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ORIGINAL ARTICLE

Association between resting heart rate and incident diabetes risk: a Mendelian randomization study

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Abstract

Aims Observational studies indicated that resting heart rate (RHR) was associated with diabetes mellitus (DM) risk; however, it remains unclear whether the association between RHR and DM is causal. We aimed to examine whether there was causal association of RHR with DM risk.

Methods A prospective study including 16,201 middle-aged and older Chinese (7031 males and 9170 females) derived from the Dongfeng-Tongji cohort was performed. Cox proportional hazard regression models were conducted to estimate the associations between RHR and incident DM risk. In 7481 participants, 65 single nucleotide polymorphisms related to RHR were genotyped. A genetic risk score (GRS) of RHR was calculated based on the RHR-associated variants. The causal associations of RHR with DM risk were investigated by Mendelian randomization analysis.

Results During a mean (SD) follow-up of 4.5 (0.5) years, 1110 diabetes were identified. Compared with the referential RHR group (≤ 60 beats per minute [bpm]), individuals with RHR > 80 bpm have a higher incident diabetes risk, with a hazard ratio of 1.40 (95% confidence interval [CI], 1.05–1.88). With per SD increase in the weighted genetic risk score, the resting heart rate increased by 0.71 bpm (95% CI 0.49–0.93). By using the GRS to estimate the unconfounded effect, we found that higher resting heart rate did not have a causal effect on diabetes risk (OR 1.00 [95% CI 0.95–1.05]).

Conclusions The present study supported a positive but not a causal association of RHR with incident diabetes risk. More studies are needed to verify our findings.

Keywords Diabetes · Mendelian randomization analysis · Prospective cohort study · Resting heart rate

Introduction

Diabetes mellitus is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs. The prevalence of diabetes has been increasing rapidly worldwide [1]. In 2015, more than 415 million people live with diabetes worldwide, and an estimated 212 million people have undiagnosed diabetes [2]. In China, the prevalence of diabetes and prediabetes was estimated to be 11.6% and 50.1%, respectively [3]. Thus, identification of risk factors of diabetes is crucial and urgent.

Resting heart rate (RHR) is known to be a sensitive indicator of the autonomic nervous system [4], reflecting a balance of sympathetic and parasympathetic activity. Evidence suggested that increased sympathetic tone not only elevates resting heart rate but also amplifies insulin resistance [5]. Some epidemiological studies also indicated that

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a high resting heart rate was independently associated with increased risk of diabetes [6–13], whereas other studies found no significant association between them after adjustment for potential confounders [14, 15]. Therefore, whether resting heart rate was related to incident diabetes risk still remained to be validated in the further prospective study. In addition, if there is association between resting heart rate and incident diabetes risk, the association is causal or not needs to be investigated.

The Mendelian randomization was widely applied to test and estimate the causal effects of risk factors on disease outcomes [16]. Because alleles are randomly allocated during gamete formation, the association of genetic variant with disease risk is unlikely to be confounded by other factors. Also, reverse causality is abrogated. With the discovery of RHR-related single nucleotide polymorphisms (SNPs) in recent GWAS studies [17, 18], variants at such loci can be used as genetic instruments to estimate the unconfounded effects of resting heart rate on diabetes risk. However, to the best of our knowledge, till now no study performed the Mendelian randomization analysis to investigate the causal effects of resting heart rate on diabetes risk.

In the present study, firstly we conducted a prospective cohort to investigate the association between resting heart rate and incident diabetes risk among a middle-aged and elderly population. Furthermore, we conducted a Mendelian randomization study using the resting heart rate-related SNPs as instruments to explore whether there were causal associations between RHR and diabetes risk.

Participants and methods

Study design and population

Details of the study population have been described elsewhere [19]. Briefly, a total of 27,009 retired employees of the Dongfeng Motor Corporation (DMC) completed the baseline questionnaire and medical examinations and provided fasting blood samples between September 2008 and June 2010. These participants were followed through October 2013 with repeated questionnaires and clinical and laboratory examinations. In the present study, we excluded participants who failed to finish the follow-up ($n = 1031$), those with missing data on RHR at baseline examination ($n = 601$); those with diabetes ($n = 5059$); self-reported cardiovascular disease or cancer at baseline ($n = 3898$); and those with physician-diagnosed atrial fibrillation or other arrhythmia ($n = 219$). Finally, 16,201 participants (7031 males and 9170 females) remained for further analysis. To examine the association between RHR and incident prediabetes risk, we further excluded 7010 participants with prediabetes at baseline and diabetes at follow-up, leaving 9191 participants for analysis.

The present study was approved by the Medical Ethics Committee of the School of Public Health, Tongji Medical College, HUST and Dongfeng General Hospital, DMC. All participants gave their written informed consents.

Assessment of resting heart rate and covariates

After resting 5 min or longer, the resting heart rate was measured by physician with a stethoscope placed over the heart. Resting heart rate was divided into 4 categories (≤ 60 bpm, 61–70 bpm, 71–80 bpm, and > 80 bpm).

Epidemiological information including socio-demographic factors (age, sex, education, and marital status), health status, lifestyle (smoking status, drinking status, and physical activity), family history, medical history, and medication history were collected during face-to-face interviews by trained interviewers at baseline examination. Self-reported education attainment was classified into primary school or below, junior high school, senior high school, and college or above. Smoking status was categorized into current (smoked at least 1 cigarette per day in the past 6 months), former, and never smoking groups. Drinking status was categorized into current (drink at least once per week in the past 6 months), former, and never drinking groups. Height, body weight, and waist circumference were measured with participants in light indoor clothing and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure (BP) was measured following the recommended standard procedures. Baseline hypertension was defined as individuals with a self-reported physician diagnosis of hypertension, or blood pressure ≥ 140/90 mmHg, or current usage of antihypertensive medication. Baseline hyperlipidemia was defined as total cholesterol (TC) > 5.72 mmol/L or triglycerides (TG) > 1.70 mmol/L at the medical examination, current usage of lipid-lowering medication, or a self-reported physician diagnosis of hyperlipidemia. Blood samples, after an overnight fast, were collected in the morning. Blood glucose level was determined through glucose oxidase method by Abbott Aeroset analyzer. Levels of TG, TC, and low-density lipoprotein cholesterol (LDL-C) were measured using ARCHITECT Ci8200 automatic analyzer (ABBOTT Laboratories, Abbott Park, Illinois, USA) in the hospital's laboratory following standard laboratory procedures. HbA1c levels were determined with high-performance liquid chromatography D-10 system (Bio-Rad Laboratories. Hercules, CA, USA).

Genotyping

We selected 65 RHR-associated variants that were identified in previous genome-wide association studies (GWAS) [17, 18] to construct genetic risk score as instrumental variable in the Mendelian randomization analysis (Supplementary Table 1). The genotypes of the 65 SNPs were derived from the GWAS scan with Affymetrix Genome-Wide Human SNP Array 6.0 chips [20] and Illumina Infinium OmniZhongHua-8 Chips. The genotype procedure and quality control have been described in more detail in previous studies [20, 21]. No SNPs were in linkage disequilibrium with each other, and all of the 65 SNPs were in Hardy–Weinberg equilibrium ($P > 0.05$).

Definition of outcomes

Diabetes and prediabetes were defined according to the American Diabetes Association criteria [22]. Participants were identified as having diabetes if they met any of the following criteria during the follow-up period: (1) self-report of a physician's diagnosis of diabetes, (2) fasting blood glucose level ≥ 7.0 mmol/L, (3) usage of diabetes medication (insulin or oral hypoglycemic agent), (4) HbA1c ≥ 6.5%. Because HbA1c levels were not available at baseline examination, diabetes was defined based on 1–3 criteria at baseline. We defined incident diabetes based on all of the 1–4 criteria at the first follow-up. Prediabetes was defined as participants without diabetes but 5.6 mmol/L ≤ FPG < 7.0 mmol/L. We additionally defined prediabetes with 5.7% ≤ HbA1c ≤ 6.4% at the first follow-up.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and compared by Student's *t* test or analysis of variation (ANOVA) unless otherwise specified, and the categorical variables were presented as number (%) and compared by Chi-square analysis.

We computed hazard ratios (HRs) and 95% confidence intervals (CIs) for diabetes using the Cox proportional hazard regression model. Odds ratio (ORs) and 95% CIs for prediabetes was calculated by logistic regression model. In model 1, age and sex were adjusted. In model 2, BMI was further included in the model to examine the independent effects of RHR on incident diabetes risk. In the model 3, we further adjusted for education level, smoking status, drinking status, physical activity, BMI, hypertension, hyperlipidemia, use of medication (hypotensor, lipid-lowering), family history of diabetes and cardiovascular disease. In sensitivity analysis, we excluded those who developed diabetes within the first 2 years of follow-up to avoid reverse causality. Because hypertension might influence resting heart rate, we further excluded individuals with hypertension at baseline to do the similar analysis. Finally, we repeated analysis by excluding participants with RHR less than 50 bpm or larger than 100 bpm.

To further verify whether there was causal association between resting heart rate and diabetes risk, we selected 65 reported RHR-associated SNPs as instrumental variable to conduct Mendelian randomization analysis. A total of 7481 participants were included in the Mendelian randomization analysis. The alleles were coded 0, 1, or 2 according to the number of RHR-raising alleles. GRS was calculated by summing the number of RHR-raising alleles. For weighted GRS, we multiplied the risk alleles from each SNP by the predicted effect size of each SNP on resting heart rate (according to linear regression analysis). The associations of individual SNP or GRS with RHR and diabetes-related traits were assessed by linear regression model or logistic regression model. We further adjusted for RHR to examine whether the associations of individual SNP or GRS with diabetes risk were mediated by their effects on resting heart rate. The attenuation of the associations between the SNPs or GRS and diabetes risk after adjustment for resting heart rate suggested the potential causal association between resting heart rate and diabetes [23]. We calculated the expected effect sizes (β_E) of the individual SNP or GRS on diabetes risk based on the effect sizes of individual SNP or genetic score on resting heart rate (β_{GB}) and the effect sizes of resting heart rate on diabetes risk (β_{BD}). The formula is $\beta_E = \beta_{GB} * \beta_{BD}$, as previously indicated [24]. The differences between expected effects sizes of individual SNP or GRS on diabetes and observed effect sizes were compared by student's *t* test [25].

Statistical calculation was performed using SAS version 9.2 (SAS Institute, Cary, NC). A two-sided *P* value < 0.05 was considered statistical significant.

Results

Characteristics of the study population

Baseline characteristics of the study participants according to different levels of resting heart rate are presented in Table 1. Compared with participants with lower resting heart rate, those with higher resting heart rate appeared to have lower education levels and higher levels of blood pressure, TG, and fasting plasma glucose, and higher proportion of hyperlipidemia at baseline. No significant differences were found for drinking status, physical activity, HDL and TC levels, and family history of diabetes.

Table 1 Baseline characteristics of the study participants according to different levels of resting heart rate

Characteristic	Resting heart rate (bpm)				
	≤ 60 (*n* = 1358)	61–70 (*n* = 5670)	71–80 (*n* = 7085)	> 80 (*n* = 2088)	*P* value
Age (years)	63.5 (7.9)	62.2 (7.6)	62.3 (7.5)	63.1 (7.7)	< 0.001
Sex, male, *n* (%)	701 (51.6)	2351 (41.5)	2987 (42.2)	992 (47.5)	< 0.001
Education, *n* (%)					< 0.001
Primary school or below	371 (27.7)	1561 (27.8)	1940 (27.6)	650 (31.4)	
Middle school	448 (33.4)	2064 (36.7)	2629 (37.4)	777 (37.5)	
High school or above	522 (38.9)	1992 (35.5)	2466 (35.1)	645 (31.1)	
Smoking status, *n* (%)					< 0.001
Current smoker	295 (21.8)	1035 (18.4)	1305 (18.6)	412 (19.8)	
Former smoker	163 (12.0)	527 (9.3)	666 (9.5)	230 (11.1)	
Never smoker	898 (66.2)	4078 (72.3)	5039 (71.9)	1436 (69.1)	
Drinking status, *n* (yes, %)					0.096
Current drinker	967 (71.2)	4170 (73.6)	5176 (73.2)	1481 (71.0)	
Former drinker	337 (24.8)	1245 (22.0)	1613 (22.8)	514 (24.6)	
Never drinker	54 (4.0)	250 (4.4)	283 (4.0)	92 (4.4)	
Physical activity, *n* (yes, %)	1224 (90.1)	5046 (89.0)	6305 (89.0)	1825 (87.4)	0.074
Hypertension, *n* (%)	570 (42.0)	2410 (42.5)	3046 (43.0)	886 (42.4)	0.878
Hypotensor, *n* (yes, %)	304 (22.4)	1159 (20.4)	1533 (21.6)	521 (25.0)	< 0.001
Hyperlipidemia, *n* (yes, %)	519 (38.2)	2413 (42.6)	3499 (49.4)	1218 (58.3)	< 0.001
Lipid-lowering drugs, *n* (yes, %)	105 (7.7)	376 (6.6)	462 (6.5)	146 (7.0)	0.394
Family history of diabetes, *n* (yes, %)	56 (4.2)	214 (3.9)	287 (4.2)	68 (3.3)	0.352
Family history of CVD, *n* (yes, %)	104 (7.7)	47 (8.2)	610 (8.6)	141 (6.8)	0.048
BMI (kg/m^2)	24.0 (3.2)	24.2 (3.3)	24.3 (3.3)	23.9 (3.6)	< 0.001
WC (cm)	80.9 (9.0)	81.9 (9.3)	82.5 (9.2)	82.9 (9.9)	< 0.001
SBP (mmHg)	123.7 (17.2)	126.6 (17.4)	129.0 (18.9)	133.3 (19.7)	< 0.001
DBP (mmHg)	73.9 (9.6)	76.9 (10.3)	78.6 (10.8)	80.2 (11.7)	< 0.001
TG (mmol/L)	1.32 (1.00)	1.35 (0.94)	1.39 (1.05)	1.38 (0.90)	0.021
TC (mmol/L)	5.17 (0.93)	5.16 (0.93)	5.18 (0.93)	5.18 (0.95)	0.665
HDL-C (mmol/L)	1.47 (0.38)	1.48 (0.42)	1.46 (0.40)	1.47 (0.48)	0.159
FPG (mmol/L)	5.53 (0.54)	5.49 (0.58)	5.51 (0.58)	5.62 (0.59)	< 0.001

The data are summarized as the mean (SD) for continuous variables or as a numerical proportion for categorical variables

P value were derived from the analyses of covariance for continuous variables or Chi squared analysis for categorical variables

bpm beats per minute, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *FPG* fasting plasma glucose, *CVD* cardiovascular disease

Associations between RHR and incident risk of diabetes or prediabetes

During a mean (SD) follow-up of 4.5 (0.5) years (total person-years, 73,412), we documented 1110 incident diabetes cases (1294 incident diabetes cases diagnosed with additionally inclusion of HbA1c levels as criteria). As shown in Table 2, after adjustment for potential confounders, higher resting heart rate was independently associated with increased incident risk of diabetes and prediabetes, respectively. Each 10 bpm increase in RHR was associated with 10% (95% CI 3.0–18%) increased incident diabetes risk and 12% (95% CI 6.0–18%) increased prediabetes risk. Compared with the reference group (≤ 60 bpm), participants with 61–70 bpm (HR = 1.19; 95% CI 0.91–1.56), 71–80 bpm (HR = 1.37; 95% CI 1.05–1.78), and > 80 bpm (HR = 1.40; 95% CI 1.05–1.88) had a higher risk of incident diabetes (*P* trend = 0.005). Similar results were obtained for RHR and prediabetes (*P* trend < 0.001). When we additionally included HbA1c (≥ 6.5% for diabetes and 5.7–6.4% for prediabetes) as criteria to diagnose diabetes and prediabetes, the associations between RHR and incident diabetes risk (*P* trend = 0.008) and prediabetes risk (*P* trend = 0.021) remained similar (Supplementary Table 2). With Each 10 bpm of resting heart rate increase, the corresponding HR and OR was 1.09 (1.03–1.16) and 1.06 (1.01–1.12), respectively. In the sensitivity analysis, excluding participants who developed diabetes during the first 2 years of follow-up,

Table 2 HRs (95% CIs) and ORs (95% CIs) for incident diabetes and prediabetes according to resting heart rate

	Resting heart rate (bpm)				*P* trend	Each 10 bpm increment
	≤60	61–70	71–80	>80		
Diabetes						
Case/person-years	55/6134.6	378/25,802.5	512/32,100.7	155/9374.1		1110/73,411.6
Model 1	1.00	1.26 (0.97–1.64)	1.44 (1.11–1.87)	1.50 (1.13–2.01)	0.001	1.11 (1.04–1.19)
Model 2	1.00	1.21 (0.93–1.58)	1.39 (1.07–1.79)	1.45 (1.08–1.93)	0.002	1.11 (1.04–1.19)
Model 3	1.00	1.19 (0.91–1.56)	1.37 (1.05–1.78)	1.40 (1.05–1.88)	0.005	1.10 (1.03–1.18)
Prediabetes						
Case/subjects	213/741	926/3230	1368/4135	395/1085		2902/9191
Model 1	1.00	0.99 (0.83–1.18)	1.22 (1.03–1.45)	1.42 (1.16–1.74)	<0.001	1.13 (1.07–1.19)
Model 2	1.00	0.98 (0.82–1.17)	1.20 (1.01–1.43)	1.41 (1.15–1.73)	<0.001	1.13 (1.07–1.19)
Model 3	1.00	0.97 (0.81–1.16)	1.16 (0.98–1.39)	1.37 (1.12–1.69)	<0.001	1.12 (1.06–1.18)

Model 1: Adjusted for age and sex

Model 2: Adjusted for Model 1 and further adjusted for BMI

Model 3: Adjusted for Model 2 and further adjusted for education, smoking status, drinking status, physical activity, hypertension, hyperlipidemia, use of medications (hypotensor, lipid-lowering), family history of diabetes, and cardiovascular disease

excluding participants with hypertension, or exclusion of participants with RHR less than 50 bpm or larger than 100 bpm did not materially change the positive associations of RHR with incident risk of diabetes and prediabetes (Supplementary Table 3).

Associations of individual SNP and RHR-related GRS with RHR and diabetes risk

Among the 65 SNPs identified in the previous GWAS on RHR, five SNPs were associated with RHR with statistical significance in the present study. The strongest effects were observed for rs1015451 in *GJA1* on RHR ($\beta = 0.59$; 95% CI 0.27–0.91; $P < 0.001$). However, none of the 5 SNPs were significantly associated with diabetes risk (all $P > 0.05$; Table 3). Among the study participants, the weighted GRS was normally distributed with mean (SD) of 3.1 (0.7). Each SD increase in GRS was associated with 0.71 bpm (95% CI 0.49–0.93) increase in resting heart rate (Table 3). The unweighted GRS and weighted GRS of RHR were not associated with the potential confounders of RHR (Supplementary Table 4).

As shown in Table 3, when we used the weighted GRS to estimate the unconfounded effects of resting heart rate on diabetes risk, no significant association was observed (OR = 1.00 [95% CI 0.95–1.05]). Further adjustment for RHR slightly attenuated the association between weighted GRS and diabetes risk (OR = 0.99, 95% CI 0.94–1.04, $P = 0.75$). Similar trend was detected when unweighed GRS was used as instrumental variable. There were no statistically significant differences between the observed and the expected effects of GRS on diabetes risk ($P > 0.05$).

In addition, no differential effects were found in subgroups based on age, sex, BMI, hypertension, and hyperlipidemia (Supplementary Table 5). Furthermore, as Supplementary Table 6 indicates, the weighted GRS based on all 65 SNPs were significantly and positively associated with RHR but not associated with diabetes risk. Similar results were obtained for the simple unweighted GRS.

Discussion

In the present large prospective cohort study, elevated resting heart rate was independently and significantly associated with increased incident risk of diabetes. However, the Mendelian randomization analysis did not find causal association between them but provided limited evidence for the causal association between resting heart rate and diabetes risk.

Resting heart rate has been reported as an independent risk factor of diabetes in previous studies. Most previous studies were conducted in Western populations [8, 13–15]. A few studies evaluated the association between RHR and diabetes in China [7, 9, 11]. Zhang et al. [7] reported that a high RHR was independently associated with a moderately increased diabetes risk in which only female participants were included. The other cross-sectional study including 16,636 subjects from rural communities demonstrated that a fast RHR is associated with an increased risk of undiagnosed diabetes [9], but the cross-sectional design does not offer support to causality statements. Most recently, a Kailuan prospective study also reported that a high versus low RHR was associated with a 40% increased risk of diabetes [11]; however, this study failed to exclude participants with atrial fibrillation or other rhythm disturbances. Therefore,

Table 3 Association of individual RHR-related SNPs and GRS with RHR and diabetes risk

SNP/GRS	Gene	MAF	RHR increasing allele/other allele	Effect size on RHR (bpm)		Observed association with diabetes risk		Expected association with diabetes risk	*P* value[b]	Observed association with diabetes adjusted for RHR	
				Beta (95% CI)	*P* value[a]	OR (95% CI)	*P* value[a]	OR (95% CI)		OR (95% CI)	*P* value[a]
rs7612445	*GNB4*	0.14	G/T	0.66 (0.20–1.11)	0.004	0.93 (0.84–1.03)	0.14	1.009 (1.009–1.009)	0.10	0.92 (0.83–1.02)	0.10
rs2358740	*CACNA1D*	0.35	G/T	0.43 (0.09–0.76)	0.012	0.99 (0.92–1.06)	0.71	1.006 (1.006–1.006)	0.61	0.98 (0.91–1.06)	0.60
rs6845865	*ARHGAP10*	0.40	T/C	0.39 (0.01–0.78)	0.043	0.93 (0.86–1.01)	0.10	1.005 (1.005–1.005)	0.08	0.93 (0.85–1.01)	0.08
rs1015451	*GJA1*	0.42	C/T	0.59 (0.27–0.91)	< 0.001	1.07 (0.99–1.15)	0.06	1.008 (1.008–1.008)	0.08	1.07 (0.99–1.15)	0.08
rs16974196	*C19orf47*	0.40	A/G	0.44 (0.12–0.76)	0.007	1.02 (0.95–1.10)	0.54	1.006 (1.006–1.006)	0.65	1.02 (0.95–1.09)	0.64
Unweighted GRS (1-SD increase)				0.70 (0.48–0.92)	< 0.001	1.00 (0.95–1.05)	0.92	1.009 (1.009–1.009)	0.63	0.99 (0.94–1.04)	0.64
Weighted GRS (1-SD increase)				0.71 (0.49–0.93)	< 0.001	1.00 (0.95–1.05)	0.96	1.009 (1.009–1.009)	0.74	0.99 (0.94–1.04)	0.75

RHR resting heart rate, *SNPs* single nucleotide polymorphisms, *GRS* genetic risk score, *MAF* minor allele frequency

[a] Adjusted for age, sex, BMI, smoking status, drinking status, and physical activity

[b] *P* value for difference between expected and observed association with diabetes

large prospective cohorts to validate the association between RHR and incident diabetes risk were warranted. The findings of the present study were in line with these reports. Compared with the reference group (≤ 60 bpm), participants with RHR ≥ 80 bpm had 40% higher incident risk of diabetes, which is comparable to the previous studies. Similar as diabetes, we also found positive association of RHR with prediabetes risk.

Although the epidemiology studies including the present study found positive associations between RHR and diabetes risk, however, whether RHR has causal effects on diabetes risk still remained to be investigated. Cause-and-effect relationship between exposure and diseases such as RHR and diabetes risk can be studied using the Mendelian randomization analysis [16]. The Mendelian randomization uses genetic variants as a surrogate marker for risk factors, can eliminate the influence of confounders, and avoid reverse causality [23]. Mendelian randomization analysis is a valid approach to explore evidence for causality, given that certain assumptions are met [26]. First, there should be a strong association between genetic variants (instrumental variable) and the exposure variable of resting heart rate. In the present study, all selected SNPs were strongly associated with resting heart rate in previous large GWAS study [17, 18]. Second, the instrumental variable should be independent of potential confounders (confounders in the association between resting heart rate and diabetes risk). As Supplementary Table 4 shows, no associations were found for GRS of RHR with the confounders. Third, the instrumental variable affects the outcome only through the risk factor of interest. In the present study, none of the SNPs were in linkage disequilibrium with loci known to influence diabetes risk [27–29], which strengthens this assumption. Although no statistical significance was found between the genetic variants of RHR and diabetes risk and this finding did not lend evidence for the causal association between RHR and diabetes, we could not demonstrate the causal associations of RHR with diabetes risk due to the relatively small sample size for the Mendelian randomization analysis and the small contribution of the GRS to the variation of RHR risk, which partly explained the null association. In the present study, the unweighted GRS and weighted GRS only explained 0.8% and 0.9% of the total variation of RHR risk, respectively (data not shown), comparable to the previous Mendelian randomization studies [30]. In addition, most of the loci we selected were derived from GWAS conducted in European and limited SNPs from Asian population [17, 18], which might partly contribute to the null findings for genetic differences between races. Finding more RHR-related variants especially in Asian population is warranted in further Mendelian randomization analysis.

The present study has several strengths. Firstly, to our knowledge, the present study was the first one to investigate

the causal association between RHR and diabetes risk. Although we did not provide solid evidence for the causal role of resting heart rate in the diabetes development, the expected direction of a null association might provide new clue for the future studies. Secondly, the baseline and incident diabetes cases were diagnosed in terms of rigorous standards and the false positive could be reduced to a large extent. Thirdly, the present prospective cohort study with a considerably large sample size could provide a relatively strong epidemiological evidence.

There are several limitations in the current study. Firstly, although we adjusted for a wide range of confounders, the possibility of residual confounding couldn't be ruled out. Secondly, RHR was assessed by auscultation, which was likely to be prone to measurement error. However, previous studies have indicated that auscultation by physician was strongly correlated with electrocardiographic findings and might be adequate alternative measures for RHR in the absence of electrocardiography [31].

Our findings demonstrated that higher resting heart rate was associated with higher incident risk of diabetes in the Chinese population. The Mendelian randomization analysis lent limited evidence for the causal roles of resting heart rate in the development of diabetes. Further studies with large sample size are warranted to validate these findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study has been approved by the Ethics and Human Subject Committee of the School of Public Health, Tongji Medical College, and Dongfeng General Hospital, the Dongfeng Motor Corporation (DMC).

Informed consent All study participants provided written informed consents.

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