Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 236–243

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

6-year change in resting heart rate is associated with incident type 2 diabetes mellitus

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Received 25 August 2018; received in revised form 13 November 2018; accepted 7 December 2018
Handling Editor: Simona Frontoni
Available online 14 December 2018

KEYWORDS
Resting heart rate;
Type 2 diabetes mellitus;
Epidemiology;
Prospective cohort study

Abstract *Background and aims:* Elevated resting heart rate (RHR) is associated with risk of type 2 diabetes mellitus (T2DM). However, the association of change in RHR (ΔRHR) and incident T2DM is not fully elucidated. We aimed to assess the dose–response association between 6-year ΔRHR and T2DM.
Methods and results: A total of 12155 non-T2DM participants ≥18 years old were enrolled during 2007–2008 and followed up during 2013–2014. ΔRHR was calculated by subtracting the baseline RHR from the RHR value at 6-year follow-up. Age-, sex-, and RHR-specific relative risks (RRs) and 95% confidence intervals (CIs) for the effect of ΔRHR on incident T2DM were calculated by using modified Poisson regression models. As compared with ΔRHR of 0 beats/min, the adjusted risk of T2DM was significantly increased with RHR increment and reduced with RHR reduction. ΔRHR was positively associated with future risk of T2DM [RR per unit increase: 1.03 (1.03–1.04)]. As compared with stable change in RHR group (−5<ΔRHR<5 beats/min), for ΔRHR ≤ −10 beats/min, −10<ΔRHR ≤ −5 beats/min, 5≤ΔRHR<10 beats/min, and ΔRHR ≥10 beats/min groups, the pooled adjusted RR (95% CI) of T2DM was 0.69 (0.55–0.86), 0.90 (0.73–1.11), 1.31 (1.07–1.61), and 1.90 (1.59–2.26), respectively. This significant association still existed on subgroup analyses based on age, sex, and baseline RHR and sensitivity analyses.
Conclusions: Dynamic RHR change was significantly associated with incident T2DM. Our study suggests that RHR may be a non-invasive clinical indicator for interventions aiming to reduce incident T2DM in the general population.

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https://doi.org/10.1016/j.numecd.2018.12.003
0939-4753/

Introduction

Heart rate is a simple and accessible clinical cardiovascular parameter [1]. Over the last 35 years, numerous epidemiologic studies confirmed that resting heart rate (RHR) is associated with all-cause and cardiovascular mortality in the general population and in patients with various cardiovascular diseases (hypertension, coronary heart disease, and chronic heart failure) [2,3]. Patients with coronary artery disease and heart failure may benefit from target heart rate reduction [4]. However, despite this evidence, RHR is still a neglected cardiovascular risk factor in etiological studies.

In the general population, non-randomized prospective cohort studies found RHR was an independent predictor of cardiovascular disease [5]. RHR but not heart rate variability is a sensitive marker of the autonomic nervous system and is also associated with glycemic status [6,7]. However, the association between RHR and type 2 diabetes mellitus (T2DM) is still not fully understood in the general population. Previous cohort studies found elevated RHR was positively associated with incident T2DM [8–10]; however, others found the association was no longer significant after adjustment for potential confounding factors [11,12]. A dose–response meta-analysis later showed a nonlinear association between RHR and T2DM and estimated that the risk of T2DM would increase 19% for every 10 beats/min increment in RHR [13].

From previous findings that RHR may add to the pathogenesis of T2DM, whether a change in RHR would affect future T2DM risk and whether healthy people would benefit from RHR reduction have been of recent interests, but the corresponding information is scarce. Only one Korean survey reported an increase in RHR over 2 years was significantly associated with a risk of diabetes, independent of baseline RHR and glycometabolic parameters [14]. However, this study used RHR<5 beats/min as a reference, which may overestimate the risk because people with RHR reduction may have decreased risk.

Thus, to fill in the gaps in the current research, we aimed to determine whether change in RHR would affect incident T2DM considering a stable change in RHR (−5 to 5 beats/min) as the reference group. We additionally conducted subgroup analyses to better control the confounders of age, sex, and baseline RHR, which may be associated with T2DM, or other risk factors of T2DM including smoking, obesity, and a sedentary lifestyle [15,16].

Methods

Study design and participants

The study design, participants, methods, and measurements were previously described [17,18]. Briefly, data for current analysis came from the Rural Chinese Cohort Study, which randomly recruited 20194 participants ≥18 years old living in rural area of Luoyang city in the middle of China during July to August 2007 and July to August 2008. At baseline, self-reported data on demographic information, lifestyle risk factors, and personal medical history were collected by using designed questionnaires. Well-trained examiners took anthropometric and laboratory measurements for each participant. These participants were then followed up with the same procedures as the baseline examination during July to August of 2013 and July to October of 2014. Ultimately, 17265 participants were successfully followed up (response rate 85.5%). This study protocol was approved by the Ethics Committee of Shenzhen University Health Science Center, and informed consent was obtained from all study participants.

The dynamic 6-year change in RHR (ΔRHR) was calculated by subtracting RHR measured at baseline from that measured at follow-up. ΔRHR>0 beats/min represented RHR increased from baseline to follow-up and ΔRHR<0 beats/min represented RHR decreased from baseline to follow-up. Among 20194 participants, those with a baseline diagnosis of T2DM (n = 1696) or type 1 diabetes mellitus (n = 14) or missing data on T2DM status (n = 11) were excluded. Then, 4766 participants without ΔRHR data and 1552 without complete follow-up data for T2DM were excluded from the remaining 18473 participants. Finally, 12155 participants were retained to examine the association between change in RHR and incident T2DM (Supplementary Fig. S1).

Baseline data collection

Data on demographics (age and sex), socioeconomic factors (education level and monthly individual income), lifestyle (smoking, alcohol drinking, and physical activity), and medical history (stroke, myocardial infarction, heart failure, and family history of disease) were collected during face-to-face interviews. Smoking was defined as ever smoking at least 100 cigarettes during the lifetime and participants were classified as never/ever smokers [19]. Alcohol drinking was defined as consuming alcohol at least 12 times during last year [19]. Physical activity level was classified as low, moderate or high according to the International Physical Activity Questionnaire [20]. Medical history was re-checked by consulting village physicians.

Participants were guided to wear light clothing and no shoes when measuring body weight, height, and waist circumference. The values were measured twice and the means were used for analysis. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure and RHR were measured three times in the right arm by using an electronic blood pressure monitor (HEM-770AFuzzy, Omron, Japan) with participants in a seated position after at least a 5-min rest and at 30-sec intervals [21]. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or use of anti-hypertensive medication [22].

Overnight fasting blood samples were collected for assessing fasting glucose and levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDLC). Details about the storage and measurement methods were published previously [18].

Follow-up examination

At follow-up, the same measurements were taken as for the baseline examination. According to Chinese guideline [23], T2DM was defined as fasting glucose ≥7.0 mmol/L, or the use of insulin or oral hypoglycemic agents, or a self-reported history of T2DM, which agreed with the diagnostic criteria of T2DM at both baseline and follow-up examinations.

Statistical analyses

After testing for normality, all continuous variables were presented as median (interquartile range) because of skewed distribution, and categorical variables were expressed as number (percentage). ΔRHR (beats/min) was classified into 5 groups: ΔRHR ≤ −10 beats/min, −10<ΔRHR ≤ −5 beats/min, −5<ΔRHR<5 beats/min, 5≤ΔRHR<10 beats/min, and ΔRHR≥10 beats/min. The linear trend for baseline demographic information among ΔRHR groups was tested by linear regression for continuous data and logistic regression for categorical data. Differences in incidence of T2DM among different baseline age and RHR groups were examined by chi-square test.

To describe the dose–response association between ΔRHR and incident T2DM, we used restricted cubic splines incorporated in modified Poisson models [24], with ΔRHR = 0 beats/min as a reference. Participants were then sub-grouped by age, sex, and baseline RHR. Relative risks (RRs) and 95% confidence intervals (CIs) for the association of ΔRHR (assessed in the 5 groups or per unit increment) and incident T2DM were estimated by modified Poisson regression. For the multivariate analyses, Model 1 was age- and sex-adjusted. Then Model 2 adjusted for baseline age, sex, monthly income, education, smoking, alcohol drinking, physical activity, and family history of T2DM. Finally, Model 3, based on Model 2, additionally adjusted for baseline RHR, BMI, waist circumference, SBP, fasting glucose, TC, TG, and HDLC levels. Additionally, we performed sensitivity analysis to test the robustness of the results by excluding baseline participants with impaired fasting glucose (IFG) (n = 3595) (fasting glucose, 6.1–7.0 mmol/L) [23], or known pre-existing cardiovascular diseases [hypertension (n = 3702), stroke (n = 89), myocardial infarction (n = 64), and heart failure (n = 71)].

All statistical analyses involved using Stata 12 (StataCorp, College Station, TX, USA) and SAS v9.1 (SAS Inst., Cary, NC). Statistical significance was determined with two-sided $p < 0.05$.

Results

The median age of all study participants was 51 years (interquartile range, 41–59) and 37.9% were men (Supplementary Table S1). Among the 5 groups of ΔRHR, RHR increased ≥10 beats/min was more frequently associated with the lowest RHR at baseline (Table 1). People

Table 1 Baseline characteristics of study participants by change in resting heart rate (ΔRHR) from baseline to follow-up.

Baseline characteristics	ΔRHR (beats/min)					*p* for trend
	ΔRHR ≤ −10	−10<ΔRHR ≤ −5	−5<ΔRHR<5	5≤ΔRHR<10	ΔRHR≥10	
No. of participants	2313	2095	4508	1626	1613	
Age (years)	48 (40–58)	51 (42–59)	51 (42–60)	51 (41–59)	52 (42–60)	<0.0001
Men (%)	784 (33.9)	701 (33.5)	1668 (37.0)	664 (40.8)	792 (49.1)	<0.0001
Monthly individual Income >500 CNY (%)	138 (6.0)	140 (6.7)	285 (6.3)	106 (6.5)	112 (6.9)	0.473
Education High school or higher (%)	232 (10.0)	211 (10.1)	437 (9.7)	169 (10.4)	176 (10.9)	0.207
Smoking (%)	525 (22.7)	512 (24.4)	1165 (25.8)	472 (29.0)	554 (34.4)	<0.0001
Alcohol drinking (%)	224 (9.7)	191 (9.1)	511 (11.3)	189 (11.6)	245 (15.2)	<0.0001
Physical activity Low (%)	689 (29.8)	642 (30.6)	1274 (28.3)	417 (25.7)	480 (29.8)	0.173
Family history of diabetes (%)	120 (5.2)	120 (5.7)	241 (5.4)	84 (5.2)	81 (5.0)	0.587
SBP (mmHg)	121.7 (110.0–136.0)	122.0 (111.0–136.7)	121.7 (111.3–135.7)	121.7 (111.3–136.0)	125.0 (113.0–138.7)	0.001
DBP (mmHg)	78.0 (71.0–86.7)	77.7 (71.0–85.7)	77.0 (70.3–85.0)	76.7 (70.0–85.0)	78.3 (71.0–86.3)	<0.0001
RHR (beats/min)	83 (76–89)	76 (70–82)	72 (67–78)	70 (64–75)	69 (63–75)	<0.0001
BMI (kg/m^2)	23.8 (21.5–26.5)	24.2 (21.7–26.6)	24.2 (21.9–26.6)	23.9 (21.7–26.3)	23.9 (21.6–26.5)	0.143
Waist circumference (cm)	81.0 (73.9–88.7)	81.6 (75.0–88.8)	82.1 (75.3–89.5)	81.8 (75.2–89.0)	82.0 (75.0–90.0)	<0.0001
Glucose (mmol/L)	5.34 (5.00–5.73)	5.33 (5.00–5.67)	5.30 (4.97–5.66)	5.28 (4.94–5.63)	5.31 (4.99–5.68)	0.003
TC (mmol/L)	4.31 (3.76–4.98)	4.41 (3.85–5.01)	4.40 (3.84–5.03)	4.35 (3.83–4.97)	4.37 (3.86–5.03)	0.042
TG (mmol/L)	1.31 (0.93–1.96)	1.38 (0.96–1.96)	1.35 (0.97–1.94)	1.36 (0.97–1.94)	1.35 (0.97–1.90)	0.184
HDLC (mmol/L)	1.16 (1.00–1.34)	1.14 (0.99–1.32)	1.14 (0.99–1.32)	1.14 (0.98–1.31)	1.13 (0.99–1.31)	0.005

Data are median (interquartile range) or number (percentage).
Abbreviation: CNY, Chinese Yuan; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDLC, high-density lipoprotein cholesterol.

with greater RHR increment were older, more frequently men, smokers and alcohol drinkers and had high SBP, DBP, waist circumference, fasting glucose, and TC (all $p < 0.05$).

During follow-up (median 6.01 years), the incidence of T2DM was 3.35%, 6.84%, and 7.04% with age 18−39, 40−59, and ≥60 years, respectively, with a significant upward trend ($p < 0.0001$) (Table 2). The incidence of T2DM was 5.87%, 6.02%, and 6.86% with baseline RHR<70, 70−80, and >80 beats/min, respectively (Table 2). Restricted cubic splines were used for a visual assessment of a curvilinear association between ΔRHR and incident T2DM. As compared with ΔRHR = 0 beats/min, the adjusted risk of T2DM significantly increased with ΔRHR increment and decreased with ΔRHR reduction (Fig. 1). After excluding people with stroke, myocardial infarction, heart failure, or hypertension at baseline, this trend did not change.

For all study participants, the incidence of T2DM increased with the increasing ΔRHR as compared with ΔRHR reduction ≤10 beats/min (Table 3). ΔRHR was positively associated with future risk of T2DM [RR per unit increase: 1.03 (1.03−1.04)] (**Model 3**$^{\text{for total}}$). As compared with stable ΔRHR (−5 to 5 beats/min), with ΔRHR ≤ −10 beats/min, −10<ΔRHR ≤ −5 beats/min, 5≤ΔRHR<10 beats/min, and ΔRHR≥10 beats/min, the pooled adjusted RR values for T2DM were 0.69 (0.55−0.86), 0.90 (0.73−1.11), 1.31 (1.07−1.61), and 1.90 (1.59−2.26), respectively (**Model 3**$^{\text{for total}}$). Men with ΔRHR≥10 beats/min showed a 1.52-fold risk of T2DM and women a 2.19-fold risk. Two sensitivity analyses showed similar results.

Because age and RHR may have significant effects on incident T2DM, we performed subgroup analyses. With 3 age groups (18−39, 40−59, and ≥60 years), ΔRHR was always positively associated with increased risk of T2DM (Table 3). Relatively young people (18−39 years) with ΔRHR≥10 beats/min were at higher risk of developing T2DM [RR: 2.83 (1.62−4.93)] than those with stable ΔRHR (−5 to 5 beats/min) (**Model 3**), and those with ΔRHR ≤ −10 beats/min showed significantly reduced risk [RR: 0.36 (0.16−0.79)]. For middle-aged people (40−50 years), risk of T2DM was increased with both 5≤ΔRHR<10 beats/min [RR: 1.42 (1.12−1.80)] and ΔRHR≥10 beats/min [RR: 1.81 (1.45−2.26)] (**Model 3**). Meanwhile, RHR reduction ≥10 beats/min had a protective effect on incident T2DM [RR: 0.61 (0.45−0.83)]. For older people (≥60 years), risk of T2DM was still increased with ΔRHR≥10 beats/min, but RHR reduction did not significantly reduce the T2DM risk.

When the association between ΔRHR and incident T2DM was evaluated by baseline RHR status, we still found an upward trend of T2DM incidence with RHR increment (Table 4). With both baseline RHR<70 and >80 beats/min, RHR increment ≥10 beats/min was associated with a 2-fold increased risk of T2DM as compared with stable RHR (**Model 3**). With baseline RHR 70−80 beats/min, ΔRHR ≤ −10 beats/min, 5≤ΔRHR<10 beats/min, and ΔRHR≥10 beats/min was associated with a 0.54-, 1.65-, and 1.69-fold risk of T2DM, respectively (**Model 3**). Two sensitivity analyses showed similar results.

Table 2 The incidence of type 2 diabetes mellitus (T2DM) by age, resting heart rate (RHR) and glycemic status.

Baseline characteristics	No. of participants	No. of T2DM cases	Incidence (%)
Age (years)			
18−39	2421	81	3.35
40−59	6737	461	6.84
≥60	2997	211	7.04
p for trend			<0.0001
RHR (beats/min)			
<70	3985	234	5.87
70−80	4964	299	6.02
>80	3206	220	6.86
p for trend			0.0926
Glycemic status			
Normal fasting glucose	8560	257	3.00
Impaired fasting glucose	3595	496	13.80
p			<0.0001

Discussion

This is the first Chinese population-based study to elucidate the effect of dynamic change in RHR on risk of T2DM. Our data indicate a dose−response association between RHR increment and increased risk of T2DM, independent of baseline RHR or the effects of age, socioeconomic and behavioral factors, and anthropometric and laboratory measurements. Our study also confirmed a trend to reduced risk of T2DM with RHR reduction. This association still remained after excluding people with stroke, myocardial infarction, heart failure, or hypertension at baseline.

Sustained elevated RHR has direct detrimental effects and contributes to the pathogenesis of cardiovascular diseases, including atherosclerosis, myocardial ischemia, ventricular arrhythmias, left ventricular dysfunction, and heart failure [1,25]. In addition, high RHR is considered a marker for autonomic activity and increased sympathetic nerve system activity [26]. There are several biological mechanisms by which sympathetic activation causes both acute and chronic insulin resistance and may predispose to diabetes: 1) sympathetic activation induces vasoconstriction and decreases skeletal muscle blood flow, thereby impairing glucose uptake into the skeletal muscle [27]; 2) sympathetic stimulation inhibits the secretion of insulin from pancreatic β cells [28]; and 3) sympathetic overactivity simulates the renin-angiotensin-aldosterone system, which increases heart rate and leads to insulin resistance [29]. Additionally, relatively high RHR is often found together with increased blood pressure, atherogenic blood lipid profile, inflammation, obesity, and metabolic syndrome [30,31]. These dysfunctions and diabetes seem to operate in a vicious circle in their causal relations, and elevated RHR and high blood pressure may be intermediate accelerators of the vicious circle [9].

The association between RHR and T2DM was examined in previous epidemiological studies in European [32,33], American [11,12,34], Australian [8], and Asia populations [9,10,35,36]. Although these studies had different sample size, target population, duration of follow-up, and RHR

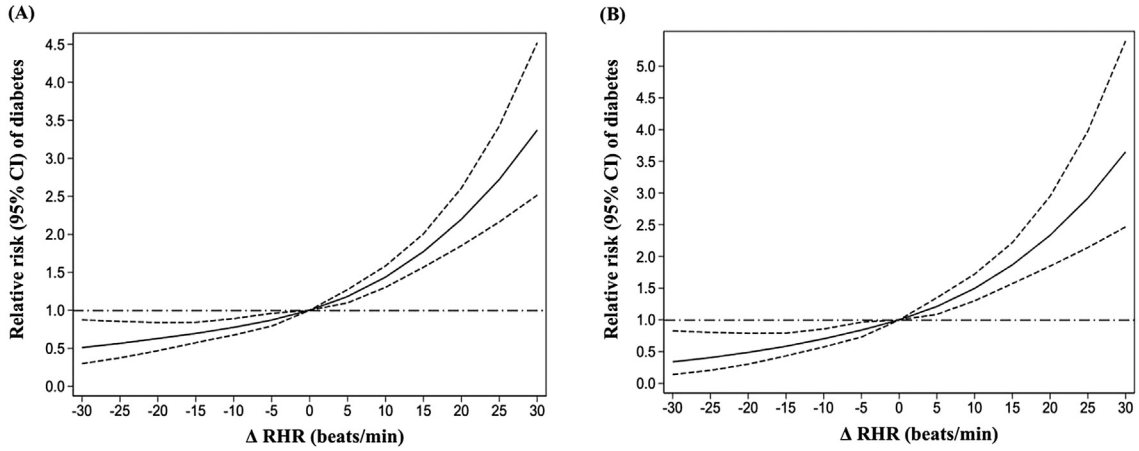

Figure 1 Change in resting heart rate (RHR) on a continuous scale and relative risk of type 2 diabetes mellitus (A) Total participants and (B) participants excluded because of stroke, myocardial infarction, heart failure, or hypertension at baseline. Relative risk (solid line) and 95% confidence intervals (CIs) (dashed lines) from modifed Poisson regression with restricted cubic splines, with ΔRHR (beats/min) = 0 as a reference. Multifactorial adjustment was for age, sex, income, education, smoking, alcohol drinking, physical activity, body mass index, waist circumference, systolic blood pressure, RHR, fasting glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol at baseline.

categories, most confirmed an association of high RHR with risk of T2DM and also that a sex difference may exist. Only two Chinese cohort studies with a large sample size have examined this issue and reported high versus low RHR associated with a 60% (only for women) and 76% (for both sexes) increase in the RR of T2DM, which strongly supports that increased RHR is an independent predictor of incident T2DM in non-Asian and also Asian populations [10,36].

Treatments to lower RHR have been beneficial in reducing all-cause mortality in patients with coronary heart disease and chronic heart failure; however, whether lowering RHR might be a preventative measure against T2DM developing in a general population with high RHR still remains unclear [4]. Studies regarding the effect of RHR change on risk of T2DM are few. Recently, a prospective cohort study of 7416 Korean adults reported a 1.31-fold greater risk of T2DM with RHR increase >10 beats/min versus <5 beats/min over 2 years and indicated the clinical importance of using RHR as prognosticator of T2DM [14]. Our study first reported the association between 6-year change in RHR and incident T2DM in a Chinese population. We considered RHR change from −5 to 5 beats/min as stable and confirmed a dose−response association between RHR increment and increased risk of T2DM. Previous studies demonstrated that the RHR-T2DM association may be affected by socioeconomic factors and anthropometric measurements as well as parameters of baseline RHR and metabolic indexes (fasting glucose and lipid profiles) [13,14,36]. Therefore, we established 3 models to identify the association step by step and found the association was not altered after considering all the probable influencing factors.

Age and sex are important unmodifiable factors associated with RHR [37]. RHR generally tends to be higher in younger than older people and in women than men [38]. Moreover, age and baseline RHR are known predictors of T2DM [36,39]. Therefore, to better control for the effect of age, sex, and baseline RHR and provide precision preventive evidence for different target populations, we stratified the study participants into 3 subgroups. Risk of T2DM was always higher with greater increases in RHR (ΔRHR≥10 beats/min) regardless of age, sex, and baseline RHR than with stable RHR. This finding indicates that a larger increase in RHR is independently associated with greater risk of T2DM. However, the effects of greater reduction in RHR on T2DM differed by subgroups. For men, young and middle-aged people, or those with baseline RHR 70−80 beats/min, lowering the increase in RHR might be a protective factor of T2DM.

Besides subgroup analyses, we also conducted 2 sensitivity analyses to ensure the validity of our findings. We excluded people with baseline IFG as those who probably had dysglycemia, which may lead to future T2DM rather than be an effect of increased RHR. We also excluded people with cardiovascular diseases because their antihypertensive (n = 2288) and cardiovascular disease medications would affect RHR and could affect the results. Finally, the results did not significantly change with these exclusions and still confirmed the dose−response association between RHR change and T2DM risk.

This study has many strengths, including its large sample size, broad range of data collected, and well-measured covariates, which allowed for age-, sex-, and RHR-stratified analyses with adjustment for potential confounders. However, some limitations should be noted. First, the sample was limited geographically and ethnically, consisting primarily of rural Chinese people. Whether our findings are also applicable to other ethnicities is unknown. Second, we did not use oral glucose tolerance test because of low rates of participation, which may lead to underestimating the incidence of T2DM. Third, the definition of smoking was neither quantity-based nor distinguished by never/ever/current smokers, so residual confounding is inevitable. Fourth, some lifestyles (smoking, alcohol drinking, and exercise) would affect changes in RHR. However, we have no information on whether a change in RHR was due to modified lifestyles or some diseases, which may bias the

Table 3 Risk of type 2 diabetes mellitus (T2DM) by dynamic change in resting heart rate (ΔRHR) from baseline to follow-up by age categories.

	ΔRHR (beats/min)					per unit increase
	ΔRHR ≤ −10	−10<ΔRHR ≤ −5	−5<ΔRHR<5	5≤ΔRHR<10	ΔRHR≥10	
Total (n = 12155)						
No. of participants	2313	2095	4508	1626	1613	
No. of T2DM cases	98	109	257	114	175	
Incidence (%)	4.2	5.2	5.7	7.0	10.9	
Model 1[a]	0.76 (0.61−0.96)	0.91 (0.74−1.14)	1.00	1.24 (1.00−1.54)	1.91 (1.59−2.30)	1.03 (1.02−1.04)
Model 2[b]	0.77 (0.62−0.97)	0.92 (0.74−1.14)	1.00	1.25 (1.01−1.54)	1.92 (1.59−2.31)	1.03 (1.02−1.04)
Model 3[c] (for total)	0.69 (0.55−0.86)	0.90 (0.73−1.11)	1.00	1.31 (1.07−1.61)	1.90 (1.59−2.26)	1.03 (1.03−1.04)
Model 3[c] (for men)	0.60 (0.41−0.87)	0.59 (0.39−0.87)	1.00	1.04 (0.74−1.46)	1.52 (1.15−1.99)	1.03 (1.02−1.04)
Model 3[c] (for women)	0.76 (0.57−1.01)	1.11 (0.87−1.42)	1.00	1.50 (1.17−1.93)	2.19 (1.75−2.74)	1.04 (1.03−1.05)
Sensitivity analysis (Model 4[d])	0.62 (0.45−0.86)	0.96 (0.72−1.27)	1.00	1.40 (1.06−1.85)	2.14 (1.68−2.72)	1.04 (1.03−1.05)
Sensitivity analysis (Model 5[e])	0.55 (0.39−0.79)	0.94 (0.70−1.26)	1.00	1.40 (1.06−1.85)	2.05 (1.60−2.61)	1.04 (1.03−1.05)
By age categories						
Age 18−39 years (n = 2421)						
No. of participants	575	385	813	314	334	
No. of T2DM cases	9	13	24	11	24	
Incidence (%)	1.6	3.4	3.0	3.5	7.2	
Model 1[a]	0.57 (0.26−1.22)	1.20 (0.62−2.32)	1.00	1.11 (0.55−2.27)	2.33 (1.31−4.15)	1.04 (1.01−1.06)
Model 2[b]	0.55 (0.26−1.18)	1.13 (0.58−2.20)	1.00	1.13 (0.55−2.32)	2.30 (1.29−4.07)	1.04 (1.02−1.06)
Model 3[c]	0.36 (0.16−0.79)	0.91 (0.47−1.78)	1.00	1.52 (0.75−3.07)	2.83 (1.62−4.93)	1.05 (1.03−1.07)
Sensitivity analysis (Model 4[d])	0.25 (0.07−0.98)	1.26 (0.49−3.23)	1.00	1.13 (0.29−4.33)	3.74 (1.47−9.48)	1.06 (1.03−1.10)
Sensitivity analysis (Model 5[e])	0.30 (0.12−0.75)	0.62 (0.26−1.49)	1.00	1.48 (0.71−3.11)	2.84 (1.55−5.21)	1.06 (1.04−1.09)
Age 40−59 years (n = 6737)						
No. of participants	1223	1210	2561	913	830	
No. of T2DM cases	53	66	165	79	98	
Incidence (%)	4.3	5.5	6.4	8.7	11.8	
Model 1[a]	0.68 (0.50−0.92)	0.84 (0.64−1.11)	1.00	1.35 (1.04−1.75)	1.85 (1.46−2.36)	1.03 (1.03−1.04)
Model 2[b]	0.68 (0.51−0.92)	0.84 (0.64−1.11)	1.00	1.38 (1.06−1.78)	1.86 (1.46−2.36)	1.03 (1.03−1.04)
Model 3[c]	0.61 (0.45−0.83)	0.86 (0.66−1.11)	1.00	1.42 (1.12−1.80)	1.81 (1.45−2.26)	1.04 (1.03−1.05)
Sensitivity analysis (Model 4[d])	0.76 (0.40−1.42)	0.95 (0.55−1.63)	1.00	2.03 (1.29−3.19)	2.33 (1.49−3.66)	1.04 (1.03−1.06)
Sensitivity analysis (Model 5[e])	0.53 (0.34−0.85)	0.86 (0.61−1.22)	1.00	1.37 (0.99−1.90)	1.96 (1.45−2.65)	1.05 (1.03−1.06)
Age ≥60 years (n = 2997)						
No. of participants	515	500	1134	399	449	
No. of T2DM cases	36	30	68	24	53	
Incidence (%)	7.0	6.0	6.0	6.0	11.8	
Model 1[a]	1.18 (0.80−1.74)	1.00 (0.66−1.52)	1.00	1.01 (0.64−1.59)	2.04 (1.45−2.89)	1.02 (1.01−1.03)
Model 2[b]	1.23 (0.83−1.81)	1.02 (0.67−1.55)	1.00	1.04 (0.66−1.63)	2.04 (1.44−2.89)	1.02 (1.01−1.03)
Model 3[c]	1.18 (0.80−1.73)	1.00 (0.65−1.52)	1.00	1.01 (0.65−1.57)	1.96 (1.40−2.73)	1.02 (1.01−1.04)
Sensitivity analysis (Model 4[d])	1.00 (0.47−2.10)	1.30 (0.69−2.46)	1.00	1.01 (0.49−2.10)	1.79 (1.01−3.18)	1.02 (1.00−1.04)
Sensitivity analysis (Model 5[e])	1.11 (0.49−2.40)	1.68 (0.83−3.41)	1.00	1.40 (0.65−2.99)	2.03 (1.05−3.95)	1.02 (1.00−1.04)

[a] Adjusted for age and sex at baseline only.
[b] Adjusted for age, sex, income, education, smoking, alcohol drinking, physical activity, and family history of diabetes at baseline.
[c] Adjusted for variables in Model 2 as well as RHR, body mass index, waist circumference, systolic blood pressure, fasting glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol at baseline.
[d] Adjusted for Model 3 and further excluding participants with impaired fasting glucose at baseline.
[e] Adjusted for Model 3 and further excluding participants with stroke, myocardial infarction, heart failure, or hypertension at baseline.

results. Fifth, RHR measurements can be affected by participants' posture, measurement time, and resting state [1]. Our study allowed for participants to remain in a seated position after at least a 5-min rest and measured RHR by pulse three times during 30-sec intervals, which was recommended in a consensus meeting [40], to better ensure the accuracy of RHR. Finally, RHR was measured only twice at both baseline and 6-year follow-up; repeated-measure data are still needed to avoid making biased results due to the regression to the mean phenomenon.

Table 4 Risk of type 2 diabetes mellitus (T2DM) by dynamic change in resting heart rate (ΔRHR) from baseline to follow-up by baseline RHR.

	ΔRHR (beats/min)					per unit increase
	ΔRHR ≤ -10	−10<ΔRHR ≤ -5	−5<ΔRHR<5	5≤ΔRHR<10	ΔRHR≥10	
RHR < 70 (n = 3985)						
No. of participants	143	514	1643	809	876	
No. of T2DM cases	4	23	83	40	84	
Incidence (%)	2.8	4.5	5.1	4.9	9.6	
Model 1[a]	0.55 (0.21−1.48)	0.88 (0.56−1.38)	1.00	1.00 (0.69−1.45)	1.99 (1.48−2.67)	1.04 (1.03−1.05)
Model 2[b]	0.59 (0.22−1.57)	0.89 (0.57−1.41)	1.00	1.01 (0.70−1.46)	2.02 (1.51−2.72)	1.04 (1.03−1.05)
Model 3[c]	0.70 (0.26−1.85)	0.93 (0.60−1.43)	1.00	0.98 (0.69−1.41)	2.01 (1.52−2.64)	1.04 (1.03−1.05)
Sensitivity analysis (Model 4[d])	0.57 (0.14−2.36)	0.96 (0.49−1.89)	1.00	1.12 (0.65−1.92)	2.11 (1.37−3.25)	1.04 (1.03−1.06)
Sensitivity analysis (Model 5[e])	0.43 (0.06−3.05)	1.14 (0.63−2.07)	1.00	1.03 (0.62−1.72)	2.12 (1.43−3.15)	1.04 (1.02−1.05)
RHR 70−80 (n = 4196)						
No. of participants	784	934	2051	621	574	
No. of T2DM cases	23	45	115	55	61	
Incidence (%)	2.9	4.8	5.6	8.9	10.6	
Model 1[a]	0.52 (0.34−0.81)	0.86 (0.61−1.20)	1.0	1.59 (1.17−2.17)	1.86 (1.38−2.51)	1.04 (1.03−1.05)
Model 2[b]	0.53 (0.34−0.82)	0.85 (0.61−1.19)	1.00	1.59 (1.17−2.17)	1.86 (1.38−2.51)	1.04 (1.03−1.05)
Model 3[c]	0.54 (0.36−0.83)	0.84 (0.61−1.15)	1.00	1.65 (1.24−2.19)	1.69 (1.27−2.25)	1.04 (1.03−1.05)
Sensitivity analysis (Model 4[d])	0.71 (0.33−1.52)	1.40 (0.81−2.43)	1.00	1.92 (1.08−3.40)	1.87 (1.03−3.40)	1.03 (1.01−1.05)
Sensitivity analysis (Model 5[e])	0.51 (0.28−0.90)	0.71 (0.44−1.13)	1.00	1.63 (1.11−2.40)	1.64 (1.11−2.41)	1.04 (1.03−1.06)
RHR > 80 (n = 3206)						
No. of participants	1386	647	814	196	163	
No. of T2DM cases	71	41	59	19	30	
Incidence (%)	5.1	6.3	7.3	9.7	18.4	
Model 1[a]	0.71 (0.51−1.00)	0.88 (0.60−1.29)	1.00	1.32 (0.81−2.17)	2.45 (1.63−3.69)	1.03 (1.02−1.04)
Model 2[b]	0.71 (0.51−1.00)	0.86 (0.59−1.27)	1.00	1.33 (0.81−2.17)	2.42 (1.61−3.63)	1.03 (1.02−1.04)
Model 3[c]	0.81 (0.58−1.12)	0.96 (0.66−1.39)	1.00	1.44 (0.91−2.29)	2.13 (1.45−3.14)	1.03 (1.01−1.04)
Sensitivity analysis (Model 4[d])	0.79 (0.38−1.64)	0.96 (0.43−2.12)	1.00	2.11 (0.85−5.25)	2.98 (1.18−7.52)	1.04 (1.02−1.07)
Sensitivity analysis (Model 5[e])	0.68 (0.40−1.18)	1.25 (0.71−2.19)	1.00	1.90 (1.04−3.46)	3.72 (2.18−6.34)	1.05 (1.03−1.06)

[a] Adjusted for age and sex at baseline only.
[b] Adjusted for age, sex, income, education, smoking, alcohol drinking, physical activity, and family history of diabetes at baseline.
[c] Adjusted for variables in Model 2 as well as RHR, body mass index, waist circumference, systolic blood pressure, fasting glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol at baseline.
[d] Adjusted for Model 3 and further excluding participants with impaired fasting glucose at baseline.
[e] Adjusted for Model 3 and further excluding participants with stroke, myocardial infarction, heart failure, or hypertension at baseline.

Conclusion

In summary, with this large prospective cohort of rural Chinese adults, we found greater increase in RHR strongly associated with risk of T2DM and that age-, sex-, and baseline RHR differences may exist and affect the RHR change-T2DM risk association. Because RHR is characterized as a potential modifiable risk factor for cardiovascular diseases, our study suggests that RHR may be a non-invasive clinical indicator for interventions aiming to reduce incident T2DM. Because of the observational design of the study, which may not reveal a causal relation, further experimental studies regarding RHR management are needed to provide advanced evidence for T2DM prevention in the general population.

Funding

This work was supported by the National Natural Science Foundation of China (grant nos. 81373074, 81402752, and 81673260); the Natural Science Foundation of Guangdong Province (grant no. 2017A030313452); the Medical Research Foundation of Guangdong Province (grant no. A2017181); and the Science and Technology Development Foundation of Shenzhen (grant nos. JCYJ20140418091413562, JCYJ20160307155707264, JCYJ20170302143855721, and JCYJ20170412110537191).

Declaration of interests

All authors declare no conflict of interest relative to this study.

Contributor statements

Y.Z. and D.H. substantially contributed to the design and drafting of the study and the analysis and interpretation of the data. M.Z., Y.L., Z.Y., H.L., H.S. C.W, Y.R., D.L., C.C., F.L., X.C., L.L., Q.Z., Y.X., Q.X., J.L., S.H., Z.Y., J.L., J.C., and J.H. were involved in data collection and revised it critically for important intellectual content. All authors read and approved the final manuscript. D.H. is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

The investigators are grateful to the dedicated participants and all research staff of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2018.12.003.

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