SUPPLEMENTAL MATERIAL

Supplementary Table 1. Baseline characteristics of study participants and the participants who were excluded from the analysis due to missing data

Characteristic	Study participants	Excluded participants with missing data*
Number of participants	111576	34522
Age, years	56.1 (9.0)	56.3 (8.8)
Sex, n (%)		
Men	38005 (34.1)	11407 (33.0)
Women	73571 (65.9)	23115 (67.0)
BMI, kg/m^2	24.4 (3.3)	25.0 (3.4)
Waist circumference, cm	83.6 (9.8)	84.3 (9.7)
Fasting plasma glucose, mg/dL	103.0 (21.8)	103.3 (23.8)
HbA1c, %	5.8 (0.8)	5.9 (0.8)
HOMA-IR	1.7 (1.1-2.4)	1.7 (1.2-2.5)

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.

*There were 15,504 participants with missing data on baseline HOMA-IR or glucose tolerance status and 19,018 participants whose information on ascertainment of incident CVD during follow-up was not available.

Abbreviations: BMI=body mass index; HbA1c=hemoglobin A1c; HOMA-IR=homoeostasis model assessment of insulin resistance.

Supplementary Table 2. Median value (interquartile range) of HOMA-IR according to glucose tolerance status

Glucose tolerance status	Sex-specific quartile of HOMA-IR*							
	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	Men	Women	Men	Women	Men	Women	Men	Women
Glucose tolerance status defined by fasting glucose, 2h glucose, and HbA1c								
Normal glucose tolerance (n=28890)	0.57 (0.43-0.69)	0.80 (0.65-0.91)	0.97 (0.88-1.06)	1.18 (1.09-1.27)	1.39 (1.27-1.53)	1.57 (1.46-1.70)	2.20 (1.89-2.71)	2.31 (2.05-2.78)
Prediabetes (n=64972)	0.76 (0.58-0.90)	1.00 (0.81-1.14)	1.25 (1.13-1.37)	1.51 (1.39-1.63)	1.80 (1.64-1.98)	2.06 (1.90-2.23)	2.83 (2.45-3.49)	3.09 (2.71-3.75)
Diabetes (n=17714)	1.02 (0.75-1.24)	1.39 (1.10-1.61)	1.91 (1.68-2.13)	2.25 (2.04-2.45)	2.89 (2.60-3.24)	3.21 (2.94-3.52)	4.93 (4.16-6.31)	5.12 (4.41-6.49)
Glucose tolerance status defined by fasting and 2h glucose								
Normal glucose tolerance (n=50632)	0.59 (0.45-0.71)	0.82 (0.67-0.93)	0.98 (0.90-1.08)	1.22 (1.12-1.31)	1.41 (1.29-1.56)	1.62 (1.51-1.76)	2.22 (1.92-2.72)	2.39 (2.11-2.86)
Prediabetes (n=46752)	0.85 (0.65-1.00)	1.14 (0.93-1.29)	1.38 (1.26-1.51)	1.70 (1.56-1.83)	1.97 (1.80-2.16)	2.29 (2.12-2.48)	3.05 (2.66-3.79)	3.40 (3.00-4.09)
Diabetes (n=14188)	1.05 (0.75-1.28)	1.48 (1.16-1.72)	2.00 (1.75-2.23)	2.40 (2.20-2.63)	3.02 (2.73-3.38)	3.44 (3.16-3.81)	5.11 (4.36-6.62)	5.47 (4.74-6.90)
Glucose tolerance status defined by fasting glucose and HbA1c								
Normal glucose tolerance (n=32032)	0.65 (0.49-0.79)	0.89 (0.73-1.03)	1.08 (0.94-1.24)	1.33 (1.18-1.52)	1.55 (1.34-1.73)	1.78 (1.55-2.02)	2.40 (1.99-2.92)	2.60 (2.16-3.09)
Prediabetes (n=65851)	0.79 (0.60-0.94)	1.05 (0.86-1.21)	1.28 (1.14-1.42)	1.55 (1.40-1.70)	1.83 (1.65-2.03)	2.11 (1.92-2.32)	2.87 (2.46-3.59)	3.14 (2.73-3.88)
Diabetes (n=13691)	1.00 (0.70-1.36)	1.32 (1.04-1.65)	2.03 (1.69-2.30)	2.24 (1.96-2.54)	2.99 (2.62-3.45)	3.19 (2.45-3.61)	4.78 (3.99-6.17)	4.85 (4.03-6.21)
Glucose tolerance status defined by 2h glucose and HbA1c								
Normal glucose tolerance (n=37554)	0.63 (0.47-0.75)	0.84 (0.68-0.96)	1.06 (0.95-1.16)	1.25 (1.16-1.35)	1.52 (1.38-1.68)	1.69 (1.56-1.83)	2.43 (2.10-3.02)	2.53 (2.22-3.08)
Prediabetes (n=57987)	0.75 (0.57-0.89)	0.99 (0.80-1.13)	1.25 (1.13-1.38)	1.50 (1.38-1.63)	1.82 (1.66-2.01)	2.07 (1.91-2.25)	2.92 (2.51-3.64)	3.13 (2.74-3.83)
Diabetes (n=16034)	1.00 (0.72-1.22)	1.37 (1.09-1.59)	1.87 (1.64-2.09)	2.22 (2.01-2.42)	2.84 (2.56-3.17)	3.17 (2.90-3.47)	4.78 (4.04-6.04)	5.03 (4.35-6.29)

Glucose tolerance status was defined by different combinations of glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the American Diabetes Association 2010 criteria. There were 111576 participants included in the analysis of glucose tolerance status defined by all three glycemic measures. The number of missing value was 4 for definition by fasting and 2h glucose, 2 for definition by fasting glucose and HbA1c, and 1 for definition by 2h glucose and HbA1c.

*Sex-specific quartiles of HOMA-IR were defined among participants with normal glucose tolerance, prediabetes, and diabetes, separately.

Abbreviations: HbA1c=hemoglobin A1c; HOMA-IR=homoeostasis model assessment of insulin resistance.

Supplementary Table 3. Baseline blood pressures and lipids of participants according to HOMA-IR quartiles stratified by glucose tolerance status

Characteristic	Sex-specific HOMA-IR quartile*			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Normal glucose tolerance (n=28890)				
Blood pressure				
Systolic blood pressure, mmHg	127 (21)	128 (21)	129 (20)	132 (20)
Diastolic blood pressure, mmHg	75 (11)	76 (11)	78 (11)	80 (11)
Lipid profile				
Total cholesterol, mg/dL	181.1 (38.9)	182.3 (40.6)	186.3 (41.1)	189.2 (42.3)
LDL cholesterol, mg/dL	100.2 (30.1)	103.8 (31.5)	107.6 (32.0)	110.1 (32.7)
HDL cholesterol, mg/dL	58.1 (14.7)	54.9 (13.9)	52.5 (13.4)	49.5 (12.6)
Triglycerides, mg/dL	96.1 (63.6)	106.3 (65.0)	124.5 (83.4)	153.2 (106.9)
Prediabetes (n=64972)				
Blood pressure				
Systolic blood pressure, mmHg	129 (22)	131 (20)	133 (20)	136 (20)
Diastolic blood pressure, mmHg	76 (11)	78 (11)	80 (11)	82 (11)
Lipid profile				
Total cholesterol, mg/dL	187.4 (42.6)	190.3 (43.7)	193.6 (44.5)	196.0 (44.7)
LDL cholesterol, mg/dL	106.2 (32.4)	110.4 (33.1)	113.2 (34.1)	114.4 (34.5)
HDL cholesterol, mg/dL	56.7 (15.3)	52.7 (14.0)	50.3 (13.0)	47.5 (12.3)
Triglycerides, mg/dL	106.7 (71.7)	127.6 (82.6)	150.5 (103.4)	182.6 (125.6)
Diabetes (n=17714)				
Blood pressure				
Systolic blood pressure, mmHg	135 (22)	138 (21)	140 (20)	142 (21)
Diastolic blood pressure, mmHg	78 (11)	81 (11)	82 (11)	84 (11)
Lipid profile				
Total cholesterol, mg/dL	194.9 (47.0)	196.8 (46.6)	200.1 (48.1)	201.6 (47.4)
LDL cholesterol, mg/dL	111.4 (35.2)	114.7 (34.7)	116.6 (36.1)	116.8 (35.6)
HDL cholesterol, mg/dL	54.4 (16.1)	48.9 (12.8)	47.2 (12.3)	46.1 (11.7)
Triglycerides, mg/dL	134.3 (104.5)	171.7 (123.7)	197.6 (141.3)	219.7 (157.9)

Values are mean (SD). Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the ADA 2010 criteria. SI conversion factors: To convert LDL, HDL, and total cholesterol to mmol/L, multiply by 0.0259; and triglycerides to mmol/L, multiply by 0.0113.

*Sex-specific quartiles of HOMA-IR were defined among participants with normal glucose tolerance, prediabetes, and diabetes, separately.

Abbreviations: HDL=high-density lipoprotein; HOMA-IR=homoeostasis model assessment of insulin resistance; LDL=low-density lipoprotein.

Supplementary Table 4. Hazard ratio (95% CI) of CVD events associated with insulin resistance among overall participants

Category	Person-years	Cases	HR (95% CI)		
			Model 1*	Model 2†	Model 3‡
HOMA-IR quartile					
Quartile 1	100437	653	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Quartile 2	100248	556	0.91 (0.81-1.02)	0.91 (0.81-1.02)	0.90 (0.80-1.01)
Quartile 3	100977	627	1.01 (0.91-1.13)	1.00 (0.90-1.12)	0.99 (0.89-1.11)
Quartile 4	100494	872	1.36 (1.22-1.50)	1.30 (1.17-1.45)	1.29 (1.16-1.44)
Each 1-SD increment in HOMA-IR	-	-	1.15 (1.11-1.19)	1.13 (1.09-1.17)	1.14 (1.10-1.18)

There were 111576 participants included in the analysis. Insulin resistance was assessed by sex-specific quartiles of HOMA-IR or sex-specific 1-SD of HOMA-IR (1-SD of HOMA-IR equals to 1.23 in men and 1.18 in women).

*Model 1 was adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.

†Model 2 was further adjusted for HbA1c, on the basis of Model 1.

‡Model 3 was further adjusted for glucose tolerance status (normal glucose tolerance, prediabetes, diabetes), on the basis of Model 1.

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio; SD=standard deviation.

Supplementary Table 5. Hazard ratio (95% CI) of CVD events associated with insulin resistance according to glucose tolerance status defined by different combinations of glycemic parameters

Category	Normal glucose tolerance			Prediabetes			Diabetes		
	Person-years	Cases	HR (95% CI)*	Person-years	Cases	HR (95% CI)*	Person-years	Cases	HR (95% CI)*
Glucose tolerance status defined by fasting and 2h glucose									
HOMA-IR quartile†									
Quartile 1	46060	285	1.00 (Ref.)	41134	263	1.00 (Ref.)	12571	130	1.00 (Ref.)
Quartile 2	46037	245	0.94 (0.79-1.12)	41250	244	1.01 (0.84-1.20)	12648	105	0.88 (0.68-1.13)
Quartile 3	46454	253	0.99 (0.84-1.18)	41764	281	1.17 (0.99-1.39)	12575	150	1.29 (1.02-1.64)
Quartile 4	46878	271	1.05 (0.88-1.24)	42035	312	1.30 (1.10-1.53)	12736	169	1.42 (1.13-1.79)
P value for trend	-	-	0.50	-	-	0.0006	-	-	0.0001
Each 1-SD increment in HOMA-IR‡	-	-	1.07 (0.98-1.16)	-	-	1.14 (1.08-1.21)	-	-	1.13 (1.07-1.19)
Glucose tolerance status defined by fasting glucose and HbA1c									
HOMA-IR quartile†									
Quartile 1	29166	176	1.00 (Ref.)	58722	394	1.00 (Ref.)	12122	94	1.00 (Ref.)
Quartile 2	29026	154	0.98 (0.79-1.21)	58762	332	0.92 (0.80-1.07)	12239	94	1.01 (0.76-1.34)
Quartile 3	29414	160	1.03 (0.83-1.27)	59250	368	1.03 (0.90-1.19)	12146	141	1.57 (1.21-2.04)
Quartile 4	29759	185	1.17 (0.95-1.45)	59281	446	1.26 (1.10-1.45)	12262	164	1.79 (1.39-2.31)
P value for trend	-	-	0.12	-	-	0.0003	-	-	<0.0001
Each 1-SD increment in HOMA-IR‡	-	-	1.11 (0.99-1.23)	-	-	1.12 (1.06-1.18)	-	-	1.18 (1.11-1.25)
Glucose tolerance status defined by 2h glucose and HbA1c									
HOMA-IR quartile†									
Quartile 1	33928	198	1.00 (Ref.)	52188	342	1.00 (Ref.)	14227	128	1.00 (Ref.)
Quartile 2	33647	167	0.94 (0.77-1.16)	52187	307	0.99 (0.84-1.15)	14351	130	1.06 (0.83-1.35)
Quartile 3	33909	169	0.98 (0.80-1.21)	52533	344	1.11 (0.95-1.29)	14331	147	1.24 (0.98-1.58)
Quartile 4	34030	185	1.06 (0.87-1.30)	52343	402	1.32 (1.14-1.53)	14478	189	1.60 (1.28-2.01)
P value for trend	-	-	0.52	-	-	<0.0001	-	-	<0.0001
Each 1-SD increment in HOMA-IR‡	-	-	1.06 (0.97-1.16)	-	-	1.15 (1.09-1.21)	-	-	1.13 (1.07-1.20)

Glucose tolerance status was defined by different combinations of glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the ADA 2010 criteria. There were 111572 participants included in the analysis of glucose tolerance

status defined by fasting and 2h glucose (normal glucose tolerance, n=50632; prediabetes, n=46752; diabetes, n=14188), 111574 participants included in the analysis of glucose tolerance status defined by fasting glucose and HbA1c (normal glucose tolerance, n=32032; prediabetes, n=65851; diabetes, n=13691), and 111575 participants included in the analysis of glucose tolerance status defined by 2h glucose and HbA1c (normal glucose tolerance, n=37554; prediabetes, n=57987; diabetes, n=16034).

*HRs (95% CIs) were adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.

†Sex-specific quartiles of HOMA-IR were defined among participants with normal glucose tolerance, prediabetes, and diabetes, separately.

‡1-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 0.022 for glucose tolerance status defined by fasting and 2h glucose, 0.011 for glucose tolerance status defined by fasting glucose and HbA1c, and 0.093 for glucose tolerance status defined by 2h glucose and HbA1c.

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HbA1c=hemoglobin A1c; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio; SD=standard deviation.

Supplementary Table 6. Median value (interquartile range) of HOMA-IR and hazard ratio (95% CI) of CVD events associated with insulin resistance among participants with diabetes taking or not taking hypoglycemic pharmacologic therapy

Category	Median (IQR)	Person-years	Cases	HR (95% CI)*
Overall diabetes (n=27022)				
HOMA-IR quartile†				
Quartile 1	1.28 (0.99-1.53)	24034	250	1.00 (Ref.)
Quartile 2	2.20 (1.98-2.42)	24052	257	1.08 (0.91-1.29)
Quartile 3	3.23 (2.93-3.59)	24036	320	1.37 (1.16-1.61)
Quartile 4	5.45 (4.61-7.26)	24394	377	1.56 (1.33-1.83)
P for trend	-	-	-	<0.0001
Diabetes not taking hypoglycemic pharmacologic therapy (n=17714)				
HOMA-IR quartile†				
Quartile 1	1.23 (0.93-1.48)	15681	139	1.00 (Ref.)
Quartile 2	2.13 (1.91-2.34)	15847	135	1.02 (0.81-1.30)
Quartile 3	3.10 (2.82-3.42)	15769	172	1.36 (1.08-1.70)
Quartile 4	5.04 (4.33-6.42)	15944	207	1.61 (1.30-2.00)
P for trend	-	-	-	<0.0001
Diabetes taking hypoglycemic pharmacologic therapy (n=9308)				
HOMA-IR quartile†				
Quartile 1	1.38 (1.10-1.65)	8255	118	1.00 (Ref.)
Quartile 2	2.36 (2.12-2.62)	8278	124	1.07 (0.83-1.38)
Quartile 3	3.51 (3.17-3.95)	8279	152	1.29 (1.01-1.64)
Quartile 4	6.56 (5.24-9.33)	8464	157	1.30 (1.02-1.65)
P for trend	-	-	-	0.012

*HRs (95% CIs) were adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.

†Sex-specific quartiles of HOMA-IR were defined among overall participants with diabetes and among participants with diabetes taking or not taking hypoglycemic pharmacologic therapy, separately.

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio; IQR=interquartile range.

Supplementary Table 7. Hazard ratio (95% CI) of CVD events associated with insulin resistance in prediabetes or diabetes compared with the overall normal glucose tolerance defined by different combinations of glycemic parameters

Category	Person-years	Cases	HR (95% CI)*
Glucose tolerance status defined by fasting and 2h glucose			
Normal glucose tolerance (n=50632)	185429	1054	1.00 (Ref.)
Prediabetes (n=46752)			
HOMA-IR quartile†			
Quartile 1	41134	263	0.89 (0.78-1.02)
Quartile 2	41250	244	0.90 (0.78-1.03)
Quartile 3	41764	281	1.05 (0.92-1.20)
Quartile 4	42035	312	1.16 (1.03-1.32)
Diabetes (n=14188)			
HOMA-IR quartile†			
Quartile 1	12571	130	1.23 (1.03-1.48)
Quartile 2	12648	105	1.08 (0.88-1.32)
Quartile 3	12575	150	1.61 (1.36-1.92)
Quartile 4	12736	169	1.76 (1.50-2.07)
Glucose tolerance status defined by fasting glucose and HbA1c			
Normal glucose tolerance (n=32032)	117366	675	1.00 (Ref.)
Prediabetes (n=65851)			
HOMA-IR quartile†			
Quartile 1	58722	394	0.89 (0.79-1.01)
Quartile 2	58763	332	0.82 (0.72-0.93)
Quartile 3	59250	368	0.92 (0.81-1.04)
Quartile 4	59281	446	1.12 (0.99-1.26)
Diabetes (n=13691)			
HOMA-IR quartile†			
Quartile 1	12122	94	0.93 (0.75-1.15)
Quartile 2	12239	94	0.94 (0.76-1.17)
Quartile 3	12146	141	1.48 (1.23-1.77)
Quartile 4	12262	164	1.67 (1.41-1.98)
Glucose tolerance status defined by 2h glucose and HbA1c			
Normal glucose tolerance (n=37554)	135515	719	1.00 (Ref.)
Prediabetes (n=57987)			
HOMA-IR quartile†			
Quartile 1	52188	342	0.92 (0.81-1.05)
Quartile 2	52187	307	0.91 (0.79-1.04)
Quartile 3	52533	344	1.02 (0.90-1.16)
Quartile 4	52343	402	1.21 (1.07-1.37)
Diabetes (n=16034)			
HOMA-IR quartile†			
Quartile 1	14227	128	1.07 (0.89-1.30)
Quartile 2	14351	130	1.14 (0.94-1.38)
Quartile 3	14331	147	1.36 (1.14-1.63)
Quartile 4	14478	189	1.75 (1.49-2.05)

Glucose tolerance status was defined by different combinations of glycemic

parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the ADA 2010 criteria. There were 111572 participants included in the analysis of glucose tolerance status defined by fasting and 2h glucose, 111574 participants included in the analysis of glucose tolerance status defined by fasting glucose and HbA1c, and 111575 participants included in the analysis of glucose tolerance status defined by 2h glucose and HbA1c.

*HRs (95% CIs) were adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.

†Sex-specific quartiles of HOMA-IR were defined among participants with prediabetes and diabetes, separately.

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HbA1c=hemoglobin A1c; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio.

Supplementary Table 8. Hazard ratio (95% CI) of CVD events associated with insulin resistance and obesity in prediabetes or diabetes compared with the overall normal glucose tolerance defined by different combinations of glycemic parameters

Category	Person-years	Cases	HR (95% CI)*
Glucose tolerance status defined by fasting and 2h glucose			
Normal glucose tolerance (n=50632)	185429	1054	1.00 (Ref.)
Prediabetes (n=46752)			
HOMA-IR quartile and obesity status†			
Quartile 1 non-obese	29185	172	0.82 (0.70-0.97)
obese	11949	91	1.04 (0.84-1.29)
Quartile 2 non-obese	22077	131	0.92 (0.77-1.11)
obese	19173	113	0.88 (0.72-1.07)
Quartile 3 non-obese	16563	84	0.81 (0.65-1.01)
obese	25201	197	1.20 (1.03-1.40)
Quartile 4 non-obese	9587	68	1.13 (0.88-1.44)
obese	32448	244	1.18 (1.02-1.35)
Diabetes (n=14188)			
HOMA-IR quartile and obesity status†			
Quartile 1 non-obese	7598	83	1.27 (1.02-1.59)
obese	4973	47	1.17 (0.87-1.57)
Quartile 2 non-obese	4896	38	0.99 (0.71-1.36)
obese	7752	67	1.14 (0.89-1.46)
Quartile 3 non-obese	3315	39	1.62 (1.18-2.24)
obese	9261	111	1.61 (1.32-1.96)
Quartile 4 non-obese	2214	35	2.02 (1.44-2.83)
obese	10522	134	1.70 (1.42-2.04)
Glucose tolerance status defined by fasting glucose and HbA1c			
Normal glucose tolerance (n=32032)	117366	675	1.00 (Ref.)
Prediabetes (n=65851)			
HOMA-IR quartile and obesity status†			
Quartile 1 non-obese	42496	269	0.84 (0.73-0.97)
obese	16227	125	1.03 (0.85-1.25)
Quartile 2 non-obese	33523	190	0.82 (0.70-0.97)
obese	25239	142	0.81 (0.68-0.97)
Quartile 3 non-obese	25010	137	0.82 (0.68-0.98)
obese	34240	231	0.99 (0.85-1.15)
Quartile 4 non-obese	14269	98	1.04 (0.84-1.29)
obese	45012	348	1.14 (1.01-1.30)
Diabetes (n=13691)			
HOMA-IR quartile and obesity status†			
Quartile 1 non-obese	6787	51	0.90 (0.67-1.19)
obese	5335	43	0.97 (0.71-1.32)
Quartile 2 non-obese	4375	27	0.75 (0.51-1.11)
obese	7864	67	1.05 (0.82-1.35)
Quartile 3 non-obese	2844	32	1.47 (1.03-2.10)
obese	9302	109	1.48 (1.21-1.81)

Quartile 4	non-obese	2014	31	1.78 (1.24-2.55)
	obese	10248	133	1.65 (1.37-1.99)
Glucose tolerance status defined by 2h glucose and HbA1c				
Normal glucose tolerance (n=37554)		135515	719	1.00 (Ref.)
Prediabetes (n=57987)				
HOMA-IR quartile and obesity status†				
Quartile 1	non-obese	37862	230	0.86 (0.74-0.99)
	obese	14326	112	1.11 (0.90-1.35)
Quartile 2	non-obese	29396	170	0.90 (0.76-1.06)
	obese	22791	137	0.93 (0.77-1.11)
Quartile 3	non-obese	21761	132	0.95 (0.79-1.15)
	obese	30772	212	1.07 (0.92-1.25)
Quartile 4	non-obese	12326	84	1.10 (0.87-1.38)
	obese	40016	318	1.25 (1.10-1.43)
Diabetes (n=16034)				
HOMA-IR quartile and obesity status†				
Quartile 1	non-obese	8593	83	1.14 (0.91-1.43)
	obese	5634	45	0.98 (0.72-1.32)
Quartile 2	non-obese	5204	42	0.97 (0.71-1.32)
	obese	9147	88	1.25 (1.00-1.56)
Quartile 3	non-obese	3619	36	1.31 (0.94-1.83)
	obese	10712	111	1.38 (1.13-1.69)
Quartile 4	non-obese	2137	28	1.75 (1.20-2.56)
	obese	12342	161	1.75 (1.47-2.08)

Glucose tolerance status was defined by different combinations of glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the ADA 2010 criteria. There were 111572 participants included in the analysis of glucose tolerance status defined by fasting and 2h glucose, 111574 participants included in the analysis of glucose tolerance status defined by fasting glucose and HbA1c, and 111575 participants included in the analysis of glucose tolerance status defined by 2h glucose and HbA1c.

*HRs (95% CIs) were adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.

†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).

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HbA1c=hemoglobin A1c; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio.

Supplementary Table 9. Hazard ratio (99% CI) of CVD events associated with insulin resistance and the combination of insulin resistance and obesity

Analysis	HR (99% CI)*	P value
CVD risk associated with insulin resistance by glucose tolerance status (corresponding to Table 2)		
Normal glucose tolerance (n=28890)		
HOMA-IR quartile†		
Quartile 1	1.00 (Ref.)	-
Quartile 2	0.94 (0.70-1.28)	0.63
Quartile 3	0.96 (0.70-1.30)	0.70
Quartile 4	1.03 (0.76-1.40)	0.78
Each 1-SD increment in HOMA-IR‡	1.04 (0.89-1.22)	0.50
Prediabetes (n=64972)		
HOMA-IR quartile†		
Quartile 1	1.00 (Ref.)	-
Quartile 2	0.94 (0.78-1.15)	0.44
Quartile 3	1.10 (0.91-1.33)	0.19
Quartile 4	1.23 (1.02-1.48)	0.0039
Each 1-SD increment in HOMA-IR‡	1.12 (1.04-1.20)	<0.0001
Diabetes (n=17714)		
HOMA-IR quartile†		
Quartile 1	1.00 (Ref.)	-
Quartile 2	1.02 (0.75-1.40)	0.85
Quartile 3	1.36 (1.01-1.82)	0.0080
Quartile 4	1.61 (1.21-2.14)	<0.0001
Each 1-SD increment in HOMA-IR‡	1.15 (1.08-1.23)	<0.0001
CVD risk associated with insulin resistance in prediabetes or diabetes versus normal glucose tolerance (corresponding to Figure 1)		
Normal glucose tolerance (n=28890)	1.00 (Ref.)	-
Prediabetes (n=64972)		
HOMA-IR quartile†		
Quartile 1	0.92 (0.78-1.09)	0.22
Quartile 2	0.87 (0.72-1.04)	0.040
Quartile 3	1.01 (0.85-1.20)	0.85
Quartile 4	1.13 (0.96-1.34)	0.058
Diabetes (n=17714)		
HOMA-IR quartile†		
Quartile 1	1.05 (0.82-1.34)	0.60
Quartile 2	1.08 (0.84-1.39)	0.42
Quartile 3	1.45 (1.16-1.82)	<0.0001
Quartile 4	1.71 (1.39-2.11)	<0.0001
CVD risk associated with insulin resistance and obesity in prediabetes or diabetes versus normal glucose tolerance (corresponding to Figure 2)		
Normal glucose tolerance (n=28890)	1.00 (Ref.)	-
Prediabetes (n=64972)		
HOMA-IR quartile and obesity status†		
Quartile 1 non-obese	0.85 (0.70-1.04)	0.037
obese	1.11 (0.86-1.44)	0.31

	HR (99% CI)	p
Quartile 2 non-obese	0.83 (0.67-1.04)	0.035
obese	0.91 (0.72-1.16)	0.32
Quartile 3 non-obese	0.96 (0.76-1.21)	0.64
obese	1.06 (0.86-1.30)	0.50
Quartile 4 non-obese	1.03 (0.77-1.37)	0.82
obese	1.17 (0.97-1.40)	0.027
Diabetes (n=17714)		
HOMA-IR quartile and obesity status†		
Quartile 1 non-obese	1.13 (0.85-1.51)	0.28
obese	0.93 (0.63-1.37)	0.62
Quartile 2 non-obese	0.85 (0.56-1.30)	0.33
obese	1.23 (0.92-1.64)	0.069
Quartile 3 non-obese	1.50 (1.01-2.23)	0.0082
obese	1.44 (1.11-1.85)	0.0008
Quartile 4 non-obese	1.77 (1.14-2.74)	<0.0001
obese	1.70 (1.36-2.14)	<0.0001

Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the ADA 2010 criteria. There were 111576 participants included in the analysis.
*HRs (99% CIs) were adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.
†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).
‡1-SD of HOMA-IR was 1.23 in men and 1.18 in women.
Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio; SD=standard deviation.

Supplementary Figure 1. Hazard ratio (95% CI) of CVD events associated with insulin resistance and general obesity among participants with prediabetes or diabetes compared with the overall participants with normal glucose tolerance

Category		Person-years	Cases	HR (95% CI)	
Normal glucose tolerance		105558	560	1.00 (Ref.)	
Prediabetes					
HOMA-IR Quartile 1	non-obese	55648	359	0.91 (0.80-1.04)	
	obese	2473	21	1.21 (0.78-1.87)	
HOMA-IR Quartile 2	non-obese	52760	287	0.85 (0.73-0.98)	
	obese	5355	38	1.06 (0.76-1.47)	
HOMA-IR Quartile 3	non-obese	48389	288	0.94 (0.82-1.08)	
	obese	10186	88	1.36 (1.08-1.70)	
HOMA-IR Quartile 4	non-obese	38147	246	1.04 (0.90-1.21)	
	obese	20398	168	1.29 (1.08-1.53)	
Diabetes					
HOMA-IR Quartile 1	non-obese	14400	127	1.04 (0.86-1.26)	
	obese	1281	12	1.19 (0.67-2.11)	
HOMA-IR Quartile 2	non-obese	12683	112	1.12 (0.91-1.37)	
	obese	3165	23	0.93 (0.61-1.41)	
HOMA-IR Quartile 3	non-obese	10796	111	1.38 (1.12-1.69)	
	obese	4973	61	1.61 (1.24-2.10)	
HOMA-IR Quartile 4	non-obese	8552	118	1.76 (1.44-2.15)	
	obese	7392	89	1.65 (1.32-2.07)	

(x-axis: 0.5 1 2 4)

Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the ADA 2010 criteria. Person-years might not add to total because of rounding. There were 111576 participants included in the analysis.

Sex-specific quartiles of HOMA-IR were defined among participants with prediabetes and diabetes, separately.
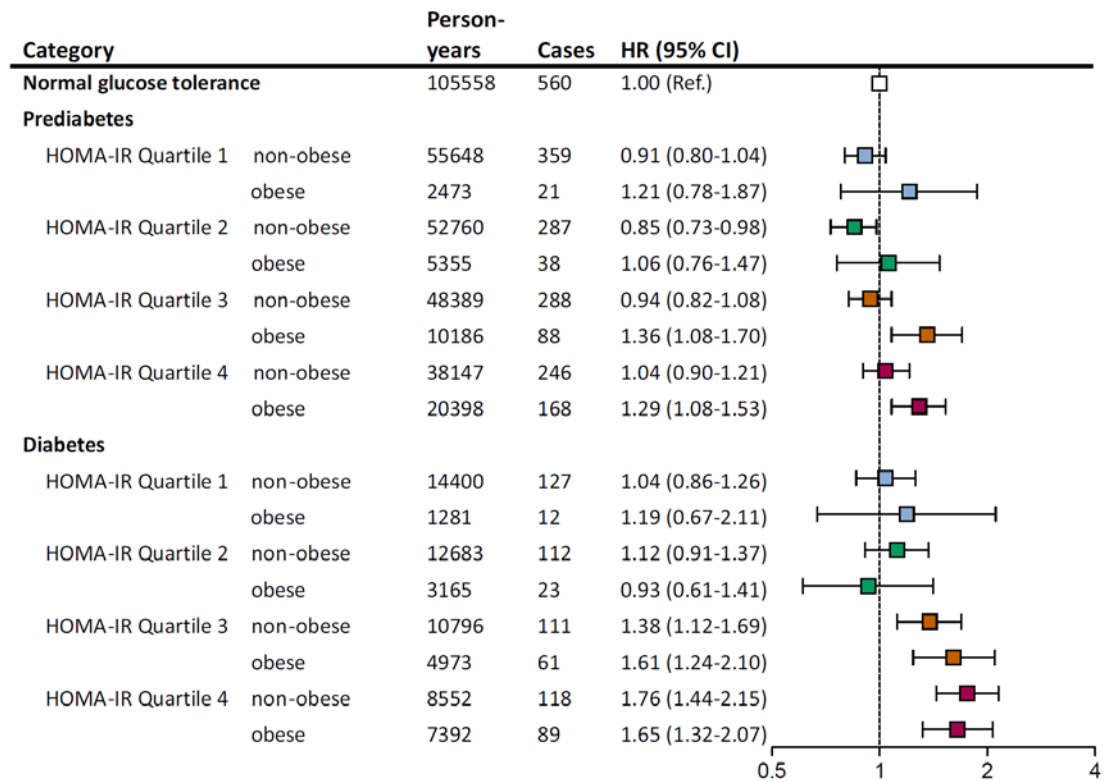
General obesity was defined as BMI $\geq$27.5 kg/m^2.

HRs (95% CIs) were adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio.

Supplementary Figure 2. Hazard ratio (95% CI) of CVD events associated with insulin resistance and abdominal obesity among participants with prediabetes or diabetes compared with the overall participants with normal glucose tolerance

Category		Person-years	Cases	HR (95% CI)	
Normal glucose tolerance		105558	560	1.00 (Ref.)	
Prediabetes					
HOMA-IR Quartile 1	non-obese	42947	262	0.86 (0.74-1.00)	
	obese	15174	118	1.10 (0.90-1.35)	
HOMA-IR Quartile 2	non-obese	34284	186	0.85 (0.72-1.00)	
	obese	23831	139	0.90 (0.74-1.08)	
HOMA-IR Quartile 3	non-obese	26165	158	0.96 (0.81-1.15)	
	obese	32410	218	1.05 (0.90-1.23)	
HOMA-IR Quartile 4	non-obese	16035	101	1.03 (0.83-1.28)	
	obese	42511	313	1.17 (1.02-1.35)	
Diabetes					
HOMA-IR Quartile 1	non-obese	9698	92	1.12 (0.89-1.39)	
	obese	5983	47	0.95 (0.70-1.28)	
HOMA-IR Quartile 2	non-obese	6162	42	0.85 (0.62-1.16)	
	obese	9685	93	1.24 (0.99-1.54)	
HOMA-IR Quartile 3	non-obese	4397	51	1.54 (1.15-2.05)	
	obese	11372	121	1.42 (1.17-1.73)	
HOMA-IR Quartile 4	non-obese	2988	39	1.69 (1.22-2.33)	
	obese	12956	168	1.72 (1.45-2.05)	

Glucose tolerance status was defined by all three glycemic parameters along with a self-reported previous diagnosis of diabetes by health care professionals, according to the ADA 2010 criteria. Person-years might not add to total because of rounding. There were 111576 participants included in the analysis.
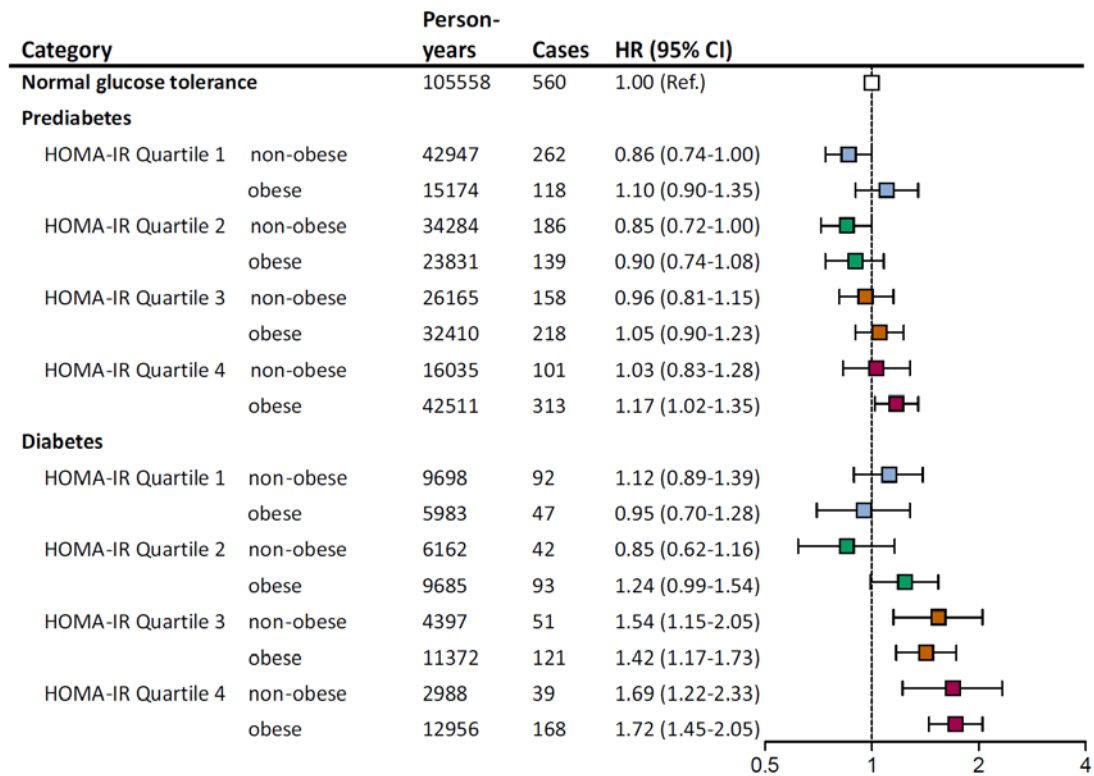
Sex-specific quartiles of HOMA-IR were defined among participants with prediabetes and diabetes, separately.

Abdominal obesity was defined as waist circumference ≥90 cm in men and ≥80 cm in women.

HRs (95% CIs) were adjusted for age, sex, education attainment (below high school, high school or above), alcohol drinking status (never, former, current), smoking status (never, former, current), physical activity (inactive, insufficiently active, active), and diet quality score.

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HOMA-IR=homoeostasis model assessment of insulin resistance; HR=hazard ratio.