect information on demographic characteristics, education, medical history, and lifestyle factors. Educational attainment was classified as less than high school ($<$9 years) or high school or further ($\geq$9 years). Alcohol drinking and smoking status were categorized as never, former, or current. The International Physical Activity Questionnaire was used to assess leisure-time physical activity, and metabolic equivalent task (MET) was calculated to evaluate average weekly energy expenditure (11). Leisure-time

[14]The First Hospital of Jilin University, Changchun, China
[15]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[16]The First Affiliated Hospital of Guangxi Medical University, Nanning, China
[17]Qilu Hospital of Shandong University, Jinan, China
[18]Jiangxi Provincial People's Hospital Affiliated to Nanchang University, Nanchang, China
[19]The Second Affiliated Hospital of Harbin Medical University, Harbin, China
[20]Central Hospital of Shanghai Jiading District, Shanghai, China
[21]Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing, China
[22]The First Affiliated Hospital of Anhui Medical University, Hefei, China
[23]Karamay Municipal People's Hospital, Xinjiang, China
[24]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China
[25]The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[26]Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China
[27]Affiliated Hospital of Guiyang Medical College, Guiyang, China

Corresponding authors: Jieli Lu, jielilu@hotmail.com, Weiqing Wang, wqingw61@163.com, or Yufang Bi, byf10784@rjh.com.cn

Received 31 January 2022 and accepted 18 April 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.19689160.

T.W., M.L., T.Z., R.H., and Y.X. contributed equally as first authors.

physical activity was categorized as active (≥600 MET-min/week), insufficiently active (1 to <600 MET-min/week), or inactive (0 MET-min/week) (12). A food frequency questionnaire was used to collect habitual dietary intake by asking about the consumption frequency and portion size of typical food items during the previous 12 months. A diet quality score was calculated based on five healthy dietary behaviors: high intake of fruits and vegetables (≥4.5 cups/day), fish (two or more 3.5-oz servings/week), cereal grains (three or more 1-oz servings/day), and soy food (soy protein ≥25 g/day) and low intake of sugar-sweetened beverages (≤450 kcal/week). The healthy score of each dietary behavior was 1; otherwise, it was 0. The scores of each component were summed to obtain a diet quality score ranging from 0 to 5, with a higher score indicating a healthier diet.

Height, body weight, and waist circumference were measured, and BMI was calculated as weight in kilograms divided by the square of height in meters. To facilitate international comparisons, BMI categories were defined as <23.0, 23.0 to <27.5, and ≥27.5 kg/m$^2$ based on the recommendations of the WHO Expert Consultation for Asian populations (13). Obesity was defined as general obesity (BMI ≥27.5 kg/m$^2$) or abdominal obesity (waist circumference ≥90 cm in men and ≥80 cm in women) (13,14). Three measurements of systolic and diastolic blood pressure obtained by an automated electronic device (Model HEM-752 FUZZY; Omron Healthcare, Dalian, China) in a seated position after at least a 5-min quiet rest were averaged for analysis.

All participants underwent a 75-g oral glucose tolerance test (OGTT) after an overnight fast of at least 10 h, and blood samples were collected at 0 and 2 h during the test. Fasting and OGTT 2-h plasma glucose concentrations were measured locally using the glucose oxidase or hexokinase method within 2 h after blood sample collection. Finger capillary whole-blood samples were collected using the Hemoglobin Capillary Collection System (Bio-Rad Laboratories, Hercules, CA) and were shipped and stored at 2–8°C until $HbA_{1c}$ was measured within 4 weeks after collection by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (Bio-Rad Laboratories) at the central laboratory at the Shanghai Institute of Endocrine and Metabolic Diseases, which was certificated by the National Glycohemoglobin Standardization Program and the College of American Pathologists Laboratory Accreditation Program. Fasting serum insulin, serum LDL cholesterol, HDL cholesterol, triglycerides, and total cholesterol were measured at the central laboratory using an automated analyzer (ARCHITECT ci16200; Abbott Laboratories, Chicago, IL).

### Definition of Insulin Resistance and Glucose Tolerance Status

Insulin resistance was evaluated by HOMA-IR index, which was calculated using the following formula: fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405 (15). Sex-specific quartiles of HOMA-IR were defined among participants with normal glucose tolerance, prediabetes, and diabetes, separately. Median values (interquartile ranges) of HOMA-IR in sex-specific quartiles by glycose tolerance status are shown in Supplementary Table 2. The highest quartile of HOMA-IR indicates relative insulin resistance, whereas the lower quartiles indicate relative insulin sensitivity.

We excluded participants with hypoglycemic pharmacologic therapy at baseline and defined glucose tolerance status according to the ADA 2010 criteria (16). Diabetes was defined as fasting glucose ≥126 mg/dL (7.0 mmol/L), 2-h glucose ≥200 mg/dL (11.1 mmol/L), $HbA_{1c}$ ≥6.5%, or a self-reported previous diagnosis of diabetes by a health care professional. In participants without diabetes, normal glucose tolerance was defined as fasting glucose <100 mg/dL (5.6 mmol/L), 2-h glucose <140 mg/dL (7.8 mmol/L), and $HbA_{1c}$ <5.7%; prediabetes was defined as fasting glucose between ≥100 and <126 mg/dL (5.6 and 7.0 mmol/L), 2-h glucose between ≥140 and <200 mg/dL (7.8 and 11.1 mmol/L), or $HbA_{1c}$ between ≥5.7 and <6.5%.

### Ascertainment of Incident CVD

CVD events were a composite of incident nonfatal or fatal CVD, including myocardial infarction, stroke, hospitalized or treated heart failure, or CVD death, whichever occurred first (9). Myocardial infarction was defined as characteristic changes in troponin T and creatine kinase-MB isoform levels, symptoms of myocardial ischemia, changes in electrocardiogram results, or a combination of these. Stroke was defined as a fixed neurologic deficit of at least 24 h with a presumed vascular cause. Heart failure was identified by hospitalization or an emergency department visit requiring treatment with infusion therapy and defined as a clinical syndrome presenting with multiple signs and symptoms consistent with cardiac decompensation or inadequate cardiac pump function. Information on vital status and clinical outcomes was collected from local death and disease registries of the National Disease Surveillance Point System and National Health Insurance System. The Clinical Outcome Adjudication Committee is composed of 10 unbiased experts in cardiology, oncology, neurology, and endocrine and metabolic diseases in Ruijin Hospital, Shanghai Jiao Tong University. All members of the committee were unaware of baseline risk factors of study participants. Two members of the committee independently verified each clinical event and assigned a potential cause of mortality according to a standard clinical outcome adjudication procedure. Discrepancies were adjudicated by discussions involving other members of the committee.

### Statistical Analysis

Baseline characteristics of participants are presented as means with SDs or medians with interquartile ranges for continuous variables and numbers with proportions for categorical variables by HOMA-IR quartiles stratified by glucose tolerance status. In all analyses, the sex-specific HOMA-IR quartiles represented the levels of insulin resistance for participants with normal glucose tolerance, prediabetes, or diabetes, respectively, while the 1 SD of HOMA-IR represented the SD for all study participants. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% CIs for incident CVD associated with sex-specific quartiles or 1 SD of HOMA-IR among overall participants and among participants stratified by glucose tolerance status defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals. Models were adjusted for age, sex, education attainment, alcohol drinking status, smoking status, physical activity, and diet quality score. In the

**Table 1—Baseline characteristics of participants according to HOMA-IR quartiles stratified by glucose tolerance status**

| Characteristic | Sex-specific HOMA-IR quartile* | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Normal glucose tolerance (*n* = 28,890) | | | | |
| Age, years | 53.8 (9.2) | 53.1 (8.9) | 52.9 (8.8) | 52.8 (8.7) |
| Men, *n* (%) | 2,378 (32.9) | 2,381 (33.0) | 2,379 (32.9) | 2,379 (32.9) |
| High school or more education, *n* (%) | 2,123 (29.4) | 2,538 (35.1) | 2,715 (37.6) | 2,978 (41.2) |
| Alcohol drinking status, *n* (%) | | | | |
| Never | 6,138 (85.0) | 6,379 (88.3) | 6,413 (88.8) | 6,475 (89.6) |
| Former | 108 (1.5) | 112 (1.6) | 142 (2.0) | 155 (2.2) |
| Current | 975 (13.5) | 732 (10.1) | 668 (9.3) | 593 (8.2) |
| Smoking status, *n* (%) | | | | |
| Never | 5,615 (77.8) | 5,848 (81.0) | 5,917 (81.9) | 6,002 (83.1) |
| Former | 202 (2.8) | 238 (3.3) | 277 (3.8) | 311 (4.3) |
| Current | 1,404 (19.4) | 1,137 (15.7) | 1,029 (14.3) | 910 (12.6) |
| Physical activity, *n* (%) | | | | |
| Active | 3,928 (54.4) | 4,119 (57.0) | 4,153 (57.5) | 4,131 (57.2) |
| Insufficiently active | 3,010 (41.7) | 2,786 (38.6) | 2,764 (38.3) | 2,771 (38.4) |
| Inactive | 283 (3.9) | 318 (4.4) | 306 (4.2) | 321 (4.4) |
| Dietary quality score | 2.3 (0.7) | 2.3 (0.7) | 2.3 (0.7) | 2.3 (0.7) |
| BMI, kg/m$^2$, *n* (%) | | | | |
| <23.0 | 4,795 (66.4) | 3,683 (51.0) | 2,661 (36.8) | 1,458 (20.2) |
| 23.0 to <27.5 | 2,235 (31.0) | 3,151 (43.6) | 3,779 (52.3) | 3,922 (54.3) |
| ≥27.5 | 191 (2.7) | 389 (5.4) | 783 (10.8) | 1,843 (25.5) |
| Waist circumference, cm, *n* (%) | | | | |
| <90 in men, <80 in women | 5,835 (80.8) | 5,091 (70.5) | 4,203 (58.2) | 2,867 (39.7) |
| ≥90 in men, ≥80 in women | 1,386 (19.2) | 2,132 (29.5) | 3,020 (41.8) | 4,356 (60.3) |
| Fasting glucose, mg/dL | 88.9 (7.4) | 91.2 (6.8) | 92.8 (6.6) | 94.8 (7.5) |
| OGTT 2-h glucose, mg/dL | 101.3 (20.2) | 103.8 (19.6) | 105.8 (19.4) | 108.8 (19.9) |
| $HbA_{1c}$, % | 5.3 (0.3) | 5.3 (0.3) | 5.3 (0.3) | 5.4 (0.3) |
| $HbA_{1c}$, mmol/mol | 34 (3.3) | 34 (3.3) | 34 (3.3) | 36 (3.3) |
| Fasting insulin, μIU/mL | 3.2 (2.5–3.9) | 5.0 (4.5–5.5) | 6.7 (6.1–7.3) | 9.9 (8.7–11.9) |
| HOMA-IR | 0.7 (0.6–0.9) | 1.1 (1.0–1.2) | 1.5 (1.4–1.7) | 2.3 (2.0–2.8) |
| Prediabetes (*n* = 64,972) | | | | |
| Age, years | 57.1 (9.1) | 56.6 (8.6) | 56.4 (8.7) | 56.3 (8.8) |
| Men, *n* (%) | 5,440 (33.5) | 5,439 (33.5) | 5,438 (33.5) | 5,440 (33.5) |
| High school or more education, *n* (%) | 4,733 (29.1) | 5,534 (34.1) | 5,933 (36.5) | 6,291 (38.7) |
| Alcohol drinking status, *n* (%) | | | | |
| Never | 13,822 (85.1) | 14,165 (87.2) | 14,275 (87.9) | 14,473 (89.1) |
| Former | 270 (1.7) | 302 (1.9) | 360 (2.2) | 345 (2.1) |
| Current | 2,152 (13.3) | 1,780 (11.0) | 1,606 (9.9) | 1,422 (8.8) |
| Smoking status, *n* (%) | | | | |
| Never | 12,771 (78.6) | 13,033 (80.2) | 13,362 (82.3) | 13,448 (82.8) |
| Former | 564 (3.5) | 691 (4.3) | 758 (4.7) | 857 (5.3) |
| Current | 2,909 (17.9) | 2,523 (15.5) | 2,121 (13.1) | 1,935 (11.9) |
| Physical activity, *n* (%) | | | | |
| Active | 9,483 (58.4) | 10,023 (61.7) | 10,308 (64.5) | 10,478 (64.5) |
| Insufficiently active | 6,119 (37.7) | 5,570 (34.3) | 5,373 (33.1) | 5,185 (31.9) |
| Inactive | 642 (4.0) | 654 (4.0) | 560 (3.5) | 577 (3.6) |
| Dietary quality score | 2.4 (0.7) | 2.4 (0.8) | 2.3 (0.8) | 2.3 (0.7) |
| BMI, kg/m$^2$, *n* (%) | | | | |
| <23.0 | 9,993 (61.5) | 6,450 (39.7) | 4,047 (24.9) | 2,044 (12.6) |
| 23.0 to <27.5 | 5,585 (34.4) | 8,307 (51.1) | 9,394 (57.8) | 8,577 (52.8) |
| ≥27.5 | 666 (4.1) | 1,490 (9.2) | 2,800 (17.2) | 5,619 (34.6) |
| Waist circumference, cm, *n* (%) | | | | |
| <90 in men, <80 in women | 12,012 (74.0) | 9,575 (58.9) | 7,246 (44.6) | 4,465 (27.5) |
| ≥90 in men, ≥80 in women | 4,232 (26.1) | 6,672 (41.1) | 8,995 (55.4) | 11,775 (72.5) |
| Fasting glucose, mg/dL | 95.6 (9.4) | 99.4 (8.8) | 101.8 (8.8) | 104.9 (9.0) |
| OGTT 2-h glucose, mg/dL | 122.2 (30.5) | 126.1 (29.6) | 129.7 (29.7) | 136.0 (30.0) |
| $HbA_{1c}$, % | 5.8 (0.3) | 5.8 (0.3) | 5.8 (0.3) | 5.8 (0.3) |
| $HbA_{1c}$, mmol/mol | 40 (3.3) | 40 (3.3) | 40 (3.3) | 40 (3.3) |
| Fasting insulin, μIU/mL | 3.8 (3.0–4.5) | 5.8 (5.2–6.5) | 7.9 (7.2–8.7) | 11.8 (10.3–14.3) |
| HOMA-IR | 0.9 (0.7–1.1) | 1.4 (1.3–1.6) | 2.0 (1.8–2.2) | 3.0 (2.6–3.7) |

*Continued on p. 1867*

**Table 1—Continued**

| Characteristic | Sex-specific HOMA-IR quartile* | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Diabetes (*n* = 17,714) | | | | |
| Age, years | 59.6 (9.0) | 59.0 (8.5) | 58.7 (8.5) | 58.4 (9.0) |
| Men, *n* (%) | 1,683 (38.0) | 1,682 (38.0) | 1,683 (38.0) | 1,683 (38.0) |
| High school or more education, *n* (%) | 1,203 (27.2) | 1,466 (33.1) | 1,550 (35.0) | 1,528 (34.5) |
| Alcohol drinking status, *n* (%) | | | | |
| Never | 3,642 (82.3) | 3,818 (86.2) | 3,830 (86.5) | 3,846 (86.8) |
| Former | 120 (2.7) | 127 (2.9) | 100 (2.3) | 124 (2.8) |
| Current | 666 (15.0) | 484 (10.9) | 498 (11.3) | 459 (10.4) |
| Smoking status, *n* (%) | | | | |
| Never | 3,430 (77.5) | 3,489 (78.8) | 3,527 (79.7) | 3,545 (80.0) |
| Former | 187 (4.2) | 266 (6.0) | 282 (6.4) | 272 (6.1) |
| Current | 811 (18.3) | 674 (15.2) | 619 (14.0) | 612 (13.8) |
| Physical activity, *n* (%) | | | | |
| Active | 2,695 (60.9) | 2,819 (63.7) | 2,890 (65.3) | 2,709 (61.2) |
| Insufficiently active | 1,567 (35.4) | 1,439 (32.5) | 1,352 (30.5) | 1,507 (34.0) |
| Inactive | 166 (3.8) | 171 (3.9) | 186 (4.2) | 213 (4.8) |
| Dietary quality score | 2.3 (0.7) | 2.3 (0.7) | 2.3 (0.8) | 2.3 (0.7) |
| BMI, kg/m$^2$, *n* (%) | | | | |
| <23.0 | 2,156 (48.7) | 960 (21.7) | 561 (12.7) | 331 (7.5) |
| 23.0 to <27.5 | 1,917 (43.3) | 2,598 (58.7) | 2,468 (55.7) | 2,056 (46.4) |
| ≥27.5 | 355 (8.0) | 871 (19.7) | 1,399 (31.6) | 2,042 (46.1) |
| Waist circumference, cm, *n* (%) | | | | |
| <90 in men, <80 in women | 2,750 (63.1) | 1,731 (39.1) | 1,229 (27.8) | 829 (18.7) |
| ≥90 in men, ≥80 in women | 1,678 (37.9) | 2,698 (60.9) | 3,199 (72.2) | 3,600 (81.3) |
| Fasting glucose, mg/dL | 112.4 (25.8) | 123.3 (30.4) | 132.4 (35.4) | 153.5 (50.9) |
| OGTT 2-h glucose, mg/dL | 201.5 (71.1) | 209.6 (71.9) | 225.3 (77.3) | 256.0 (97.6) |
| $HbA_{1c}$, % | 6.5 (1.1) | 6.7 (1.2) | 6.8 (1.3) | 7.3 (1.7) |
| $HbA_{1c}$, mmol/mol | 48 (12.0) | 50 (13.1) | 51 (14.2) | 56 (18.6) |
| Fasting insulin, μIU/mL | 4.5 (3.4–5.5) | 7.3 (6.2–8.4) | 10.0 (8.6–11.5) | 14.9 (12.4–18.6) |
| HOMA-IR | 1.2 (0.9–1.5) | 2.1 (1.9–2.3) | 3.1 (2.8–3.4) | 5.0 (4.3–6.4) |

Values are mean (SD) for continuous variables with normal distribution, median (interquartile range) for continuous variables with skewed distribution, and number (proportion) for categorical variables. Proportions may not sum to 100% because of rounding. Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by a health care professional, according to the ADA 2010 criteria. SI conversion factors: to convert fasting and OGTT 2-h glucose to mmol/L, multiply by 0.0555; to convert $HbA_{1c}$ to proportion of total hemoglobin, multiply by 0.01. *Sex-specific quartiles of HOMA-IR were defined among participants with normal glucose tolerance, prediabetes, and diabetes separately.

time-to-event analysis, participants were censored at the date of the end of follow-up or date of non-CVD death. Person-time for each participant was calculated from the date of enrollment to the date of first CVD event, non-CVD death, or end of follow-up, whichever came first. We used the quartile rank as a continuous variable in the models to test linear risk trends. We examined the multiplicative interactions between 1 SD of HOMA-IR and glucose tolerance status by including the product term in models to assess whether the association of 1 SD of HOMA-IR with incident CVD varied by different glucose tolerance status. We further analyzed the HRs (95% CIs) for incident CVD associated with sex-specific quartiles of HOMA-IR with and without the combination of obesity (general or abdominal obesity) among participants with prediabetes or diabetes compared with overall participants with normal glucose tolerance.

We also assessed HRs (99% CIs) for CVD risks associated with quartiles or 1 SD of HOMA-IR and the combined categories of HOMA-IR quartiles and obesity by glucose tolerance status. We performed three sensitivity analyses. First, we replicated the main analyses using glucose tolerance status defined by different combinations of each two of fasting and OGTT 2-h glucose and $HbA_{1c}$ along with a self-reported previous diagnosis of diabetes by a health care professional to support the robustness of the main findings. Second, we evaluated the associations between sex-specific quartiles of HOMA-IR and CVD risk among overall participants with diabetes (with complete study information *n* = 27,022) including those taking hypoglycemic pharmacologic therapy to enhance the generalizability of the findings in individuals with diabetes. Third, we repeated the analysis of the combined effect of HOMA-IR quartiles and obesity on CVD risk for general obesity and abdominal obesity, respectively. Statistical significance was analyzed using a two-sided *P* value of <0.05. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc.).

## RESULTS

Of 111,576 participants included in the analysis, the mean (SD) age was 56.1 (9.1) years, and the proportion of men was 34.1%. Within each glucose tolerance category, participants with higher HOMA-IR had higher proportions of general or abdominal obesity and poorer

**Table 2—HRs (95% CIs) of CVD events associated with insulin resistance according to glucose tolerance status**

| Category | Normal glucose tolerance ($n$ = 28,890) | | | Prediabetes ($n$ = 64,972) | | | Diabetes ($n$ = 17,714) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Person-years | Cases | HR (95% CI)* | Person-years | Cases | HR (95% CI)* | Person-years | Cases | HR (95% CI)* |
| HOMA-IR quartile† | | | | | | | | | |
| 1 | 26,288 | 156 | 1.00 (reference) | 58,121 | 380 | 1.00 (reference) | 15,681 | 139 | 1.00 (reference) |
| 2 | 26,196 | 132 | 0.94 (0.75–1.19) | 58,115 | 325 | 0.94 (0.81–1.09) | 15,847 | 135 | 1.02 (0.81–1.30) |
| 3 | 26,389 | 130 | 0.96 (0.76–1.21) | 58,575 | 376 | 1.10 (0.95–1.27) | 15,769 | 172 | 1.36 (1.08–1.70) |
| 4 | 26,685 | 142 | 1.03 (0.82–1.30) | 58,546 | 414 | 1.23 (1.07–1.42) | 15,944 | 207 | 1.61 (1.30–2.00) |
| Each 1-SD increment in HOMA-IR‡ | — | — | 1.04 (0.92–1.18) | — | — | 1.12 (1.06–1.18) | — | — | 1.15 (1.09–1.21) |

Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by a health care professional, according to the ADA 2010 criteria. Person-years might not add to total because of rounding. There were 111,576 participants included in the analysis. *HRs (95% CIs) were adjusted for age, sex, education attainment (below high school or high school or above), alcohol drinking status (never, former, or current), smoking status (never, former, or current), physical activity (inactive, insufficiently active, or active), and diet quality score. †Sex-specific quartiles of HOMA-IR were defined among participants with normal glucose tolerance, prediabetes, and diabetes separately. $P$ value for trend of associations between HOMA-IR quartiles and CVD risk was 0.78 among participants with normal glucose tolerance, 0.0008 among participants with prediabetes, and $<$0.0001 among participants with diabetes. ‡One SD of HOMA-IR was 1.23 in men and 1.18 in women. $P$ value for interaction between each 1-SD increment in HOMA-IR and glucose tolerance status on CVD risk was 0.011.

glucose and insulin profiles, blood pressures, and lipids (Table 1 and Supplementary Table 3). Compared with participants with normal glucose tolerance, participants with prediabetes or diabetes presented worse metabolic profiles.

During 402,156 person-years (mean [SD] 3.60 [1.04] years) of follow-up, 2,708 participants developed CVD events. Among overall participants, the highest quartile versus the lowest quartile of HOMA-IR was associated with a greater hazard of CVD (multivariable-adjusted HR 1.36; 95% CI 1.22–1.50), as was each 1-SD increment in HOMA-IR (1.15; 1.11–1.19); such associations were not substantially changed after further adjustment for $HbA_{1c}$ or glucose tolerance status (Supplementary Table 4). Regarding glucose tolerance status defined by fasting glucose, 2-h glucose, and $HbA_{1c}$ along with a previous diagnosis of diabetes, among participants with normal glucose tolerance, compared with the lowest quartile of HOMA-IR, higher quartiles of HOMA-IR conferred no excess risk of CVD (Table 2). Among participants with prediabetes, the highest quartile of HOMA-IR was associated with a greater hazard of CVD (multivariable-adjusted HR in quartile 4 vs. quartile 1 1.23; 95% CI 1.07–1.42; $P$ for trend = 0.0008). This association was amplified among participants with diabetes; compared with the lowest quartile of HOMA-IR, HRs (95% CIs) for CVD associated with the third and the highest quartiles of HOMA-IR were 1.36 (1.08–1.70) and 1.61 (1.30–2.00), respectively ($P$ for trend $<$ 0.0001). The HR (95% CI) for CVD per 1-SD increment in HOMA-IR was 1.04 (0.92–1.18) among participants with normal glucose tolerance, 1.12 (1.06–1.18) among participants with prediabetes, and 1.15 (1.09–1.21) among participants with diabetes ($P$ for interaction = 0.011). We observed consistent association patterns of insulin resistance with CVD by glucose tolerance status defined according to different combinations of each two of the glycemic parameters (Supplementary Table 5).

When we incorporated participants with diabetes taking hypoglycemic pharmacologic therapy into overall participants with diabetes, compared with the lowest quartile of HOMA-IR, the third (HR 1.37; 95% CI 1.16–1.61) and the highest (1.56; 1.33–1.83) quartiles of HOMA-IR were associated with greater

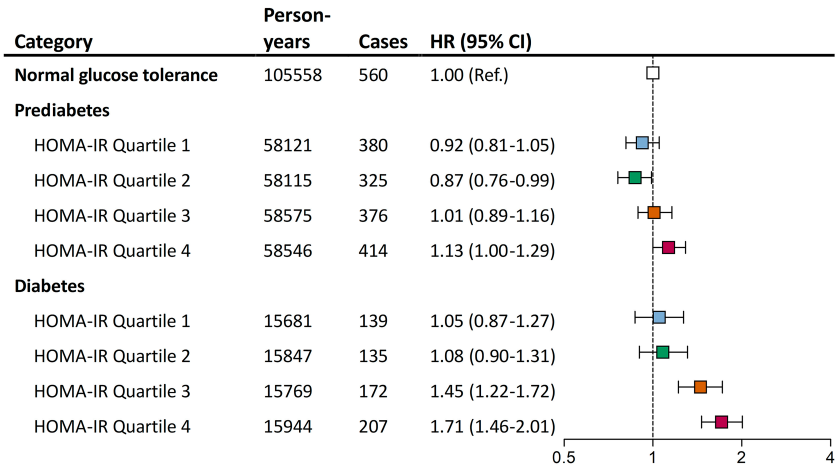


**Figure 1**—HRs (95% CIs) of CVD events associated with insulin resistance among participants with prediabetes or diabetes compared with overall participants with normal glucose tolerance. Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by a health care professional, according to the ADA 2010 criteria. Person-years might not add to total because of rounding. There were 111,576 participants included in the analysis. Sex-specific quartiles of HOMA-IR were defined among participants with prediabetes and diabetes separately. HRs (95% CIs) were adjusted for age, sex, education attainment (below high school or high school or above), alcohol drinking status (never, former, or current), smoking status (never, former, or current), physical activity (inactive, insufficiently active, or active), and diet quality score.

risk of CVD ($P$ for trend $<$ 0.0001) (Supplementary Table 6). The magnitude of this association was slightly greater in participants with diabetes not taking hypoglycemic medications than in those with diabetes taking hypoglycemic medications.

Generally, compared with participants with normal glucose tolerance, among participants with prediabetes, only the highest quartile of HOMA-IR was associated with a greater hazard of CVD (Fig. 1 and Supplementary Table 7), especially for prediabetes defined by 2-h glucose accompanied with fasting glucose (HR 1.16; 95% CI 1.03–1.32) or $HbA_{1c}$ (1.21; 1.07–1.37). Among participants with diabetes, both the third and the highest quartiles of HOMA-IR were associated with a greater hazard of CVD compared with participants with normal glucose tolerance, with the definition by fasting and 2-h glucose presenting the largest HRs (third quartile 1.61; 95% CI: 1.36–1.92; highest quartile 1.76; 1.50–2.07) in magnitude (Fig. 1 and Supplementary Table 7).

When analyzing the joint effect of HOMA-IR quartiles and obesity status, for glucose tolerance status defined by all three glycemic parameters, compared with participants with normal glucose tolerance, participants with prediabetes in the highest quartile of HOMA-IR with obesity showed greater risk of CVD (HR 1.17; 95% CI 1.02–1.34), while participants with prediabetes in the lowest (0.85; 0.74–0.99) and the second (0.83; 0.71–0.99) quartiles of HOMA-IR without obesity exhibited no increased risk of CVD (Fig. 2). Compared with participants with normal glucose tolerance, participants with diabetes in the third and the highest quartiles of HOMA-IR had greater risk of CVD, with HRs of 1.44 (95% CI 1.18–1.74) to 1.50 (1.11–2.03) and 1.70 (1.43–2.02) to 1.77 (1.26–2.46), respectively, regardless of obesity status. Similar results were observed for glucose tolerance status defined by different combinations of each two of the glycemic parameters (Supplementary Table 8). We replicated consistent results for general obesity (Supplementary Fig. 1) and abdominal obesity (Supplementary Fig. 2) for the combined effect of HOMA-IR quartiles and obesity on CVD risk in prediabetes and diabetes as compared with normal glucose tolerance.

When the significance level was set to 1%, although the CIs became slightly wider as expected, the association patterns of quartiles or 1 SD of HOMA-IR with CVD risk by glucose tolerance status and the association patterns of the combined categories of HOMA-IR quartiles and obesity with CVD risk in prediabetes and diabetes versus normal glucose tolerance were not substantially changed (Supplementary Table 9).

## CONCLUSIONS

In this nationwide prospective cohort study of 111,576 Chinese adults, when defining glucose tolerance status by all three glycemic parameters, the highest versus the lowest quartile of HOMA-IR was associated with 23 and 61% higher risks of CVD events among participants with prediabetes and diabetes, respectively, but no excess CVD risk among participants with normal glucose tolerance. More importantly, insulin resistance significantly interacted with glucose tolerance status, with each 1 SD of HOMA-IR associated with no significant excess CVD risk in participants with normal glucose tolerance, 12% higher CVD risk in participants with prediabetes, and 15% higher CVD risk in participants with diabetes. Compared with participants with normal glucose tolerance, in participants with prediabetes, the combination of the highest quartile of HOMA-IR and obesity was associated with 17% higher risk of CVD, while the combination of the lowest two quartiles of HOMA-IR and nonobesity exhibited 15–17% lower risk of CVD. By contrast, in participants with diabetes, the upper two quartiles of HOMA-IR had 44–77% higher risk of CVD, regardless of obesity status. The consistent results from varied definitions of glucose tolerance status support the robustness of the main findings.

In this study, we used the HOMA index as a surrogate measure of insulin sensitivity. Although HOMA-IR typically reflects hepatic insulin resistance, whereas the insulin resistance causally associated with accelerated atherosclerotic CVD occurs in skeletal and vascular smooth muscle (17), HOMA-IR does correlate reasonably well with insulin resistance indices measured by the euglycemic insulin clamp that primarily reflects insulin resistance in skeletal muscle (18,19). Also, the misclassification of insulin resistance is rare with HOMA-IR in both individuals without diabetes and those with type 2 diabetes (18). However, the use of HOMA-IR is inappropriate when blood glucose levels drop rapidly following the administration of hypoglycemic therapies, and the assumptions about liver extraction included in the model do

| Category | | Person-years | Cases | HR (95% CI) |
|---|---|---|---|---|
| **Normal glucose tolerance** | | 105558 | 560 | 1.00 (Ref.) |
| **Prediabetes** | | | | |
| HOMA-IR Quartile 1 | non-obese | 42499 | 257 | 0.85 (0.74-0.99) |
| | obese | 15623 | 123 | 1.11 (0.91-1.35) |
| HOMA-IR Quartile 2 | non-obese | 33688 | 180 | 0.83 (0.71-0.99) |
| | obese | 24427 | 145 | 0.91 (0.76-1.10) |
| HOMA-IR Quartile 3 | non-obese | 25333 | 151 | 0.96 (0.80-1.15) |
| | obese | 33242 | 225 | 1.06 (0.90-1.23) |
| HOMA-IR Quartile 4 | non-obese | 14776 | 92 | 1.03 (0.82-1.28) |
| | obese | 43769 | 322 | 1.17 (1.02-1.34) |
| **Diabetes** | | | | |
| HOMA-IR Quartile 1 | non-obese | 9539 | 92 | 1.13 (0.91-1.41) |
| | obese | 6142 | 47 | 0.93 (0.69-1.25) |
| HOMA-IR Quartile 2 | non-obese | 5955 | 41 | 0.85 (0.62-1.17) |
| | obese | 9892 | 94 | 1.23 (0.98-1.53) |
| HOMA-IR Quartile 3 | non-obese | 4064 | 46 | 1.50 (1.11-2.03) |
| | obese | 11705 | 126 | 1.44 (1.18-1.74) |
| HOMA-IR Quartile 4 | non-obese | 2655 | 37 | 1.77 (1.26-2.46) |
| | obese | 13289 | 170 | 1.70 (1.43-2.02) |

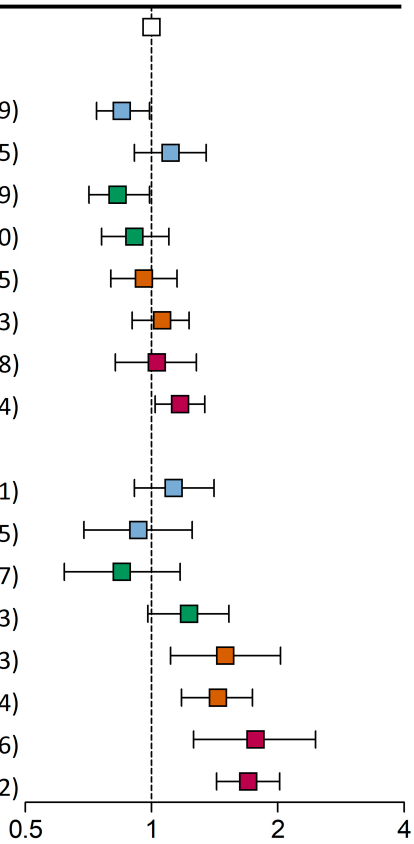


**Figure 2**—HRs (95% CIs) of CVD events associated with insulin resistance and obesity among participants with prediabetes or diabetes compared with overall participants with normal glucose tolerance. Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by a health care professional, according to the ADA 2010 criteria. Person-years might not add to total because of rounding. There were 111,576 participants included in the analysis. Sex-specific quartiles of HOMA-IR were defined among participants with prediabetes and diabetes separately. Obesity was defined as general obesity (BMI ≥27.5 kg/m$^2$) or abdominal obesity (waist circumference ≥90 cm in men and ≥80 cm in women). HRs (95% CIs) were adjusted for age, sex, education attainment (below high school or high school or above), alcohol drinking status (never, former, or current), smoking status (never, former, or current), physical activity (inactive, insufficiently active, or active), and diet quality score.

not apply when participants are treated with exogenous insulin (19). Therefore, we excluded participants taking hypoglycemic pharmacologic therapies from the main analyses. Previous studies have associated HOMA-estimated insulin resistance with higher risk of CVD in general population and in adults with or without diabetes (20–22). So far, few studies have investigated the interaction between insulin resistance and glucose tolerance status including normal glucose tolerance, prediabetes, and diabetes with regard to CVD. In this analysis, we provide novel evidence that glucose intolerance (i.e., prediabetes and especially diabetes) could strengthen the effect of insulin resistance on CVD risk. Such effect modification by glucose tolerance status was generally consistent with varied definitions by different combinations of glycemic parameters based on the ADA 2010 criteria, which further confirms the robustness of the observations. Our findings underline the importance of improving insulin sensitivity for the prevention and control of CVD in adults with prediabetes or diabetes, and more intensive efforts should be devoted to combination therapy for insulin resistance and hyperglycemia.

With regard to the potential influence of obesity, previous studies have associated joint phenotypes of insulin resistance and obesity with different susceptibilities to the risk of CVD and cardiometabolic risk factors in nondiabetic individuals, demonstrating that insulin resistance at any given degree of obesity increases the risk of CVD and diabetes (23,24). Our study extended previous investigations by providing additional evidence that compared with adults with normal glucose tolerance, adults with prediabetes who had both insulin resistance (HOMA-IR in the highest quartile) and obesity manifested an increased risk of CVD, while those who were insulin sensitive (HOMA-IR in the lowest two quartiles) and nonobese manifested no excess risk of CVD. In adults with diabetes, the impact of insulin resistance on CVD risk was sustained regardless of obesity. Emerging evidence, mainly from cardiovascular outcome trials, has supported weight loss as a worthwhile intervention in specific cardiovascular conditions (25). Our results further suggest that intervention strategies targeting obesity and insulin resistance to reduce CVD risk should be tailored according to glucose tolerance

status and highlight the joint management of obesity and insulin resistance in prediabetes and diabetes.

Potential mechanisms could partially explain our observations. Insulin resistance is a central mechanism linking multiple key components of cardiometabolic disturbance, such as hyperglycemia, atherogenic dyslipidemia, and hypertension (3,26–30). Obesity, which represents a state of tissue fat overload, is a driving force for insulin resistance (28,29). The molecular causes of insulin resistance (i.e., impaired insulin signaling through the phosphoinositol-3 kinase pathway with intact signaling through the mitogen-activated protein kinase pathway) are responsible for insulin-stimulated glucose intolerance, vascular smooth muscle proliferation, increased collagen formation, and excessive production of inflammatory cytokines, contributing to accelerated atherosclerosis and adverse cardiovascular events (28).

To our knowledge, this study is the first to delineate the association patterns between insulin resistance and CVD risk according to different glucose tolerance status defined by varied combinations of glycemic parameters. The strengths of this study include the large nationwide population-based prospective cohort, reliable measurement of insulin resistance, comprehensive assessment of glucose tolerance status, and well-validated definitions of CVD events. Our research also has limitations. First, the relatively short follow-up duration may limit the statistical power for evaluating the risk of CVD associated with insulin resistance by glucose tolerance stratification. Second, although we carefully controlled for confounding factors in the analyses, and the main findings were highly consistent across different definitions of glucose tolerance status, bias from unmeasured or residual confounders cannot be fully ruled out. Third, in this study, information on cardioprotective medications was not available, which limits the understanding of the characteristics of study participants and their CVD risks. Fourth, we performed stratified analyses to detect specific association patterns; conversely, the multiple tests may have introduced type I error, and a statistically significant finding may not necessarily have clinical significance. However, our main findings and conclusions were not materially changed whether the significance level was set to 1 or 5%. Fifth, the findings of this study were based on a middle-aged and elderly Chinese population. In addition to the difference in genetic background, Chinese adults have relatively low BMI levels compared with most Western adults (31), so it is possible that among adults with insulin resistance, a further increase in obesity, as occurs in more obese populations, may result in an additional increase in CVD risk. Also, the proportion of men in this study was relatively low, although we used sex-specific quartiles of HOMA-IR, which could have largely limited the potential bias resulting from sex proportion. Therefore, our results should be interpreted and generalized with caution.

In summary, this nationwide prospective cohort study in China showed that the impact of insulin resistance on the risk of CVD events was accentuated across glucose intolerance status. Compared with adults with normal glucose tolerance, in adults with prediabetes, only those with insulin resistance and obesity had higher risk of CVD, while in adults with diabetes, the CVD risk associated with insulin resistance persisted regardless of obesity. Our findings provide novel insights into individualized prevention strategies to improve insulin resistance and obesity in order to lower CVD risk in adults with prediabetes or diabetes.

**Funding**. This work was supported by the grants from the National Natural Science Foundation of China (82022011, 81970706, 82170819, 81970691, 82088102, 81970728, 81730023, and 81941017), the Chinese Academy of Medical Sciences (2018PT32017 and 2019PT330006), the Shanghai Municipal Education Commission–Gaofeng Clinical Medicine Grant Support from Shanghai Jiao Tong University School of Medicine (20171901 Round 2), the Shanghai Science and Technology Committee (20Y11905100), the Shanghai Shenkang Hospital Development Center (SHDC12019101, SHDC2020CR1001A, and SHDC2020CR3064B), the Shanghai Jiao Tong University School of Medicine (DLY201801), and the Ruijin Hospital (2018CR002).

The funders had no role in study design, data collection or analysis, decision to publish, or preparation of the manuscript.

**Duality of Interest**. No potential conflicts of interest relevant to this article were reported.

**Author Contributions**. T.W., Y.B., W.W., and J.L. contributed to the conception and design of the study. T.W. performed statistical analysis and wrote the manuscript. T.W., G.N., Y.B., W.W., and J.L. obtained funding. All authors contributed to the acquisition or interpretation of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. Y.B., W.W., and J.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## References

1. James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol 2021;22:751–771
2. Laakso M, Kuusisto J. Insulin resistance and hyperglycaemia in cardiovascular disease development. Nat Rev Endocrinol 2014;10:293–302
3. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med 2017;23:804–814
4. King GL, Park K, Li Q. Selective insulin resistance and the development of cardiovascular diseases in diabetes: the 2015 Edwin Bierman Award Lecture. Diabetes 2016;65:1462–1471
5. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol 2018;17:122
6. Reaven G. Insulin resistance and coronary heart disease in nondiabetic individuals. Arterioscler Thromb Vasc Biol 2012;32:1754–1759
7. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444:840–846
8. Wang T, Lu J, Shi L, et al.; China Cardiometabolic Disease and Cancer Cohort Study Group. Association of insulin resistance and β-cell dysfunction with incident diabetes among adults in China: a nationwide, population-based, prospective cohort study. Lancet Diabetes Endocrinol 2020;8:115–124
9. Wang T, Lu J, Su Q, et al.; 4C Study Group. Ideal cardiovascular health metrics and major cardiovascular events in patients with prediabetes and diabetes. JAMA Cardiol 2019;4:874–883
10. Lu J, He J, Li M, et al.; 4C Study Group. Predictive value of fasting glucose, postload glucose, and hemoglobin $A_{1c}$ on risk of diabetes and complications in Chinese adults. Diabetes Care 2019;42:1539–1548
11. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–1395
12. World Health Organization. Global recommendations on physical activity for health. Accessed 26 March 2022. Available from https://www.who.int/publications/i/item/9789241599979
13. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163
14. International Diabetes Federation. The IDF consensus worldwide definition of metabolic syndrome. Accessed 26 March 2022. Available from https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html.

15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69.
17. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 2009;32(Suppl. 2):S157–S163.
18. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000;23:57–63
19. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004; 27:1487–1495
20. Bonora E, Kiechl S, Willeit J, et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. Diabetes Care 2007;30:318–324
21. Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care 2002;25:1135–1141
22. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. PLoS One 2012;7:e52036
23. Abbasi F, Brown BW Jr, Lamendola C, McLaughlin T, Reaven GM. Relationship between obesity, insulin resistance, and coronary heart disease risk. J Am Coll Cardiol 2002;40: 937–943
24. Samocha-Bonet D, Chisholm DJ, Tonks K, Campbell LV, Greenfield JR. Insulin-sensitive obesity in humans - a 'favorable fat' phenotype? Trends Endocrinol Metab 2012;23:116–124
25. Neeland IJ, McGuire DK, Sattar N. Cardiovascular outcomes trials for weight loss interventions: another tool for cardiovascular prevention? Circulation 2021;144:1359–1361
26. Fryk E, Olausson J, Mossberg K, et al. Hyperinsulinemia and insulin resistance in the obese may develop as part of a homeostatic response to elevated free fatty acids: a mechanistic case-control and a population-based cohort study. EBioMedicine 2021;65:103264
27. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest 2016;126:12–22
28. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia 2010;53:1270–1287
29. Johnson AM, Olefsky JM. The origins and drivers of insulin resistance. Cell 2013;152:673–684
30. Pedersen DJ, Guilherme A, Danai LV, et al. A major role of insulin in promoting obesity-associated adipose tissue inflammation. Mol Metab 2015;4:507–518
31. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet 2016;387: 1377–1396