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Original Article

Predictive value for cumulative heart rate exposure in new-onset impaired fasting glucose and diabetes mellitus

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Abstract: To analyze the predictive value for cumulative heart rate exposure (cumHR) in new-onset impaired fasting glucose (IFG) and diabetes mellitus. The prospective cohort study included 101510 participants of Kailuan Company. During a follow-up of nearly 6 years, 33461 participants were recorded. Cumulative incidence of diabetes was calculated as new-onset diabetes, IFG and its development of each group using life table method. Statistical analysis was performed with Log-rank test to compare the different cumulative incidences of each group. Cox proportional hazard model and natural spline were used to further analyze the Hazard ratio (HR) and 95% confidence interval (95% CI) of cumHR. During the follow-up period of mean 2.22±0.38 years, new-onset diabetes were 1244 (3.7%) cases in total, new-onset IFG were 2060 (7.5%) cases in the ideal glucose group, 533 (17.5%) cases IFG developed into diabetes mellitus. Log-rank test indicated that the cumulative incidences in different cumHR groups of total people, ideal glucose people and IFG people had significant statistical differences ($P<0.05$). Cox proportional hazard model showed that when cumHR increased every standard deviation (SD), the HR (95% CI) of IFG, new-onset diabetes, IFG developed into diabetes were 1.21 (1.16~1.26), 1.22 (1.16~1.29), 1.13 (1.03~1.24) respectively. Natural spline analysis exhibited a similar 'J' curve relationship between cumHR and new-onset IFG, new-onset diabetes and IFG developed into diabetes. The increase of cumHR had a predictive value for new-onset IFG and new-onset diabetes.

Keywords: Cumulative heart rate exposure, diabetes mellitus, impaired fasting glucose, IFG developed into diabetes mellitus, prospective study

Introduction

A worldwide Epidemiological Survey in 2011 reported type 2 diabetes has reached 300 million cases and expected to increase to 500 million by 2030 [1]. A recent study from Chinese adult population observed that the prevalence of diabetes was 11.6% and of pre-diabetes was 50.1%, respectively [2]. Several factors, such as age [3], blood pressure [4], body mass index [5] and life style [6], gene [7], have been confirmed to be associated with development and progression of diabetes. Recently an hot concern is that heart rate, as a rough indicator of autonomic nervous system, associated with prevalence of diabetes [8-11].

However, the results about diabetes have not come to a concrete conclusion. ARIC study first reported the relationship between heart rate and diabetes in 2003 [8]. After that, researchers from Japan and Australia such as Nagaya *et al.* [9], Shigetoh *et al*. [10], Grantham *et al*. [11] discovered the predictive value for heart rate increase in diabetes. But Carnethon and coworkers [12] found that by adjusting body mass index (BMI), the baseline heart rate seemed to have no predictive value for long term diabetes.

Table 1. Characteristics according to the quartiles of cummulative heart rate exposure (cumHR) in the Kailuan Study, China, 2006-2007

Variables	Total people (n=33461)	Q1 (n=8364)	Q2 (n=8367)	Q3 (n=8365)	Q4 (n=8365)	*P* value
Age (year)	47.26±11.56	45.08±10.28	45.58±11.16[a]	48.17±11.77[a,b]	50.20±12.20[a,b,c]	<0.001
Men [n (%)]	25607 (76.5)	6286 (76.1)	6376 (77.2)	6358 (76.9)	6324 (76.6)	0.325
SBP (mmHg)	126.87±19.11	123.44±18.11	125.66±18.30[a]	127.77±19.12[a,b]	130.61±20.12[a,b,c]	<0.001
DBP (mmHg)	82.05±11.16	80.44±10.78	81.67±10.87[a]	82.39±11.11[a,b]	83.71±11.60[a,b,c]	<0.001
HR (bpm/min)	73.11±9.51	67.51±7.23	71.77±7.40[a]	74.16±8.80[a,b]	79.00±10.64[a,b,c]	<0.001
BMI (kg/m^2)	24.86±3.42	24.84±3.34	24.93±3.39	24.87±3.42	24.82±3.53[a,b,c]	0.130
FBG_1 (mmol/L)	5.01±0.65	4.93±0.63	4.99±0.64[a]	5.05±0.65[a,b]	5.09±0.66[a,b,c]	<0.001
FBG_2 (mmol/L)	5.19±0.61	5.07±0.59	5.15±0.59[a]	5.22±0.60[a,b]	5.33±0.62[a,b,c]	<0.001
FBG_3 (mmol/L)	5.25±0.60	5.14±0.58	5.21±0.58[a]	5.28±0.59[a,b]	5.38±0.61[a,b,c]	<0.001
TC (mmol/L)	4.89±1.11	4.79±1.10	4.83±1.14	4.90±1.09[a,b]	5.02±1.11[a,b,c]	<0.001
HDL-C (mmol/L)	1.56±0.40	1.56±0.39	1.56±0.39	1.56±0.40	1.55±0.41	0.479
LDL-C (mmol/L)	2.30±0.90	2.22±0.89	2.29±0.90[a]	2.30±0.90[a]	2.37±0.91[a,b,c]	<0.001
lgTG	0.12±0.26	0.09±0.26	0.11±0.26[a]	0.12±0.27[a]	0.13±0.26[a,b,c]	<0.001
lgCRP	-0.17±0.69	-0.17±0.68	-0.19±0.70	-0.19±0.69[a]	-0.16±0.67[b,c]	0.001
Smoking [n (%)]	10159 (30.4)	2366 (28.6)	2495 (30.2)	2584 (31.3)	2621 (31.7)	<0.001
Drinking [n (%)]	5770 (17.2)	1283 (15.5)	1407 (17.0)	1469 (17.8)	1529 (18.5)	<0.001
Physical training [n (%)]	4275 (12.8)	858 (10.4)	913 (11.1)	1059 (12.8)	1273 (15.4)	<0.001
Anti-hypertensive treatment [n (%)]	2293 (6.9)	298 (3.6)	374 (4.5)	506 (6.1)	759 (9.2)	<0.001

Note: SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; BMI: body mass index; FBG: fasting blood glucose; FBG_1: FBG tested in 2006-2007; FBG_2: FBG tested in 2008-2009; FBG_3: FBG tested in 2010-2011; TC: total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; lgTG: triglyceride after logarithmic transformation; lgCRP: C reaction protein after logarithmic transformation. [a]P<0.05, vs. Q1; [b]P<0.05 vs. Q2; [c]P<0.05, vs. Q3.

The results of these studies above concerned about heart rate and diabetes appeared to be different. That's may because of heart rate was just measured once, and could not represent a long time heart rate level.

Cumulative exposure is the sum up of exposure dose multiplied by exposure time, which can estimate the long term effect of some risk factors more accurately. It is known that studies on cumulative exposure are relatively rare through out the world. A prospective study of diabetes in England [13] put out that cumulative high blood glucose could increase the risk of complications in diabetes firstly. Lately Navar-Boggan and coworkers [14] pointed out cumulative hyperlipidemia exposure could increase the risk of coronary heart disease. Zemaitis etc. discovered high cumulative blood pressure exposure was related to renal damage [15]. In theory, the cumulative heart rate (cumHR) represents long-term heart rate levels more accurate. But there were no studies of the relationship between cumulative heart rate exposure and new-onset impaired fasting glucose (IFG) and diabetes. Therefore we performed a study according to the Kailuan cohort (registered number: ChiCTR-TNC-11001489) and analyzed the predictive value for cumulative heart rate exposure in new-onset IFG and diabetes.

Materials and methods

Study population

We collected the data from Kailuan community in Tangshan city in northern China, which represented the Chinese population from a socioeconomic perspective.

Briefly, in 2006-2007, 101510 employees and retired workers in Kailuan Company completed questionnaires by interviews and received physical examinations in 11 hospitals responsible for health care of this community. These participants were then followed through 2008-2009, 2010-2011, 2012-2013 with repeated questionnaires and physical examinations. We included 47828 participants who had taken all the fourth examinations and had completed data. The starting point of follow-up was the third time of physical examination in 2010-2011 and ending point was the fourth. We considered new-onset diabetes and IFG as the endpoint events.

The protocol for this study was in accordance with the guidelines of Helsinki Declaration, and was approved by the Ethics Committee of Kailuan Medical Group, Kailuan Company. All the participants gave their written informed consent.

Table 2. Incidence rates of IFG and new-onset diabetes in quartiles of cumHR

		Total people	Q1	Q2	Q3	Q4	Log-rank test
Total People	N	33461	8364	8367	8365	8365	
	New-onset diabetes [n (%)]	1244 (3.7)	289 (3.5)	305 (3.6)	317 (3.8)	333 (4.0)	<0.001
	Men [n (%)]	1002 (3.9)	230 (3.6)	243 (3.8)	264 (4.1)	265 (4.2)	<0.001
	Women [n (%)]	242 (3.0)	59 (2.9)	62 (3.2)	53 (2.7)	68 (3.4)	<0.001
Ideal glucose group	N	27386	6847	6845	6850	6844	
	New-onset IFG [n (%)]	2060 (7.5)	503 (7.3)	477(7.0)	523 (7.6)	557 (8.1)	<0.001
	Men [n (%)]	1591 (7.8)	376 (7.4)	380 (7.3)	411 (8.0)	424 (8.4)	<0.001
	Women [n (%)]	469 (6.8)	127 (7.3)	97 (5.9)	112 (6.4)	133 (7.4)	<0.001
IFG group	N	3042	760	761	761	760	
	New-onset diabetes [n (%)]	533 (17.5)	137 (18.0)	151 (19.8)	119 (15.6)	126 (16.6)	<0.001
	Men [n (%)]	430 (16.9)	109 (16.9)	121 (19.0)	101 (15.7)	99 (16.0)	<0.001
	Womenn [n (%)]	103 (20.7)	28 (24.1)	30 (24.2)	18 (15.5)	27 (19.0)	0.007

Note: Total people cumHR Q1: cumHR ≤265.50; Q2: 265.50 <cumHR ≤289.37; Q3: 289.37 <cumHR ≤318.25; Q4: cumHR >318.25; ideal glucose group cumHR Q1: cumHR ≤263.62; Q2: 263.62 <cumHR ≤286.89; Q3: 286.89 <cumHR ≤315.17; Q4: cumHR >315.17; IFG group cumHR Q1: cumHR ≤276.16; Q2: 276.16 <cumHR ≤301.93; Q3: 301.93 <cumHR ≤331.70; Q4: cumHR >331.70 (bpm × year).

Inclusion and exclusion criteria

In the current study, participants were included if they: (i) received all the physical examination during the follow-up years; (ii) had no physical disability and could walk independently to receive the physical examination; (iii) could complete the questionnaire with cognitive competence; (iv) agreed to take part in the study and gave their written informed consent. The exclusion criteria were: (i) refused to participate in this research; (ii) lack of data for heart rate (N=6685), fasting blood glucose (FBG) and history of diabetes (N=826); (iii) have the history of atrial fibrillation, myocardial infarction or taking pills of β blockers or calcium antagonists (N=1230); (iv) developed into diabetes during the follow-up period from 2006-2011 or taken hypoglycemic drugs (N=5626). Finally, we included 33461 people in our cohort, among whom 27386 were the ideal glucose group (FBG <6.1 mmol/L) and 3042 were IFG group (6.1 mmol/L ≤FBG <7.0 mmol/L).

Epidemiological survey and anthropometric parameters

The epidemiological survey and anthropometric parameters in this study were in accordance with the previous published articles by our research group [16]. Smoking was defined as having at least one cigarettes a day in the recent year; drinking was 100 ml/day (alcohol contents >50%) of alcohol lasts for more than one year; physical training was aerobic exercise (eg. walking, jogging, balls, swimming) ≥3 times/week, ≥30 min/time.

Assessment of FBG and other biochemical indicators

Blood samples, after an overnight fast, were collected from cubital vein for 5 ml at 7-9 am in the physical examination day. After separating and extracting serum, a same group of laboratory technicians tested the biochemical indicators using automatic biochemistry analyzer (Hitachi 7600, Tokyo, Japan). The indicators included FBG, total cholesterol (TC), triglyceride (TG) and high sensitivity C reaction protein (hs-CRP). Glucose (GO) Assay kits was provided by Biosino in Beijing, China. FBG was measured with the hexokinase/glucose-6-phosphate dehydrogenase method. The coefficient of variation using blind quality control specimens was no more than (≤) 2.0% (5.55 mmol/L), and liner ceiling was 33.3 mmol/L.

Assessment of heart rate and calculation of cumHR

After a 5-min or longer rest, heart rate was recorded based on the results of a 12-lead electrocardiogram performed with participants in the supine position. The average inverse of the interval between R-waves for five consecutive QRS complexes was used to determine heart rate. cumHR was calculated in line with the method of cumulative exposure to blood pressure [15]. cumHR=[(HR1+HR2)/2 × time 1-2]+[(HR2+HR3)/2 × time 2-3], HR1, HR2, HR3 were the first, second and third time of physical examination heart rate. Time 1-2, time 2-3 were the time interval of two adjacent measure-

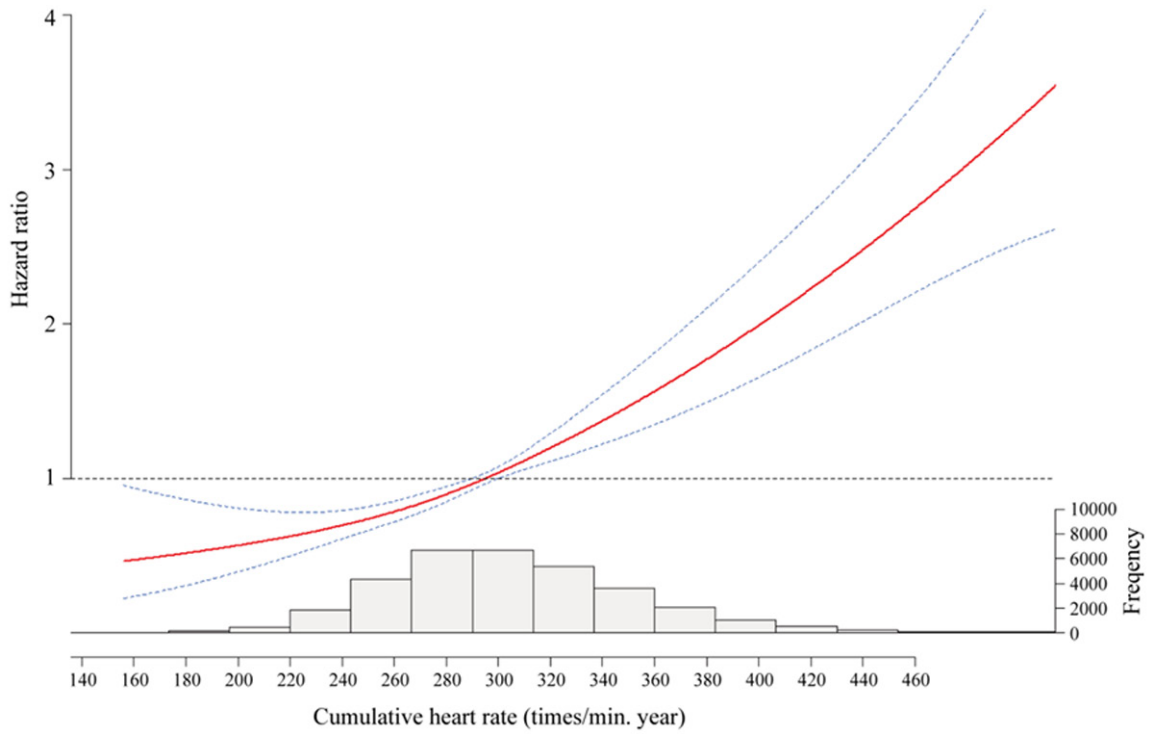

Figure 1. The harzard ratio (HR) for risk of new-onset diabetes with cumHR in total people.

ments. The average year of time 1-2, time 2-3 were 1.93 and 2.04.

Incident IFG and diabetes

We considered the starting point of follow up as the third time of physical examination in 2010-2011 and the endpoint was the fourth. The endpoint events were new-onset diabetes and IFG. In line with the American Diabetes Association guidelines, participants were identified as having diabetes mellitus if they were currently treated with anti-diabetic drugs, or had a FBG concentration 7.0 mmol/L. IFG was defined as FBG concentration between 6.1 and 7.0 mmol/L without diabetes history and hypoglycaemic agents.

Statistical analysis

Participants were divided into four categories based on cumHR quartiles. The data of physical examination during the follow up years were collected from the 11 hospitals and then gathered a Oracle 10.2 g database. The data analyses were performed using SPSS 19.0, data in normal distribution were presented as mean ± standard deviation (±s), data in skewed distribution were logarithmic transformed and then presented as mean ± standard deviation (±s). Using Variance analysis we compared differences among more than two groups. LSD (equal variance) and Dunnett T3 (heterogeneity of variance) were implied to compare mean values between groups. Enumeration data were showed in percentage (%) and comparison among groups were conducted with χ^2 test. Cumulative incidence of diabetes was calculated using life table method as new-onset diabetes, new-onset impaired fasting glucose and its development of each group. Log-rank test was performed to compare the different cumulative incidences of each group.

Cox proportional hazard model and natural spline were used to further analyze the Hazard ratio (HR) and 95% confidence interval (95% CI) of cumHR. To account for the potential confounding effects due to 11 participating hospitals, we used Cox proportional hazards model with a sandwich covariance matrix as a random effect. We fitted three multivariate proportional hazards models, confirmation of the proportional hazards assumption being satisfied. Model 1 considered new-onset IFG/new-onset diabetes/IFG developed into diabetes as the dependent variable, cumHR increased every standard deviation as the independent variable;

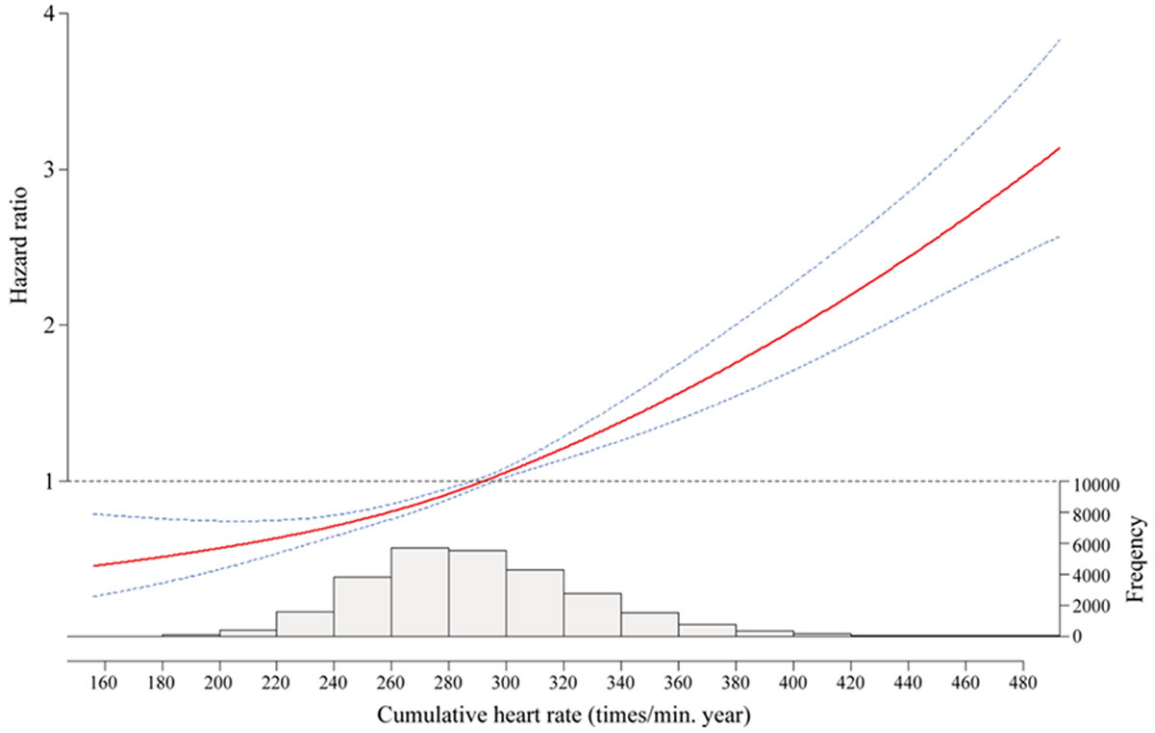

Figure 2. The harzard ratio (HR) for risk of new-onset IFG with cumHR in ideal glucose group.

model 2 further adjusted the age and gender on the basis of model 1; model 3 further adjusted SBP, baseline HR, BMI, FBG, TC, lgTG, lgCRP, smoking, drinking, physical training, anti-hypertensive treatment on the basis of model 2. Natural spline analysis exhibited a curve relationship between cumHR and new-onset IFG, new-onset diabetes and IFG developed into diabetes.

Two-sided *P*-values were reported for all analyses. A P<0.05 was considered to be statistically significant. All statistical analyses were performed by SPSS for windows, version 19.0 (SPSS Inc, Chicago, Illinois, USA).

Results

General information

The mean age of participants (N=33461) with 76.5% men (N=25607) and 23.5% women (N=7854) was 47.26±11.56 years at baseline. We separated the cumHR as quartiles (Q1: cumHR ≤265.50 bpm × year; Q2: 265.5 < cumHR ≤289.37 bpm × year; Q3: 289.37 < cumHR ≤318.25 bpm × year; Q4: cumHR ≥ 318.25 bpm × year) and found that with cumHR increasing, most indicators went up as well (P<0.05), such as age, systolic blood pressure (SBP), diastolic blood pressure (DBP), baseline heart rate (HR), FBG in the three times of physical examination (FBG_1, FBG_2, FBG_3), TC, low density lipoprotein cholesterin (LDL-C), lgTG, lgCPR level and smoking, drinking, physical training, hypotensor taking proportion (**Table 1**).

Cumulative incidence

In a follow-up period of mean 2.22±0.38 years, the new-onset diabetes were 1244 (3.7%) cases of total, new-onset IFG were 2060 (7.5%) cases in the ideal glucose group, 533 (17.5%) cases IFG developed into diabetes. Log-rank test indicated that the cumulative incidences in different cumHR groups of total people, ideal glucose people and IFG people had a significant statistical difference (P<0.05). The cumulative rates of new-onset diabetes in total people and new-onset IFG in ideal glucose people increased as the cumHR went up, while the rate IFG developed into diabetes did not increase (**Table 2**).

Cox proportional hazard model and natural spline analysis

We considered new-onset IFG, new-onset diabetes, IFG developed into diabetes as the depen-

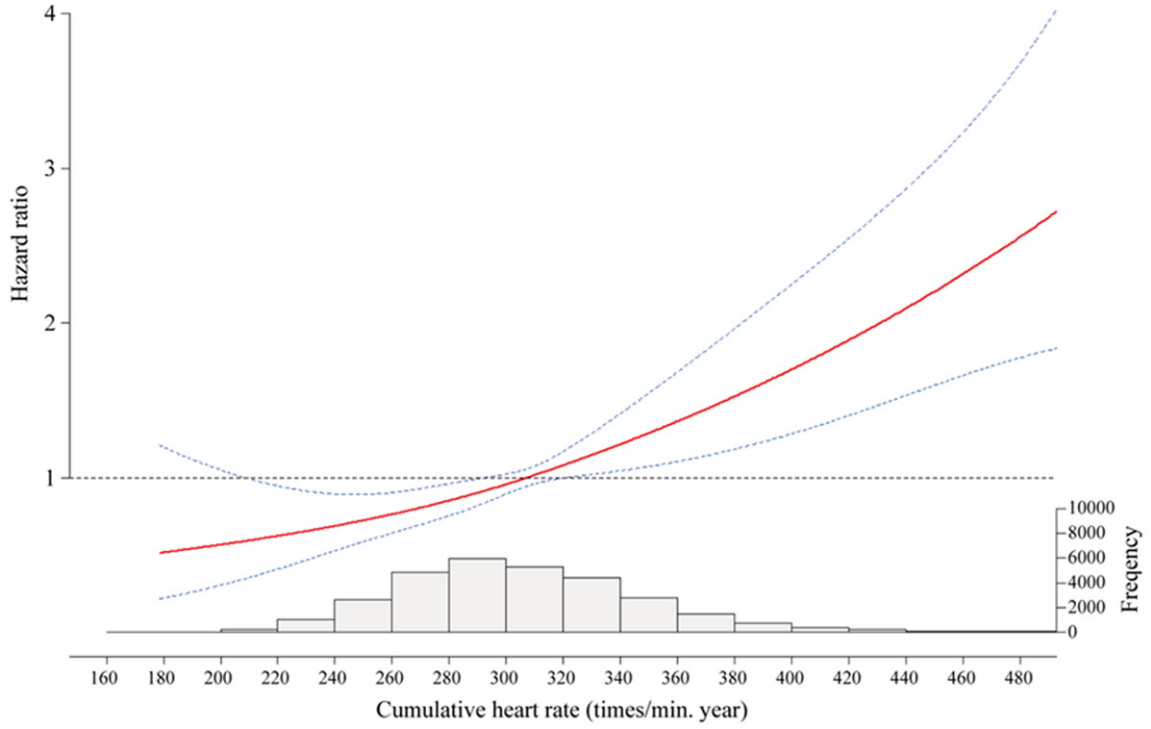

Figure 3. The harzard ratio (HR) for risk of development from IFG to diabetes with cumHR in IFG group

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of endpoints according to the quartiles of cumHR in the Kailuan study, China

		New-onset IFG		New-onset diabetes		IFG developed into diabetes	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 1	CumHR	1.18 (1.14~1.23)	<0.001	1.22 (1.17~1.28)	<0.001	1.11 (1.02~1.21)	0.015
Model 2	CumHR	1.16 (1.12~1.21)	<0.001	1.20 (1.14~1.26)	<0.001	1.09 (1.001~1.03)	0.047
Model 3	CumHR	1.21 (1.16~1.26)	<0.001	1.22 (1.16~1.29)	<0.001	1.13 (1.03~1.24)	0.013
	Baseline HR	0.98 (0.98~0.99)	<0.001	0.98 (0.98~0.99)	<0.001	0.99 (0.98~1.00)	0.005
	Gender						
	Women	1.29 (1.19~1.41)	<0.001	1.32 (1.17~1.49)	<0.001	1.12 (0.91~1.37)	0.295
	Men	1.19 (1.13~1.24)	<0.001	1.20 (1.13~1.28)	<0.001	1.13 (1.02~1.26)	0.026
	Age						
	<39 years old	1.12 (0.96~1.32)	0.157	1.23 (0.99~1.50)	0.057	0.90 (0.56~1.45)	0.671
	39~59 years old	1.21 (1.15~1.26)	<0.001	1.22 (1.15~1.30)	<0.001	1.16 (1.04~1.28)	0.006
	≥60 years old	1.31 (1.18~1.46)	<0.001	1.27 (1.09~1.48)	<0.001	1.14 (0.88~1.48)	0.328

Note: cumHR: cumulative heart rate. Model 1 considered new-onset IFG/new-onset diabetes/IFG developed into diabetes as the dependent variable, cumHR increased every standard deviation as the independent variable; model 2: adjusting for age and gender; model 3: adjusting for model 2 and SBP, baseline HR, BMI, FBG, TC, lgTG, lgCRP, smoking, drinking, physical training, anti-hypertensive treatment.

dent variable and cumHR as the independent variable to conduct the cox proportional hazard model test. After adjusting the confounding factors such as age, gender, SBP, HR, BMI, TC, FBG, smoking, drinking, physical training and anti-hypertensive treatment, results showed that when cumHR increased every SD, the HR (95% CI) of IFG, new-onset diabetes, IFG developed into diabetes were 1.21 (1.16~1.26), 1.22 (1.16~1.29), 1.13 (1.03~1.24) respectively (**Table 3**). Natural spline analysis exhibited a similar 'J' curve relationship between cumHR and new-onset IFG, new-onset diabetes and IFG developed into diabetes (**Figures 1-3**).

Gender (men and women) and age (youth: ≤39 years old; middle age: 40-59 years old; old age: ≥60 years old) were stratified in the Cox propor-

tional hazard model 3. The results indicated that except the youth group, among different genders and the middle age and old people, the risen of cumHR could increase the risk of new-onset IFG and new-onset diabetes (P<0.05). Whereas, as to the IFG developed into diabetes event, cumHR was only the risk factor in middle age and male groups (**Table 3**).

Discussion

Our study overcomes the limits of single measurement and applies the method of cumHR, which reflects the level of the long period of time. The current study shows the largest longitudinal prospective study exploring the independent association between cumHR and risk of developing diabetes and IFG. As expected, we observed a dose-response relationship between higher cumHR and a higher risk of developing diabetes, IFG and development from IFG to diabetes, even after adjusting for potential confounders. This result is consistent with several previous studies about resting heart rate and diabetes [8-11]. Therefore, this study strongly confirms cumHR as an independent risk factor for incident diabetes and IFG, and suggests that this association may be common to Asian and non-Asian populations.

Table 2 showed the cumulative rates of total people, new-onset diabetes and IFG of ideal glucose people increased as the cumHR went up, which is in line with the previous study about resting heart rate and diabetes. In the work of relationship between heart rate and blood glucose level, Stein *et al*. [17] found the heart rate of IFG and diabetes people was significantly higher than normal blood glucose group (P<0.001). Carnethon *et al*. [12] had a research among the middle aged and old aged people and discovered their diabetes relevance ratio went up as the heart rate increased. Another research conducted from Kailuan Study by Wang *et al*. [18] pointed out faster heart rate was associated with a higher risk of developing IFG and diabetes every 100,000 person-years.

Additionally, after adjusting these confounders including baseline heart rate by cox proportional hazard model, the increasing trends in risk of developing new-onset IFG, new-onset diabetes and IFG developed into diabetes were still observed when cumHR increased (**Table 3**). A cross-sectional study in 2007 [17] demonstrated that heart rate had a significant liner correlation with IFG in prediabetic states. Another study about Cantonese by Yang *et al*. [19] reported that each 10 beats/min increased in heart rate was associated with 29% increased diabetes risk and 15% increased pre-diabetes risk. The other research including 637 Japanese by Shigetoh *et al*. [10] pointed out a heart rate more than (>) 80 beats/min, comparable to the baseline heart rate less than (<) 60 beats/min, could positively predict insulin resistance (IR) and diabetes 20 years later, with the OR (95% CI) being 2.20 (1.04~5.07) and 5.39 (1.34~21.8) respectively. As mentioned above, Wang *et al*. [18] also discovered faster baseline resting heart rate had relationship with higher risk of IFG, new-onset diabetes and IFG developed into diabetes after 4 years' follow-up, and the HRs (95% CI) were 1.11 (1.09~1.13), 1.23 (1.19~1.27), 1.13 (1.08~1.17). However, heart rate has an inconformity in the predict value of diabetes. Carnethon *et al*. [12] failed to identify that baseline heart rate predicted the occurrence of long-term diabetes after adjusting for BMI. The possible reason is that his study come from the almost overweight characteristic population in Chicago, America, and higher BMI conceal the role of heart rate.

What's more, our natural spline analysis exhibited a similar 'J' curve relationship between cumHR and endpoint events in three groups, which indicated a higher risk in IFG and new-onset diabetes (**Figures 1**-**3**). Interestingly, the baseline heart rate presented a slightly protective effect to the occurrence of new-onset IFG and diabetes after adding it in our model, which remained unexplainable and needed to further explore.

For the middle age and old people, the risen of cumHR could increase the risk of new-onset IFG and new-onset diabetes in male or female (**Table 3**). As to the IFG group, though there were no increasing trends in diabetes as cumHR increased in the whole people, male or female, the incidence of endpoints was statistically different in the cumHR quartiles (**Table 2**). Afterwards the cox proportional hazard model referred cumHR as the risk factor in IFG developed into diabetes, especially in middle aged and male people (**Table 3**). Hu *et al*. [3], Chan *et al*. [5] confirmed the association between age, BMI and diabetes, and the reason may be that youth group had not come to the endpoint

events and the middle aged and male were more intend to become obesity. This study affirmed again that age, gender associated with the prevalence of diabetes.

Faster heart rate, which is the reflection of an unbalanced automatic nervous system, has some correlation with sympathetic nerve hyperactivity (SNH) [20]. Someone believed that SNH could cause an acute or chronic insulin resistance [21]. The probable mechanisms were as follows: (i) SNH caused contraction of skeletal muscle vascular, decreased the blood flow, and reduced the absorption of glucose in skeletal muscle [22]; (ii) SNH was related to risk factors of diabetes such as hypertension, metabolic syndrome and decreased insulin sensitivity [23-25]. Moreover, resting heart rate associated with age, gender, cardiorespiratory fitness and physical activity. A sedentary lifestyle and obesity, as other causes of faster heart rate, were also risk factors for diabetes prevalence and progression [5].

Cumulative exposure is influenced by exposure time and level, which can predict the chronic damage of the body. Our study was advantaged in the calculation of cumHR by 3 times' (6 years' follow-up) resting heart rate, which could more precisely estimated the predictive value to diabetes than single heart rate. In addition, our study unveiled the use of cumulative exposure index in clinical work besides science work and its immeasurable value to human health. The repeated measurements of clinical data, through collecting and sorting, will vastly encourage an era of the explosion in medical data.

Resting heart rate is related to new-onset diabetes as is known. But the single measurement of heart rate is influenced by diet, temperature, lifestyle and many other factors, which can not represent the long term heart rate level. After all our study was the first to reveal predictive value of cumHR to new-onset IFG and diabetes in the world. We discovered that increasing level of cumHR was predictive to new-onset IFG and diabetes and also the value was independent to resting heart rate. The current study showed that higher risk of new-onset IFG and diabetes were related to cumHR increase, which suggested that monitoring and maintaining heart rate at a normal and low level during long term is necessary for diabetes prevention.

This study is the first of its kind that assessed predictive value for cumulative heart rate exposure in new-onset impaired fasting glucose and diabetes mellitus in China. This study was advantaged in the calculation of cumHR by 3 times' (6 years' follow-up) resting heart rate, which could more precisely estimated the predictive value to diabetes than single heart rate. This study unveiled the use of cumulative exposure index in clinical work besides science work and its immeasurable value to human health.

However, several limitations should be considered in interpreting the current results. Firstly, our cumHR was a result of 6 years' follow-up and we used it to predict the new-onset diabetes and IFG after 2 years later. The observation time was relatively short that the endpoint events may not yet occured. Secondly, we included 783 calcium antagonists' users, who may have taken non-dihydropyridine drugs as well. That may influence heart rate and thus caused result bias. Thirdly, we tried to adjust those confounders when evaluated the predictive value of cumHR, but some factors were still not included such as temperature and genetic factors.

Conclusions

Our findings provide further evidence that increase of cumHR had a predictive value for new-onset IFG and new-onset diabetes among Chinese adults.

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Disclosure of conflict of interest

None.

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References

[1] Whiting DR, Guariguata L, Weil C and Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94: 311-321.

[2] Xu Y, Wang L, He J, Bi Y, Li M, Wang T, Wang L, Jiang Y, Dai M, Lu J, Xu M, Li Y, Hu N, Li J, Mi S, Chen CS, Li G, Mu Y, Zhao J, Kong L, Chen J, Lai S, Wang W, Zhao W, Ning G; 2010 China Noncommunicable Disease Surveillance Group. Prevalence and control of diabetes in Chinese adults. JAMA 2013; 310: 948-959.

[3] Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG and Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001; 345: 790-797.

[4] Emdin CA, Anderson SG, Woodward M and Rahimi K. Usual blood pressure and risk of new-onset diabetes: Evidence from 4.1 million adults and a meta-analysis of prospective studies. J Am Coll Cardiol 2015; 66: 1552-1562.

[5] Chan JM, Rimm EB, Colditz GA, Stampfer MJ and Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994; 17: 961-969.

[6] van Dan RM. The epidemiology of lifestyle and risk factor for type 2 diabetes. Eur J Epidemiol 2003; 18: 1115-1125.

[7] Zhang X, Zhang W, Saraf SL, Nouraie M, Han J, Gowhari M, Hassan J, Miasnikova G, Sergueeva A, Nekhai S, Kittles R, Machado RF, Garcia JG, Gladwin MT, Steinberg MH, Sebastiani P, McClain DA and Gordeuk VR. Genetic polymorphism of APOB is associated with diabetes mellitus in sickle cell disease. Hum Genet 2015; 134: 895-904.

[8] Carnethon MR, Golden SH, Folsom AR, Haskell W and Liao D. Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk In Communities study, 1987-1998. Circulation 2003; 107: 2190-2195.

[9] Nagaya T, Yoshida H, Takahashi H and Kawai M. Resting heart rate and blood pressure, independent of each other, proportionally raise the risk for type 2 diabetes mellitus. Int J Epidemiol 2009; 39: 215-222.

[10] Shigetoh Y, Adachi H, Yamagishi S, Enomoto M, Fukami A, Otsuka M, Kumagae S, Furuki K, Nanjo Y and Imaizumi T. Higher heart rate may predispose to obesity and diabetes mellitus: 20-year prospective study in a general population. Am J Hypertens 2009; 22: 151-155.

[11] Grantham NM, Magliano DJ, Tanamas SK, Söderberg S, Schlaich MP and Shaw JE. Higher heart rate increases risk of diabetes among men: The Australian Diabetes Obesity and Lifestyle (AusDiab) Study. Diabet Med 2013; 30: 421-427.

[12] Carnethon MR, Yan L, Greenland P, Garside DB, Dyer AR, Metzger B and Daviglus ML. Resting heart rate in middle age and diabetes development in older age. Diabetes Care 2008; 31: 335-339.

[13] U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995; 44: 1249-1258.

[14] Navar-Boggan AM, Peterson ED, D'Agostino RB Sr, Neely B, Sniderman AD and Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. Circulation 2015; 131: 451-458.

[15] Zemaitis P, Liu K, Jacobs DR Jr, Cushman M, Durazo-Arvizu R, Shoham D, Palmas W, Cooper R and Kramer H. Cumulative systolic BP and changes in urine albumin-to-creatinine ratios in nondiabetic participants of the multi-ethnic study of atherosclerosis. Clin J Am Soc Nephrol 2014; 9: 1922-1929.

[16] Liu Y, Jin C, Xing A, Liu X, Chen S, Li D, Feng P, Liu J, Li Z and Wu S. Serumuric acid levels and the risk of impaired fasting glucose: a prospective study in adults of north China. PLoS One 2013; 8: e84712.

[17] Stein PK, Barzilay JI, Domitrovich PP, Chaves PM, Gottdiener JS, Heckbert SR and Kronmal RA. The relationship of heart rate and heart rate variability to non-diabetic fasting glucose and the metabolic syndrome the Cardiovascular Health Study. Diabet Med 2007; 24: 855-863.

[18] Wang L, Cui L, Wang Y, Vaidya A, Chen S, Zhang C, Zhu Y, Li D, Hu FB, Wu S and Gao X. Resting heart rate and the risk of developing impaired fasting glucose and diabetes: the Kailua n prosp ective study. Int J Epidemiol 2015; 44: 689-699.

[19] Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med 2010; 362: 1090-1101.

[20] Grassi G, Vailati S, Bertinieri G, Seravalle G, Stella ML, Dell'Oro R and Mancia G. Heart rate as marker of sympathetic activity. J Hypertens 1998; 16: 1635-1639.

[21] Jamerson KA, Julius S, Gudbrandsson T, Andersson O and Brant DO. Reflex sympathetic activation induces acute insulin resistance in the human forearm. Hypertension 1993; 21: 618-623.

[22] Julius S, Gudbrandsson T, Jamerson K and Andersson O. The interconnection between sympathetics, microcirculation, and insulin resistance in hypertension. Blood Press 1992; 1: 9-19.

[23] Flanagan DE, Vaile JC, Petley GW, Moore VM, Godsland IF, Cockington RA, Robinson JS and Phillips DI. The autonomic control of heart rate and insulin resistance in young adults. J Clin Endocrinol Metab 1999; 84: 1263-1267.

[24] Mancia G, Bousquet P, Elghozi JL, Esler M, Grassi G, Julius S, Reid J and Van Zwieten PA. The sympathetic nervous system and the metabolic syndrome. J Hypertens 2007; 25: 909-920.

[25] Shibao C, Gamboa A, Diedrich A, Ertl AC, Chen KY, Byrne DW, Farley G, Paranjape SY, Davis SN and Biaggioni I. Autonomic contribution to blood pressure and metabolism in obesity. Hypertension 2007; 49: 27-33.