


Independent and interactive associations of heart rate and body mass index or blood pressure with type 2 diabetes mellitus incidence: A prospective cohort study

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ABSTRACT

Aims/Introduction: An elevated heart rate has been reported to be associated with an increased incidence of type 2 diabetes mellitus. We investigated whether heart rate independently and interactively with body mass index or blood pressure was associated with the incidence of type 2 diabetes mellitus in a rural Chinese population.

Materials and Methods: We measured the association between heart rate and type 2 diabetes mellitus in the Tongxiang China Kadoorie Biobank prospective cohort study using Cox proportional hazard models. Analyses included 53,817 participants without any history of diabetes, cancer, cardiovascular or rheumatic heart disease at baseline. Incident type 2 diabetes mellitus cases were identified through linkage with established Disease Registries and the China National Health Insurance System.

Results: After a mean follow-up period of 6.9 years, 1,766 people had developed type 2 diabetes mellitus with an incidence of 4.75 per 1,000 person-years. Multivariable-adjusted hazard ratios and for type 2 diabetes mellitus across increasing quintiles of heart rate were 1.00 (reference), 1.24 (95% confidence interval [CI] 1.05–1.45), 1.21 (95% CI 1.03–1.41), 1.24 (95% CI 1.05–1.47) and 1.49 (95% CI 1.28–1.74), respectively, with a $P_{\text{trend}} < 0.001$. This relationship was particularly evident among non-overweight/obese participants. A significant interaction between heart rate and body mass index on incident type 2 diabetes mellitus was observed with a P for interaction = 0.005.

Conclusions: Elevated heart rate is independently, in interaction with a higher body mass index, associated with a higher incidence of type 2 diabetes mellitus.

INTRODUCTION

Resting heart rate has been used as a routine clinical measurement and potential prognostic marker, because it is associated with the development of myriad chronic diseases^{1,2}, especially incident cardiovascular disease (CVD)^{3,4}, and all-cause mortality⁵. Heart rate is regulated by the autonomic nervous system, and disturbances of this system balance are considered an element in CVD pathogenesis.

Recent epidemiological studies showed that the association between increased heart rate and the occurrence of cardiovascular events among adults was independent of high systolic blood pressure, physical activity level and increased waist circumference, suggesting that heart rate can be recognized as an independent risk factor of CVD⁶. Diabetes per se is considered a major risk factor of CVD; it is highly prevalent, affecting 10.9% Chinese adults in 2013; and this prevalence has been increasing rapidly in China over the years. China bears a high diabetes-related burden⁷.

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Resting heart rate might be directly associated with the development of diabetes. A small number of prospective cohort studies have found a rapid heart rate might be predictive of diabetes development in different populations. Most studies were carried out in the USA^{8,9}, Australia¹⁰, Japan^{11,12} and the Netherlands¹³, all of which are developed nations. Alternatively, the presence of central obesity and insulin resistance per se might cause an increase in heart rate through sympathetic nervous activation, rather than the heart rate driving metabolic changes.

In this context, we investigated whether resting heart rate was associated with incident type 2 diabetes mellitus in a prospective cohort. Currently, obesity is the strongest and most extensively studied risk factor of type 2 diabetes mellitus^{14,15}. Blood pressure (BP) has also been found to be independently associated with type 2 diabetes mellitus development^{16–19}. The present study explored how resting heart rate independently and interactively with either body mass index (BMI) or BP affected incident type 2 diabetes mellitus.

METHODS

Study design and population

We designed a prospective cohort study with individuals recruited from a rural region of the Zhejiang province, nested in the China Kadoorie Biobank study. Detailed methods, recruitment criteria and others in the China Kadoorie Biobank study have been published^{20–22}. All participants in the present study lived in the rural Tongxiang county of Zhejiang province, China, and were enrolled in the China Kadoorie Biobank study between 2004 and 2008.

In this study, the enrolled participants were followed up until 1 January 2014. Participants were further excluded if presenting with physician-diagnosed diabetes at baseline ($n = 2,914$), with rheumatic heart disease, cardiovascular diseases or cancer at baseline ($n = 1,051$), or if they were lost to follow up ($n = 60$). After these exclusions, 53,817 participants (22,536 men and 31,281 women) were included in our final analyses.

The ethics board of the University of Oxford, and the National and Zhejiang Provincial and the Tongxiang Centers for Disease Control and Prevention in China all approved this study. All study participants were given a written informed consent form, and a signed consent form was obtained after they willingly participated in the study.

Measurement

Interviewer-administered electronic questionnaires of demographic data (age, sex, education and annual household income), smoking and drinking status, level of physical activity, menopausal status in women, and family history of diabetes and CVD were collected at baseline. Total physical activities were converted to metabolic equivalent task hours (MET-h/day).

Anthropometric parameters, heart rate and BP were collected while interviewing participants. Height, weight and waist

circumference were measured, and BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Heart rate was determined by pulse palpation for 30 s after a 10-min rest. BP was measured after at least 5 min of seated rest by a UA-779 digital monitor. Both BP and heart rate were measured twice, with the mean values being utilized in downstream analyses. Hypertension was identified on the basis of systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg or the prescription of antihypertensive drugs to a patient.

Follow up and outcome assessment

The vital status of all participants in the present study was periodically determined through the China CDC's Disease Surveillance Points System and the China National Health Insurance System, by regular checks by laws against local residential and administrative records, and by annual active confirmation through street committees or village administrators²¹. Information on disease diagnoses including incident diabetes for participants was collected through the linkage with an established Disease Registries and the China National Health Insurance System, and matched by a unique national identification number. The quality and completeness of morbidity and other follow-up data were regularly checked during the study time period by the coordinating study center. This was involved in monitoring the number of people who were lost to follow up each year²⁰.

By 1 January 2014, a total of 60 (0.1%) participants were lost to follow up. For this study, the primary outcome was type 2 diabetes mellitus (International Statistical Classification of Diseases and Related Health Problems 10th revision, coding E11). In line with the American Diabetes Association guidelines, incident type 2 diabetes mellitus during follow up was defined as "fasting blood glucose ≥ 7.00 mmol/L and/or reports of undergoing type 2 diabetes mellitus treatment".

Statistical analysis

Type 2 diabetes mellitus incidence and follow-up durations were calculated for men and women, respectively, and the baseline parameters in each participant were assessed. A participant's entry time in the study was the age at which their heart rate was initially measured at baseline, whereas their exit time was the age at which they were diagnosed with type 2 diabetes mellitus, died or withdrew from the study.

Descriptive statistics and mean \pm standard deviation were used to describe continuous variables or percentages for categorical variables. Incidence rates per 1,000 person-years were calculated based on the number of newly diagnosed type 2 diabetes mellitus cases divided by the total contributed person-years by all participants.

Cox proportional hazard regressions were carried out to estimate type 2 diabetes mellitus incidence by hazard ratio (HR) and 95% confidence interval (CI). The crude and multivariable-adjusted HRs and 95% CIs for incident type 2 diabetes mellitus across increasing quintiles (Q1 = reference) of heart rate were

estimated by Cox proportional hazard models, and linear trends in the HR for heart rate were tested by calculating the index of heart rate as a continuous variable. Covariates included age (continuous), education (category), annual household income (category), cigarettes smoking (yes/no), alcohol drinking (yes/no), physical activity (continuous), systolic BP (continuous), diabetes or CVD family history (yes/no), and menopausal status (yes/no; only women). A sensitivity analysis was carried out to test how robust these results were. The participants who reported taking antihypertensive medications were excluded in the sensitivity analysis, as these drugs could influence heart rate and future diabetes risk. In joint analyses, resting heart rate was regrouped into “<80 b.p.m.” and “≥80 b.p.m.”, as 80 b.p.m. has been suggested to be an optimal cut-off point^{23,24}. BMI was grouped according to overweight/obese status (BMI ≥24 kg/m²) according to the Working Group on Obesity in China²⁵, and blood pressure was grouped according to hypertension status. The multiplicative interaction term of heart rate with either BMI or hypertension was included in the Cox proportional hazards model to estimate type 2 diabetes mellitus risk independent of heart rate and BMI or hypertension adjusting for other confounding factors.

The SAS software, version 9.2 (SAS institute, Cary, NC, USA) was used for data analyses. Each test was two-sided, with a *P*-value ≤0.05 as a threshold for significance.

RESULTS

A total of 53,817 participants (22,536 men and 31,281 women) at baseline were included in the analyses. Over an average of 6.9 years' follow-up period, 1,766 people (688 men and 1,078 women) developed type 2 diabetes mellitus, with an incidence of 4.75 (4.52 for men and 4.90 for women) per 1,000 person-years.

The mean age in years was 52.8 ± 10.1 among men and 51.4 ± 9.6 among women at baseline. The mean BMI, systolic BP and heart rate were 22.7 ± 3.0 kg/m², 136.5 ± 20.5 mmHg and 74.9 ± 11.5 b.p.m. in men, and 23.0 ± 3.2 kg/m², 134.4 ± 21.7 mmHg and 79.7 ± 11.7 b.p.m. in women, respectively. Table 1 shows that participants with a higher heart rate were more likely to have a higher BMI and BP, and have a lower level of physical activity compared with those with a lower heart rate. Meanwhile, participants with a lower heart rate appeared to be current smokers compared with those with a higher heart rate. Baseline characteristics of men and women with/without incident type 2 diabetes mellitus are also shown in Tables S1 and S2.

Table 2 provides HRs and for type 2 diabetes mellitus incidence based on increasing quintiles of heart rate. On adjusting for age and sex only or for all potential confounders, heart rate was positively correlated with type 2 diabetes mellitus incidence. As compared with participants with a heart rate

Table 1 | Baseline characteristics of participants according to quintiles of heart rate in a prospective cohort of a rural coastal population in Zhejiang province nested in the China Kadoorie Biobank study, 2004–2013

Variables	Quintiles of heart rate (b.p.m.)					<i>P</i> for trend
	Q1 ≤67	Q2 67–73	Q3 73–80	Q4 80–86	Q5 >86	
<i>n</i>	10,045	10,734	12,935	8,715	11,388	
Age (years)	53.4 ± 9.7	52.4 ± 9.8	51.6 ± 9.7	51.4 ± 9.9	51.1 ± 10.1	<0.001
BMI (kg/m ²)	22.8 ± 2.9	22.9 ± 3.1	22.9 ± 3.1	22.9 ± 3.2	22.9 ± 3.3	0.022
WC (cm)	76.5 ± 8.7	76.7 ± 8.9	76.7 ± 9.0	76.5 ± 9.2	76.3 ± 9.5	0.032
SBP (mmHg)	134.4 ± 21.3	133.8 ± 20.9	134.1 ± 20.9	134.9 ± 20.7	139.0 ± 21.6	<0.001
DBP (mmHg)	78.1 ± 10.2	79.0 ± 10.3	80.0 ± 10.4	80.9 ± 10.5	83.7 ± 11.1	<0.001
Current smokers, <i>n</i> (%)	4,095 (40.8)	3,295 (30.7)	3,361 (26.0)	2,037 (23.4)	2,304 (20.2)	<0.001
Current drinkers, <i>n</i> (%)	2,456 (24.4)	2,069 (19.3)	1,973 (15.3)	1,210 (13.9)	1,508 (13.2)	<0.001
Total physical activity, MET-h/day	31.2 ± 15.2	31.1 ± 15.2	30.8 ± 15.1	30.5 ± 15.3	29.6 ± 15.3	<0.001
Education						
Illiteracy/primary	8,105 (80.7)	8,575 (79.9)	10,309 (79.7)	6,907 (79.3)	9,098 (79.9)	0.014
Middle school	1,609 (16.0)	1,759 (16.4)	2,092 (16.2)	1,474 (16.9)	1,818 (16.0)	
High school or above	331 (3.3)	400 (3.7)	534 (4.1)	334 (3.8)	472 (4.1)	
Annual household income, yuan (¥)						
<10,000	691 (6.9)	700 (6.5)	804 (6.2)	589 (6.8)	750 (6.6)	0.001
10,000–20,000	1,361 (13.5)	1,482 (13.8)	1,801 (13.9)	1,237 (14.2)	1,710 (15.0)	
20,000–35,000	4,152 (41.3)	4,389 (40.9)	5,385 (41.6)	3,615 (41.5)	4,830 (42.4)	
≥35,000	3,841 (38.2)	4,163 (38.8)	4,945 (38.2)	3,274 (37.6)	4,098 (36.0)	
Antihypertensive medication, <i>n</i> (%)	150 (1.5)	160 (1.5)	225 (1.7)	140 (1.6)	243 (2.1)	<0.001
Family history of diabetes, <i>n</i> (%)	212 (2.1)	267 (2.5)	339 (2.6)	241 (2.8)	283 (2.5)	0.050
Family history of CVD, <i>n</i> (%)	1,094 (10.9)	1,161 (10.8)	1,407 (10.9)	887 (10.2)	1,190 (10.4)	0.126

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; MET-h, metabolic equivalent task hours; Q, quintile; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Table 2 | Hazard ratios and 95% confidence intervals for incident type 2 diabetes mellitus according to quintiles of heart rate in a prospective cohort of a rural coastal population in Zhejiang province nested in the China Kadoorie Biobank study, 2004–2013

Variables	Quintiles of heart rate (b.p.m.)					P for trend
	Q1 ≤67	Q2 67–73	Q3 73–80	Q4 80–86	Q5 >86	
No. participants	10,045 (18.7)	10,734 (19.9)	12,935 (24.0)	8,715 (16.2)	11,388 (21.2)	
No. cases	259 (2.6)	349 (3.3)	415 (3.2)	286 (3.3)	457 (4.0)	
Model 1	1.00	1.26 (1.07–1.48)	1.26 (1.07–1.47)	1.29 (1.09–1.53)	1.59 (1.36–1.86)	<0.0001
Model 2	1.00	1.24 (1.06–1.46)	1.21 (1.04–1.42)	1.27 (1.07–1.50)	1.57 (1.34–1.83)	<0.0001
Model 3 (overall)	1.00	1.24 (1.05–1.45)	1.21 (1.03–1.41)	1.24 (1.05–1.47)	1.49 (1.28–1.74)	<0.0001
Men	1.00	1.25 (0.99–1.57)	1.24 (0.98–1.56)	1.38 (1.07–1.78)	1.48 (1.17–1.88)	<0.0001
Women	1.00	1.20 (0.96–1.51)	1.18 (0.95–1.47)	1.15 (0.91–1.46)	1.45 (1.17–1.80)	<0.0001
Sensitivity analysis [†]	1.00	1.23 (1.04–1.45)	1.21 (1.03–1.42)	1.26 (1.06–1.49)	1.53 (1.31–1.80)	<0.0001

Bold value indicates $P < 0.05$.

Model 1: adjusted for age (years) and sex. Model 2: adjusted for age (years), sex and body mass index (kg/m^2). Model 3: adjusted for age (years), sex, body mass index (kg/m^2), cigarette smoking status (yes/no), alcohol drinking status (yes/no), education (illiteracy/primary, middle school, high school or above), annual household income (<10,000, 10,000–<20,000, 20,000–<35,000, $\geq 35,000$), physical activity, systolic blood pressure, family history of diabetes and cardiovascular disease, and menopause status (yes/no, for women only). Variable sex is excluded from the model for stratifying by sex. [†]Adjusted for confounders in model 3 and further excluded individuals who were taking antihypertensives ($n = 918$).

≤67 b.p.m., multivariable-adjusted HRs for type 2 diabetes mellitus were 1.24 (95% CI 1.05–1.45) for participants who had a heart rate of 67–73 b.p.m., 1.21 (95% CI 1.03–1.41) for participants who had a heart rate of 73–80 b.p.m., 1.24 (95% CI 1.05–1.47) for participants who had a heart rate of 80–86 b.p.m. and 1.49 (95% CI 1.28–1.74) for participants who had a heart rate >86 b.p.m. When using as a continuous variable in the Cox model, every 12-b.p.m. rise in heart rate was significantly correlated with a 13% increase in type 2 diabetes mellitus incidence (HR 1.13, 95% CI 1.08–1.18). There was a

positive dose–response relationship between heart rate and type 2 diabetes mellitus incidence (P for trend <0.001). Heart rate >80 b.p.m. in men was linked with a higher type 2 diabetes mellitus incidence compared with men with a heart rate ≤67 b.p.m. (80–86 b.p.m. HR 1.38, 95% CI 1.07–1.78; and >86 beats/min HR 1.48, 95% CI 1.17–1.88). Heart rate >86 b.p.m. in women was associated with a significantly higher type 2 diabetes mellitus incidence compared with a heart rate ≤67 b.p.m. (HR 1.45, 95% CI 1.17–1.80). A sensitivity analysis was carried out, excluding patients taking antihypertensive medications, and

Table 3 | Hazard ratios and 95% confidence intervals for incident type 2 diabetes mellitus according to quintiles of heart rate stratified by body mass index in a prospective cohort of a rural coastal population in Zhejiang province nested in the China Kadoorie Biobank study, 2004–2013

Variables	Quintiles of heart rate (b.p.m.)				
	Q1 ≤67	Q2 67–73	Q3 73–80	Q4 80–86	Q5 >86
BMI <24 kg/m^2					
No. participants	6,775 (17.4)	7,025 (20.0)	8,370 (23.9)	5,603 (16.0)	7,290 (20.8)
No. cases	79 (1.2)	123 (1.8)	141 (1.7)	101 (1.8)	178 (2.4)
Multivariable HR (95% CI) [†]	1.00	1.51 (1.14–2.01)	1.48 (1.12–1.95)	1.61 (1.19–2.17)	2.22 (1.69–2.92)
Men	1.00	1.29 (0.88–1.89)	1.33 (0.90–1.94)	1.72 (1.14–2.60)	1.96 (1.32–2.91)
Women	1.00	1.85 (1.18–2.91)	1.73 (1.11–2.67)	1.69 (1.07–2.68)	2.56 (1.68–3.92)
BMI ≥24 kg/m^2					
No. participants	3,270 (17.4)	3,709 (19.8)	4,565 (24.3)	3,112 (16.6)	4,098 (21.9)
No. cases	180 (5.5)	226 (6.1)	274 (6.0)	185 (5.9)	279 (6.8)
Multivariable HR (95% CI) [†]	1.00	1.11 (0.92–1.36)	1.11 (0.92–1.34)	1.09 (0.89–1.34) [‡]	1.22 (1.01–1.47)[§]
Men	1.00	1.23 (0.92–1.63)	1.18 (0.89–1.57)	1.22 (0.88–1.68)	1.28 (0.96–1.73)
Women	1.00	1.02 (0.78–1.34)	1.05 (0.81–1.35)	1.00 (0.76–1.32)	1.15 (0.89–1.48)

Bold value indicates $P < 0.05$.

[†]Adjusted for age (years), sex, cigarette smoking status (yes/no), alcohol drinking status (yes/no), education (illiteracy/primary, middle school, high school or above), annual household income (<10,000, 10,000–<20,000, 20,000–<35,000, $\geq 35,000$), physical activity, systolic blood pressure, family history of diabetes and cardiovascular disease, and menopause status (yes/no, for women only). Variable sex is excluded from the model for stratifying by sex. [‡]Interaction = 1.52 (1.06–2.18), reference was heart rate <67 b.p.m. and body mass index (BMI) <24 kg/m^2 . [§]Interaction = 1.86 (1.35–2.58), reference was heart rate <67 b.p.m. and BMI <24 kg/m^2 . CI, confidence interval; HR, hazard ratio; Q, quintile.

Table 4 | Hazard ratios and 95% confidence intervals for incident type 2 diabetes mellitus according to quintiles of heart rate stratified by blood pressure status in a prospective cohort of a rural coastal population in Zhejiang province nested in the China Kadoorie Biobank study, 2004–2013

Variables	Quintiles of heart rate (beats/min)				
	Q1 ≤67	Q2 67–73	Q3 73–80	Q4 80–86	Q5 >86
SBP <140 and DBP <90 mmHg					
No. participants	5,921 (19.3)	6,458 (21.1)	7,715 (25.1)	5,026 (16.4)	5,592 (18.2)
No. cases	98 (1.7)	138 (2.1)	159 (2.1)	112 (2.2)	147 (2.6)
Multivariable HR (95% CI) [†]	1.00	1.29 (0.99–1.67)	1.24 (0.96–1.61)	1.38 (1.05–1.81)	1.69 (1.30–2.20)
Men	1.00	1.09 (0.76–1.56)	1.18 (0.83–1.68)	1.32 (0.89–1.96)	1.74 (1.19–2.53)
Women	1.00	1.53 (1.03–2.27)	1.34 (0.91–1.98)	1.48 (0.99–2.22)	1.76 (1.19–2.59)
SBP ≥140 or DBP ≥90 mmHg					
No. participants	4,124 (17.8)	4,276 (18.5)	5,220 (22.6)	3,689 (16.0)	5,796 (25.1)
No. cases	161 (3.9)	211 (4.9)	256 (4.9)	174 (4.7)	310 (5.3)
Multivariable HR (95% CI) [†]	1.00	1.22 (0.99–1.50)	1.20 (0.99–1.47)	1.16 (0.94–1.44)	1.38 (1.13–1.67)
Men	1.00	1.38 (1.03–1.86)	1.29 (0.96–1.75)	1.43 (1.03–1.99)	1.38 (1.01–1.86)
Women	1.00	1.05 (0.79–1.40)	1.12 (0.86–1.46)	0.99 (0.74–1.32)	1.28 (0.99–1.66)

Bold value indicates $P < 0.05$.

[†]Adjusted for age (years), sex, body mass index (kg/m^2), cigarette smoking status (yes/no), alcohol drinking status (yes/no), education (illiteracy/primary, middle school, high school or above), annual household income (<10,000, 10,000–<20,000, 20,000–<35,000, ≥35,000), physical activity, family history of diabetes and cardiovascular disease, and menopause status (yes/no, for women only). Variable sex is excluded from the model for stratifying by sex. CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; Q, quintile; SBP, systolic blood pressure.

a similar increased risk for type 2 diabetes mellitus was observed for high compared with low heart rate.

Stratified analyses by BMI and BP status were carried out. Table 3 shows that the relationship between heart rate and incident type 2 diabetes mellitus was particularly evident among non-overweight/obese participants. A multiplicative interaction between heart rate and BMI was significantly observed with a P for interaction = 0.005 ($80 < \text{heart rate} \leq 86$ b.p.m. and $\text{BMI} \geq 24 \text{ kg}/\text{m}^2$: HR 1.52, 95% CI 1.06–2.18; heart rate >86 b.p.m. and $\text{BMI} \geq 24 \text{ kg}/\text{m}^2$: HR 1.86, 95% CI 1.35–2.58). This association was slightly evident among non-hypertensive participants, but no such interaction between heart rate and BP was observed (Table 4). The joint associations of heart rate and BMI or BP with type 2 diabetes mellitus risk are shown in Table S3. The joint analyses results supported the findings from the stratified analyses and interaction associations.

DISCUSSION

In the present prospective cohort study, fast heart rate was independently correlated with a moderately increased risk of developing type 2 diabetes mellitus. A positive dose–response relationship between heart rate and type 2 diabetes mellitus incidence was detected either with or without adjustment for potential confounders. The independent association of heart rate with incident type 2 diabetes mellitus was particularly evident among non-overweight/obese participants. A significant interaction between heart rate and BMI with incident type 2 diabetes mellitus was found in this large prospective cohort study.

A small number of prospective studies^{8–13,24,26} have examined how heart rate is associated with diabetes incidence. The type 2 diabetes mellitus incidence estimated in the present

study is similar to that among previous studies, which ranged from 1.19–⁹ to 5.39-fold¹¹ increased risk in the highest heart rate category. Previously, there was some concern that the independent association of heart rate with diabetes incidence might be confounded by other possible confounders, such as BMI, BP and physical activity²⁷. The present study confirmed that heart rate was independently associated with type 2 diabetes mellitus incidence after adjusted for the potential confounders including BMI, BP and physical activity.

Heart rate has been considered as a marker of autonomic nervous system function and cardiorespiratory fitness, which both relate to incident diabetes⁸. Sympathetic activation promotes insulin resistance through hemodynamic and cellular mechanisms. Several mechanisms were proposed to elucidate the association between heart rate and incident diabetes. One of the most important causative explanations is that sympathetic activation might cause vasoconstriction and decrease skeletal muscle blood flow, leading to the impairment of glucose uptake into the skeleton muscle.

BMI has repeatedly been reported to be a robust independent predictor for the development of type 2 diabetes mellitus with a dose–response relationship²⁸. A study among Caucasians has shown that those who are not physically fit or who are obese have a higher rate of metabolic diseases, such as type 2 diabetes mellitus²⁹. A meta-analysis based on prospective cohort studies also found that adults with obesity had an increased incidence of diabetes (relative risk 7.28, 95% CI 6.47–8.28) compared with the normal weight group¹⁵. The present study showed similar results of the joint association of both heart rate and BMI with incident type 2 diabetes mellitus. The association between heart rate and incident type 2 diabetes

mellitus tends to be greater among non-overweight/obese than that among overweight/obese participants in the present study. Carnethon *et al.*⁹ and Gratham *et al.*¹⁰ also found a more robust relationship between heart rate and diabetes risk in non-obese individuals than that in obese individuals. A positive multiplicative interaction between fast heart rate and high BMI was observed in the present study.

BP has also been reported to be a robust independent predictor for the development of type 2 diabetes mellitus. Elevated type 2 diabetes mellitus risks among those who have a high BP are evident in Japanese¹² and other groups¹⁹. Nagaya *et al.*¹² examined the joint association of both heart rate and BP with type 2 diabetes mellitus risk, and found that men and women with a faster heart rate and higher BP had a 2.25- and 2.58-fold higher risk, respectively, of type 2 diabetes mellitus incidence compared with those with a slower heart rate and lower BP. The observed joint association in the present study also suggests that hypertension with a faster heart rate further increased the incidence of type 2 diabetes mellitus. Similar to the results from Nagaya *et al.*¹², no interaction between heart rate and BP on incident type 2 diabetes mellitus was found in the present study.

Taken together, these results show that the incidence of type 2 diabetes mellitus associated with increased heart rate is not only statistically significant, but also clinically relevant, and that participants with a higher BMI and higher resting heart rate might require more regular glucose screening and aggressive interventions.

Although these findings suggest sympathetic nerve activation as a driver of type 2 diabetes mellitus development, we do not recommend β -blocker use in patients with hypertension, because it might result in elevated rates of diabetes onset, especially with diuretics^{30,31}.

The present study had some strengths. It was a prospective cohort study for which the temporality between resting heart rate and type 2 diabetes mellitus can be delineated. Most known potential confounders, such as BMI, BP and physical activity, have been adjusted in our analyses. Data collection and management were under rigid quality control. In addition, previous cohort studies did not clarify the type of diabetes the participants had, whereas we restricted the present study to type 2 diabetes patients. We believe this is the second largest cohort study on how heart rate affects diabetes incidence in a general population. The present study had certain limitations. A baseline oral glucose tolerance test was not carried out, as it could not be done conveniently in such a large cohort. We did not measure heart rate, BMI or BP during follow up. Thus, we were unable to examine the intra-individual variation during follow up on diabetic risk, which might offer more causal insights into the relationship between these variables. The heart rate in the present study was obtained at one time point (though two measurements), which might not reflect a true resting heart rate, as 24-h ambulatory heart rate monitoring might be more informative.

In conclusion, heart rate was independently associated with the incidence of type 2 diabetes mellitus in this rural Chinese

population in a prospective cohort study, and this relationship was particularly evident among non-overweight/obese participants. There was a significant interaction between heart rate and BMI on incident type 2 diabetes mellitus.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Baseline characteristics of 22,536 men with/without incident type 2 diabetes mellitus in a prospective cohort of a rural coastal population in Zhejiang province nested in the China Kadoorie Biobank study, 2004–2013.

Table S2 | Baseline characteristics of 31,281 women with/without incident type 2 diabetes mellitus in a prospective cohort of a rural coastal population in Zhejiang province nested in the China Kadoorie Biobank study, 2004–2013.

Table S3 | Joint association of heart rate and body mass index or blood pressure with the incidence of type 2 diabetes mellitus in a prospective cohort of a rural coastal population in Zhejiang province nested in the China Kadoorie Biobank study, 2004–2013.