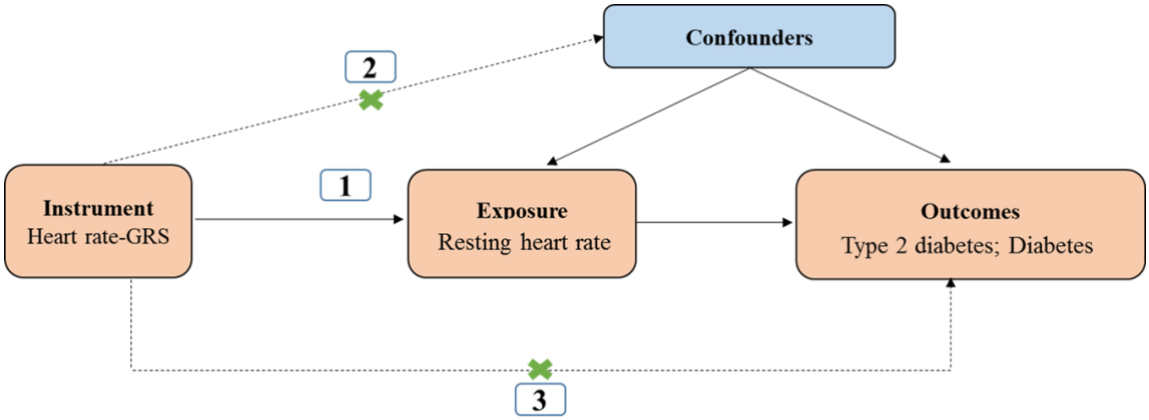
Supplemental Materials

eFigure 1

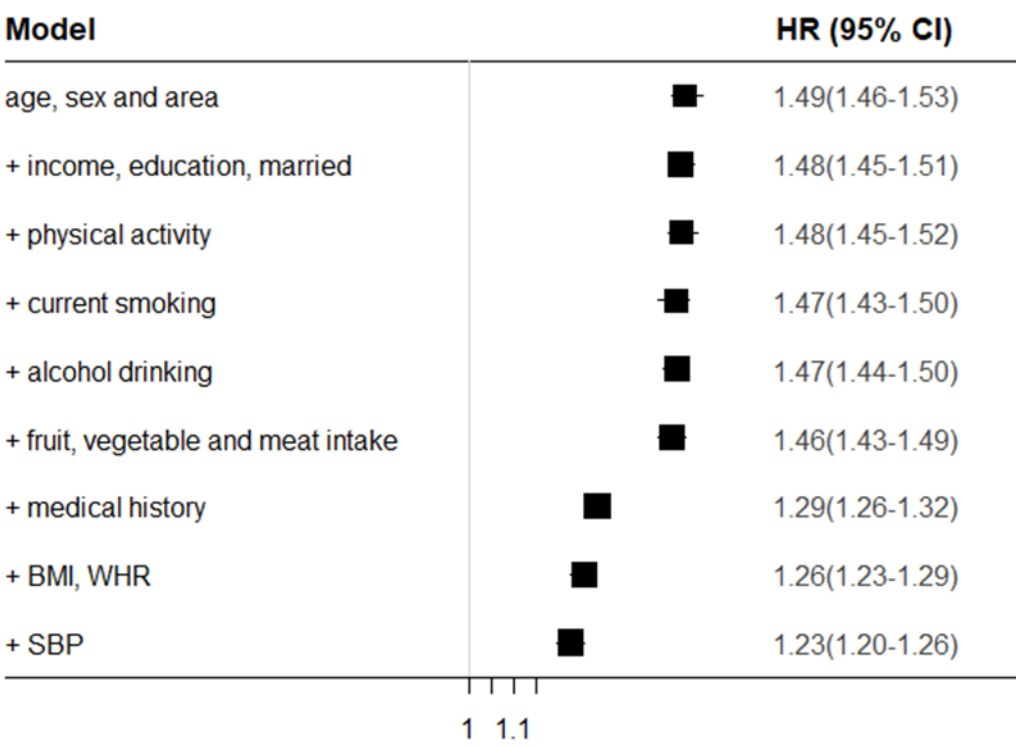


MR can be used to test the hypothesis that resting heart rate causes diabetes.

Three assumptions of MR:

1. Genetic variants must be associated with resting heart rate.
2. Genetic variants must not be associated with confounders.
3. Genetic variants must influence diabetes only through heart rate, not through other pathways.

eFigure 2



HR (95%CI) for 10 bpm higher resting heart rate

eTable 1. Regression dilution ratios for heart rate, by age- and sex-specific baseline groups[1].

Age at entry, years	Number of participants	Mean interval between baseline and resurvey measures, years	Regression dilution ratio (95% CI) [2]	
Male				
30-39	1109	2.6	0.44	(0.39-0.49)
40-49	2128	2.5	0.49	(0.46-0.52)
50-59	2205	2.6	0.47	(0.43-0.50)
60-69	1460	2.6	0.55	(0.51-0.59)
70-79	469	2.6	0.51	(0.44-0.58)
Female				
30-39	1872	2.7	0.49	(0.45-0.53)
40-49	3538	2.6	0.50	(0.47-0.53)
50-59	3707	2.6	0.52	(0.49-0.55)
60-69	1850	2.7	0.53	(0.50-0.57)
70-79	498	2.6	0.55	(0.48-0.62)

[1]Exclude participants with a baseline extreme heart rate values.

[2]Regression dilution ratios for heart rate by age- and sex-specific baseline groups (among 18,836 participants resurveyed).

eTable 2. Genome wide association study identified loci for resting heart rate[1].

Variant	Locus	EAF	Non-coded Allele	Coded Allele	β	SE	P-value
rs1050288	12p11.22	0.34	C	T	-0.213	0.036	2.738E-09
rs10739663	9q33.3	0.45	A	G	-0.266	0.033	9.62E-16
rs10841486	12p12.2	0.22	T	C	-0.238	0.040	2.983E-09
rs11083258	18q12.1	0.17	A	C	-0.276	0.045	5.508E-10
rs10880689	12q11	0.60	A	G	0.208	0.034	8.103E-10
rs11454451	1q41	0.26	C	CT	0.256	0.038	1.29E-11
rs11563648	7q31.33	0.27	G	C	-0.231	0.037	4.417E-10
rs11920570	3q21.1	0.26	G	A	0.268	0.037	5.176E-13
rs12501032	4p15.2	0.31	C	G	0.288	0.036	1.827E-15
rs12576326	11p11.2	0.34	A	G	0.253	0.036	1.197E-12
rs12579753	12q21.31	0.23	C	T	-0.246	0.039	4.805E-10
rs1260326	2p23.3	0.39	T	C	-0.275	0.034	4.285E-16
rs12713404	2p16.1	0.38	G	T	-0.199	0.035	9.327E-09
rs12721051	19q13.32	0.18	C	G	-0.287	0.044	5.226E-11
rs12889267	14q11.2	0.16	A	G	0.416	0.045	3.611E-20
rs13002735	2q37.1	0.24	A	C	-0.331	0.039	1.294E-17
rs13165531	5p13.3	0.42	A	T	-0.221	0.034	4.311E-11
rs1320761	6q22.31	0.11	C	T	0.902	0.053	1.22E-64
rs138186803	7q32.3	0.41	AT	A	-0.333	0.040	1.265E-16
rs145358377	1p36.31	0.36	G	GA	-0.259	0.039	1.941E-11
rs1468333	5q31.2	0.63	T	C	-0.255	0.034	9.53E-14
rs1483890	3p14.1	0.30	A	G	0.284	0.036	2.542E-15
rs151041685	2q31.2	0.09	G	T	1.061	0.058	7.858E-75
rs1549118	14q24.3	0.28	C	T	0.200	0.037	4.666E-08
rs16974196	19q13.2	0.32	G	A	0.244	0.036	1.105E-11
rs17180489	14q24.2	0.14	G	C	-0.490	0.055	9.15E-19
rs17201923	14q31.3	0.28	A	G	-0.410	0.037	6.549E-29
rs17265513	20q12	0.19	T	C	0.240	0.042	1.119E-08
rs174536	11q12.2	0.66	A	C	0.399	0.035	1.651E-30
rs17881696	7q22.1	0.18	G	A	0.578	0.043	1.183E-41
rs180239	7q21.3	0.35	G	C	-0.326	0.035	4.539E-21
rs1994135	12p11.1	0.47	T	C	0.400	0.033	7.19E-34
rs2076028	22q13.1	0.29	G	A	-0.295	0.036	5.451E-16
rs2152735	1p22.3	0.33	G	A	-0.306	0.036	7.232E-18
rs2283274	12p13.33	0.18	G	C	-0.405	0.044	7.212E-20
rs2358740	3p21.1	0.32	G	T	-0.208	0.035	3.578E-09
rs236349	6p21.2	0.34	A	G	0.281	0.035	1.012E-15
rs272564	1p34.1	0.28	A	C	0.351	0.037	4.507E-21
rs3749237	3p21.31	0.32	G	A	0.258	0.035	3.085E-13
rs3915499	16p13.11	0.32	G	A	0.303	0.035	1.242E-17
rs3951016	6q22.31	0.47	T	A	0.520	0.033	2.954E-55
rs41312411	3p22.2	0.15	C	G	-0.320	0.047	1.34E-11

rs41317993	1q32.2	0.10	G	A	0.630	0.055	5.421E-31
rs41748	7q31.2	0.45	T	G	-0.193	0.033	7.143E-09
rs422068	14q11.2	0.36	T	C	0.731	0.034	1.52E-100
rs4608502	2q36.3	0.33	T	C	0.249	0.035	1.853E-12
rs4868243	5q35.1	0.16	G	A	-0.361	0.044	4.076E-16
rs4900069	14q32.11	0.37	A	C	0.200	0.034	5.377E-09
rs4963772	12p12.1	0.15	G	A	-0.714	0.047	3.228E-53
rs56233017	8q24.3	0.04	G	A	-0.666	0.083	1.086E-15
rs564190295	2q31.1	0.15	G	GCCGCCGCCCCC	-0.355	0.057	4.953E-10
rs58437978	7p14.2	0.50	T	C	-0.240	0.034	2.609E-12
rs6123471	20q11.23	0.46	T	C	-0.595	0.033	6.633E-72
rs61735998	18q12.2	0.02	G	T	-0.834	0.109	2.059E-14
rs62172372	2q32.1	0.19	A	G	0.337	0.042	5.992E-16
rs6845865	4q31.23	0.16	T	C	-0.342	0.045	2.249E-14
rs7173389	15q24.1	0.16	A	T	-0.539	0.045	1.313E-32
rs7194801	16q21	0.43	T	C	-0.291	0.033	3.579E-18
rs73158705	7q33	0.16	A	G	0.393	0.045	2.806E-18
rs75190942	11q24.3	0.09	C	A	-0.496	0.060	1.193E-16
rs7612445	3q26.33	0.19	G	T	-0.428	0.042	2.413E-24
rs79121763	17p12	0.09	C	T	-0.471	0.063	7.174E-14
rs867400	12q14.2	0.43	T	C	0.298	0.033	4.583E-19
rs907683	2q35	0.43	G	T	-0.334	0.036	1.021E-20

[1]EAF, Effect Allele Frequency; β, Beta; SE, Standard Error. Allele coding is based on the positive strand.

eTable 3. Genetic association with resting heart rate in CKB.

Rs number	Risk allele	β	SE	P-value
rs1050288*	C	0.2236677	0.0599555	< 0.001
rs10739663*	A	0.2159475	0.0565528	< 0.001
rs10841486	T	0.3074854	0.1779145	0.084
rs10880689	G	0.1376566	0.1474525	0.351
rs11083258*	A	0.9525391	0.2809287	< 0.001
rs11454451	ct	0.1004882	0.0543972	0.065
rs11563648	G	0.0824509	0.1098533	0.453
rs11920570	A	0.2044197	0.0619207	0.001
rs12501032*	G	0.3472507	0.0964881	< 0.001
rs12576326	G	0.1043288	0.0575917	0.070
rs12579753	C	0.2028146	0.1253714	0.106
rs1260326	T	0.1496417	0.0528311	0.005
rs12713404*	G	0.2205705	0.0547001	< 0.001
rs12721051	C	0.1217793	0.0835866	0.145
rs12889267*	G	0.6249464	0.1555357	< 0.001
rs13002735*	A	0.2519507	0.0615976	< 0.001
rs13165531	A	0.1315589	0.0537586	0.014
rs1320761*	T	0.8769076	0.0538947	< 0.001
rs138186803	A	0.1383711	0.0632415	0.029
rs145358377	G	-0.2793338	0.1361516	0.040
rs1468333	T	-0.016609	0.055195	0.763
rs1483890*	G	0.3746383	0.0574367	< 0.001
rs1549118	T	0.008022	0.0736962	0.913
rs16974196*	A	0.3270565	0.0538131	< 0.001
rs17180489	G	-0.254424	0.5090046	0.617
rs17201923*	A	0.4516537	0.0921295	< 0.001
rs17265513	C	0.8444331	0.5717471	0.140
rs174536*	C	0.6872241	0.0510656	< 0.001
rs17881696*	A	0.6306232	0.1437594	< 0.001
rs180239*	G	0.3807382	0.0640267	< 0.001
rs1994135*	C	0.5794754	0.1131773	< 0.001
rs2076028*	G	0.2020457	0.0536101	< 0.001
rs2152735*	G	0.2279996	0.0548266	< 0.001
rs2283274*	G	0.228869	0.0530294	< 0.001
rs2358740*	G	0.4051977	0.0572004	< 0.001
rs236349	G	0.0316661	0.0562995	0.574
rs272564*	C	0.5777349	0.0548407	< 0.001
rs3749237	A	0.0999654	0.069098	0.148
rs3915499*	A	0.3855834	0.0605227	< 0.001
rs3951016*	A	0.3843813	0.0587822	< 0.001
rs41312411	C	0.3587747	0.2520067	0.155
rs41317993*	A	0.5797414	0.0882122	< 0.001

rs41748*	T	0.2301651	0.0536808	< 0.001
rs422068*	C	0.6731069	0.0689506	< 0.001
rs4608502	C	0.1247683	0.054318	0.022
rs4868243*	G	0.2392677	0.0538647	< 0.001
rs4900069	C	0.0392349	0.0951148	0.680
rs4963772*	G	0.6905244	0.07789	< 0.001
rs564190295	G	0.5852488	0.7909255	0.459
rs58437978	T	0.1216995	0.0579446	0.036
rs6123471*	T	0.4722731	0.0532208	< 0.001
rs6845865*	T	0.5364934	0.0637092	< 0.001
rs7173389*	A	0.6308023	0.1381247	< 0.001
rs7194801*	T	0.4086037	0.0706052	< 0.001
rs73158705*	G	0.4160027	0.0550777	< 0.001
rs75190942*	C	0.6502078	0.0900375	< 0.001
rs7612445*	G	0.3995886	0.0744558	< 0.001
rs79121763	C	-0.2145331	0.4938877	0.664
rs867400*	C	0.2120983	0.0618352	< 0.001
rs907683*	G	0.4473347	0.0663083	< 0.001

*The SNPs were significantly associated with resting heart rate in CKB, with a threshold set as 0.0008 (0.05/64).

eTable 4. Characteristics of the study population.

Characteristics	Quintiles of baseline heart rate			P for trend
	Quintile1	Quintile3	Quintile5	
No. of participants	97237	103147	104200	
Demographic factors				
Age, y	52.7 ± 10.6	51.1 ± 10.6	50.7 ± 10.8	< 0.001
Male, No. (%)	49,112 (50.5)	39,003 (37.8)	39,497 (37.9)	< 0.001
Urban region, No. (%)	43,687 (44.9)	47,191 (45.8)	43,388 (41.6)	< 0.001
Socioeconomic factors, No. (%)				
Household income >20,000 yuan/year	42,858 (44.1)	45,274 (43.9)	42,655 (40.9)	< 0.001
Middle school education and above	47,526 (48.9)	52,226 (50.6)	49,601 (47.6)	< 0.001
Married	88,414 (90.9)	93,616 (90.8)	93,846 (90.1)	< 0.001
Lifestyle factors				
Physical activity, MET-h/d	21.7 ± 14.4	21.2 ± 13.7	20.8 ± 13.7	< 0.001
Regular drinker, No. (%)	16,822 (17.3)	14,196 (13.8)	15,413 (14.8)	< 0.001
Drinkers-males, No. (%)	15,536 (22.5)	12,901 (18.7)	14,377 (20.8)	< 0.001
Drinkers-females, No. (%)	1,283 (20.7)	1,293 (20.9)	1,038 (16.8)	< 0.001
Regular smoker, No. (%)	30,022 (30.9)	25,573 (24.8)	26,678 (25.6)	< 0.001
Smokers-males, No. (%)	28,718 (22.7)	24,172 (19.1)	25,334 (20.1)	< 0.001
Smokers-females, No. (%)	1,304 (18.7)	1,404 (20.2)	1,345 (19.3)	< 0.001
Meat intake (everyday), No. (%)	28,217 (29.0)	31,051 (30.1)	29,391 (28.2)	< 0.001
Vegetable intake (everyday), No. (%)	92,547 (95.2)	97,832 (94.9)	97,822 (93.9)	< 0.001
Fruit intake (everyday), No. (%)	19,417 (20.0)	20,226 (19.6)	17,073 (16.4)	< 0.001
Self-reported conditions at baseline, No. (%)				
Type 2 diabetes	3,456 (3.6)	5,422 (5.3)	9,498 (9.1)	< 0.001
Cancer	474 (0.5)	495 (0.5)	629 (0.6)	< 0.001
Hypertension	10,700 (11.0)	10,244 (9.9)	13,425 (12.9)	< 0.001
Poor health	8,714 (9.0)	9,415 (9.1)	12,444 (11.9)	< 0.001
Physical measurements				
BMI, kg/m^2	23.5 ± 3.2	23.7 ± 3.3	23.8 ± 3.6	< 0.001
Waist circumference, mm	796.6 ± 93.0	801.7 ± 96.1	809.4 ± 103.5	< 0.001
Hip circumference, mm	907.8 ± 68.2	910.5 ± 67.9	908.9 ± 70.1	< 0.001
SBP, mmHg	129.5 ± 21.3	129.5 ± 20.6	135.2 ± 21.7	< 0.001
Resting heart rate, bpm	63.7 ± 4.0	77.7 ± 1.8	96.2 ± 7.7	< 0.001

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure; MET-h/d, metabolic equivalents of task per hours per day.

Data are presented as mean ± SD for continuous variables and No. (%) for categorical variables, respectively.

Tests for linear trend across categories were performed by assigning the midpoint values of each heart rate category and treating the variable as continuous in a separate regression model, , and adjusted for age, sex, region when appropriate.

eTable 5. Adjusted hazard ratios for type 2 diabetes by quintiles of baseline heart rate

Type 2 diabetes	Quintile1	Quintile2	Quintile3	Quintile4	Quintile5	P for trend
No. of participants	93,781	89,221	97,844	94,967	99,429	
No. of person years	841,975	803,741	885,450	855,620	892,045	
No. of events	1,375	1,378	1,528	1,624	1,967	
[1]Model 1	1.00	1.14 (1.05-1.24)	1.26 (1.16-1.37)	1.48 (1.35-1.62)	1.68 (1.52-1.85)	< 0.001
[2]Model 2	1.00	1.14 (1.05-1.24)	1.26 (1.16-1.37)	1.47 (1.35-1.61)	1.67 (1.51-1.84)	< 0.001
[3]Model 3	1.00	1.14 (1.05-1.24)	1.26 (1.16-1.37)	1.47 (1.34-1.61)	1.67 (1.51-1.84)	< 0.001
[4]Model 4	1.00	1.09 (1.00-1.19)	1.16 (1.07-1.27)	1.29 (1.18-1.42)	1.41 (1.27-1.55)	< 0.001
[5]Model 5	1.00	1.10 (1.01-1.19)	1.16 (1.06-1.26)	1.27 (1.16-1.39)	1.34 (1.21-1.48)	< 0.001

[1]Model 1: adjusted for age, sex, area, income, education, and married status.

[2]Model 2: model 1 + physical activity, current smoking, and current drinking.

[3]Model 3: model 2 + fruit, vegetable and meat intakes.

[4]Model 4: model 3 + self-reported general health status, family history of diabetes, stroke and cancer, BMI, and WHR.

[5]Model 5: model 4 + SBP.

eTable 6. Association of genetic risk score with confounders.

Characteristic	Genetic risk score for resting heart rate					P for trend
	Quintile1	Quintile2	Quintile3	Quintile4	Quintile5	
No. of participants	18,272	18,477	18,653	18,703	18,619	
Genetic risk score, mean (range)	29.9 (20.5~31.9)	33.1 (32.0~34.1)	35.1 (34.2~36.0)	37.1 (36.1~38.2)	40.3 (38.3~51.1)	
Heart rate, bpm	76.8 ± 11.6	77.9 ± 11.6	78.7 ± 11.8	79.3 ± 11.7	80.8 ± 11.9	< 0.001
Demographic factors						
Age, y	53.2 ± 11.0	53.2 ± 11.0	53.1 ± 11.0	53.3 ± 11.0	53.2 ± 11.0	0.304
Male, No. (%)	7,767 (42.5)	7,945 (43.0)	7,994 (42.9)	8,033 (43.0)	7,901 (42.4)	0.987
Urban region, No. (%)	7,518 (41.1)	7,628 (41.3)	7,683 (41.2)	7,981 (42.7)	8,359 (44.9)	0.239
Socioeconomic factors						
Household income >20,000 yuan/year, No. (%)	6,909 (37.9)	7,135 (38.6)	7,312 (39.2)	7,407 (39.6)	7,254 (39.0)	0.218
Middle school and above, No. (%)	8,676 (47.5)	8,610 (46.6)	8,800 (47.2)	8,763 (46.9)	8,695 (46.7)	0.663
Married, No. (%)	16,343 (89.4)	16,542 (89.5)	16,650 (89.3)	16,814 (89.9)	16,631 (89.3)	0.781
Lifestyle factors						
Physical activity, MET-h/d	20.5 ± 13.9	20.6 ± 14.0	20.5 ± 13.9	20.2 ± 13.8	20.0 ± 13.6	0.458
Regular drinker, No. (%)	2,931 (16.0)	2,972 (16.1)	2,924 (15.7)	2,879 (15.4)	2,766 (14.9)	0.052
Regular smoker, No. (%)	5,093 (27.9)	5,274 (28.5)	5,223 (28.0)	5,215 (27.9)	5,040 (27.0)	0.278
Meat intake (everyday), No. (%)	5,062 (27.7)	5,173 (28.0)	5,427 (29.1)	5,587 (29.9)	5,944 (31.9)	0.314
Vegetable intake (everyday), No. (%)	17,229 (94.3)	17,429 (94.3)	17,609 (94.4)	17,749 (94.9)	17,599 (94.5)	0.950
Fruit intake (everyday), No. (%)	3,705 (20.3)	3,542 (19.2)	3,545 (19.0)	3,444 (18.4)	3,256 (17.5)	0.370
Physical and blood measurements,						
BMI, kg/m^2	23.7 ± 3.5	23.6 ± 3.5	23.6 ± 3.4	23.5 ± 3.4	23.4 ± 3.4	0.029
Waist-hip ratio, %	88.0 ± 7.2	88.0 ± 7.0	88.0 ± 7.0	88.0 ± 6.9	87.9 ± 7.0	0.696
SBP, mmHg	133.3 ± 22.6	132.8 ± 22.6	132.6 ± 22.3	132.6 ± 22.5	132.1 ± 22.0	0.668
Self-reported conditions at baseline						
Cancer, No. (%)	74 (0.4)	72 (0.4)	81 (0.4)	70 (0.4)	68 (0.4)	0.733
Hypertension, No. (%)	2,127 (11.6)	2,155 (11.7)	2,131 (11.4)	2,215 (11.8)	2,120 (11.4)	0.260
Poor health, No. (%)	1,947 (10.7)	1,975 (10.7)	1,989 (10.7)	1,976 (10.6)	1,869 (10.0)	0.215

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure; MET-h/d, metabolic equivalents of task per hours per day.

Data are presented as mean ± SD for continuous variables and No. (%) for categorical variables, respectively.

Tests for linear trend across categories were performed by assigning the midpoint values of each heart rate category and treating the variable as continuous in a separate regression model, and adjusted for age, sex, region and the first five principal component when appropriate.

eTable 7. Adjusted Hazard Ratios for type 2 diabetes by region[1]

	No. of events	HR (95% CI) per 10 bpm
Urban		
Qingdao	1,626	1.18 (1.09,1.28)
Harbin	3,900	1.25 (1.19,1.32)
Haikou	1,231	1.21 (1.10,1.32)
Suzhou	2,408	1.24 (1.16,1.32)
Liuzhou	3,094	1.19 (1.12,1.26)
Rural		
Sichuan	4,855	1.32 (1.26,1.38)
Gansu	4,338	1.23 (1.17,1.29)
Henan	4,817	1.23 (1.17,1.28)
Zhejiang	3,614	1.20 (1.14,1.26)
Hunan	4,922	1.38 (1.32,1.45)

[1] The results were corrected for regression-dilution bias for age- and sex-specific groups. Results are adjusted for age, sex, income (<20,000 yuan/year, or ≥20,000 yuan/year), educational level (no formal school, primary school, middle school, high school, college, or university or higher), marital status (married, widowed, divorced or separated, or never married), smoking status (never smoker, occasional smoker, former smoker, or regular smoker), alcohol intake (non-drinker, occasional drinker, former drinker, or regular drinker), physical activity (METs, h/day) , frequency of fruit intake, vegetable intake (daily, 4 to 6 days/wk, 1 to 3 days/wk, monthly, or rarely or never), self-reported general health status, BMI, WHR, and SBP.

eTable 8. Adjusted hazard ratios per 10 bpm higher resting heart rate for sensitivity analyses of type 2 diabetes[1]

Incidence type 2 diabetes	No. of cases	No. of participants	HR (95% CI) per 10 bpm
Excluding participants taking blood pressure-lowering medication at baseline	5,905	428,294	1.20 (1.15, 1.26)
Excluding first three years of follow-up	5,814	475,242	1.14 (1.09, 1.20)
Excluding participants without genetic genotyping	2,458	92,724	1.06 (1.03, 1.10)

[1]The results were corrected for regression-dilution bias for age- and sex-specific groups. Results are adjusted for age, sex, region, income (<20,000 yuan/year, or ≥20,000 yuan/year), educational level (no formal school, primary school, middle school, high school, college, or university or higher), marital status (married, widowed, divorced or separated, or never married), smoking status (never smoker, occasional smoker, former smoker, or regular smoker), alcohol intake (non-drinker, occasional drinker, former drinker, or regular drinker), physical activity (METs, h/day) , frequency of fruit intake, vegetable and meat intake (daily, 4 to 6 days/wk, 1 to 3 days/wk, monthly, or rarely or never), self-reported general health status, BMI, WHR, and SBP.