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## Observational Study

# Heart rate is an independent predictor of all-cause mortality in individuals with type 2 diabetes: The diabetes heart study

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**Author contributions:** Bowden D enrolled subjects and collected data for the Diabetes Heart Study; Prasada S and Yeboah J designed the study and performed statistical analysis using Statistical Analysis System JMP; Prasada S and Oswalt C wrote the manuscript; Yeboah P and Yeboah J helped write and edit the manuscript; all authors contributed to this article.

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## Abstract

### AIM

To assess the association of resting heart rate with all-cause and cardiovascular disease (CVD) mortality in the Diabetes Heart Study (DHS).

### METHODS

Out of a total of 1443 participants recruited into the DHS, 1315 participants with type 2 diabetes who were free of atrial fibrillation and supraventricular tachycardia during the baseline exam were included in this analysis. Heart rate was collected from baseline resting electrocardiogram and mortality (all-cause and CVD) was obtained from state and national death registry. Kaplan-Meier (K-M) and Cox proportional hazard analyses were used to assess the association.

### RESULTS

The mean age, body mass index (BMI) and systolic blood

pressure (SBP) of the cohort were  $61.4 \pm 9.2$  years,  $32.0 \pm 6.6$  kg/m<sup>2</sup>, and  $139.4 \pm 19.4$  mmHg respectively. Fifty-six percent were females, 85% were whites, 15% were blacks, 18% were smokers. The mean  $\pm$  SD heart rate was 69.8 (11.9) beats per minute (bpm). After a median follow-up time of 8.5 years (maximum follow-up time is 14.0 years), 258 participants were deceased. In K-M analysis, participants with heart rate above the median had a significantly higher event rate compared with those below the median (log-rank  $P = 0.0223$ ). A one standard deviation increase in heart rate was associated with all-cause mortality in unadjusted (hazard ratio 1.16, 95%CI: 1.03-1.31) and adjusted (hazard ratio 1.20, 95%CI: 1.05-1.37) models. Similar results were obtained with CVD mortality as the outcome of interest.

### CONCLUSION

Heart rate is an independent predictor of all-cause mortality in this population with type 2 diabetes. In this study, a 1-SD increase in heart rate was associated with a 20% increase in risk suggesting that additional prognostic information may be gleaned from this ubiquitously collected vital sign.

**Key words:** Diabetes mellitus; Mortality; Resting heart rate; Prevention

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**Core tip:** Persons with type 2 diabetes mellitus (T2DM) have a higher rate of morbidity and mortality compared with those without diabetes. Prevention is the best way of reducing the risk in this population. Unlike the general population, the predictive value of resting heart rate for mortality in persons with T2DM is not well established. We used baseline data and a median of 8.5 years of follow up from the Diabetes Heart Study to show that resting heart rate is an independent predictor of mortality in individuals with T2DM. Our data suggests that efforts that reduce heart rate in T2DM may be useful.

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### INTRODUCTION

Diabetes mellitus is a major health problem affecting 29.1 million (9.3%) Americans<sup>[1-3]</sup>. Type 2 diabetes mellitus comprises 90-95% of these diagnosed cases<sup>[1,2]</sup>. The Center for Disease Control (CDC) estimates that one-third of Americans will develop type 2 diabetes at some point in their lifetime. Cardiovascular disease (CVD) death rates are 1.7 times higher for adults with

diabetes than those without diabetes<sup>[1]</sup>. Understanding which specific factors and findings are associated with increased risk of mortality may help us prognosticate patients as well as provide specific, earlier therapies for those at highest risk.

Resting heart rate (RHR) is an easily and ubiquitously collected vital sign at every clinical patient encounter. RHR is a function of many factors including recent activity, tobacco use, medications, emotional stability, air temperature, and position<sup>[4-7]</sup>. Resting heart rate is associated with increased cardiovascular risk in the general population<sup>[4-18]</sup>. Zhang *et al*<sup>[4]</sup> in meta-analysis of 46 studies including 1246203 patients showed that higher resting heart rate is associated with increased risk of all-cause and cardiovascular mortality, independent of traditional cardiovascular risk factors. Zhang *et al*<sup>[4]</sup> hypothesized that association is due to higher resting heart rate signaling an imbalance between vagal and sympathetic tone and thus dysfunctional autonomic nervous system activity. The prevalence of autonomic dysfunction is very high in individuals with diabetes mellitus raising the possibility that resting heart rate may not be as informative as a risk marker in diabetes as in the general population. It remains unclear if the association between resting heart rate and CVD risk exist in higher risk populations such as those with type-2 diabetes mellitus<sup>[19-25]</sup>. We sought to examine the association between resting heart rate, all-cause and CVD mortality in individuals with type 2 diabetes in the Diabetes Heart Study (DHS).

### MATERIALS AND METHODS

#### Study population

The details of the National Institutes of Health -funded Diabetes Heart Study have been published<sup>[26-30]</sup>. There were 1443 type 2 diabetic concordant siblings from 564 different families included in the study. Type 2 Diabetes mellitus (DM) was defined as diagnosed diabetes after 35 years of age managed with oral agents and/or insulin without any history of diabetic ketoacidosis. Of these participants, 85% are European Americans and 15% are African Americans. From 1998 to 2005, participants were recruited primarily from western North Carolina from outpatient medicine clinics, health fairs, community outreach programs, and referrals by physicians without any inclusions or exclusions based on prior cardiovascular disease history. Potential participants were recruited by letters which included a telephone number to call if interested. Interviews were performed by telephone and then by an examination visit. Potential participants were sent the informed consent forms and questionnaires before their examination visits for them to review. Written informed consent was obtained at these visits for all participants. The Wake Forest School of Medicine Institutional Review Board approved all study protocols. The study sample represents a cross-section of the diabetic community

living in western North Carolina.

Participant examination visits were performed in the General Clinical Research Center at Wake Forest Baptist Medical Center. Exams included medical history and health behavior interviews. In addition, anthropometric measures, blood pressure, fasting blood draw, and a spot urine collection were measured. Laboratory analyses included total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, glycated hemoglobin, blood chemistries, and urine albumin and creatinine. Prior CVD history was based on each participant's history including events (heart attack, stroke) and/or interventions (coronary artery bypass grafting, carotid endarterectomy, coronary angiography). Hypertension was defined as blood pressure measurements over 140 mmHg systolic/90 mmHg diastolic or prescription of anti-hypertensive medication. The four-variable Modification of Diet in Renal Disease equation was used to calculate estimated glomerular filtration rate (eGFR). In DHS patients' medication list was not rigorously collected during the baseline exam and therefore is not complete.

### **Resting heart rate measurement**

All DHS participants had a resting electrocardiogram (ECG) during the baseline examination. The resting 12-lead electrocardiogram was performed using Marquette MAC 500 ECG instrument (Marquette Electronics, Milwaukee, WI, United States) after a uniform resting period (after 5 min of rest). The electrocardiogram was read at the Wake Forest Epidemiologic Cardiology Research Center using analytical software. Resting heart rate used in this analysis were those reported from the participants resting ECG. For this study, we included type 2 diabetic participants ( $n = 1315$ ) without atrial fibrillation and supraventricular tachycardia.

### **Ascertainment of outcomes ascertainment**

Ascertainment has been described in detail previously<sup>[25,27]</sup>. For all participants in this study, the National Social Security Death Index maintained by the United States Social Security Administration was used to determine vital status. Length of follow-up was measured from the date of the initial study visit to the end of 2012, unless the participant was confirmed as deceased. In those cases, length of follow-up was measured from the date of the initial examination visit to the date of death.

### **Statistical analysis**

Summary statistics were described for continuous variables as mean  $\pm$  SD and for categorical variables as frequency (percentage). Summary statistics of participants above and below the median heart rate [heart rate (HR) = 69] was compared using chi-square test for categorical variables and students *t*-test for continuous variables. Kaplan-Meier analysis was used to assess the events-free survivals of DHS participants with resting heart rate above and below the median

heart rate and the curves compared using log-rank test.

Cox proportional hazards regression analysis was subsequently used to assess the association between resting heart rate, all-cause and cardiovascular disease mortality adjusting for confounders *via* 4 models; Model 1- unadjusted; Model 2- adjusted for age, sex, and ethnicity; Model 3- Model 2+ body mass index (BMI), hemoglobin A1c, diabetes duration, systolic blood pressure, hypertension, total cholesterol level, triglyceride level, current smoking status, and eGFR and Model 4- Model 3+ comorbidities. A two sided *P* value of  $< 0.05$  was accepted as statistically significant. All analyses were performed using Statistical Analysis System (SAS) JMP Pro software, version 12.0.1 (SAS Institute, Cary, NC, United States).

## **RESULTS**

### **Baseline characteristics**

At baseline, mean age, diabetes duration, HbA1c, RHR, BMI, and systolic blood pressure of the cohort were 61.4 years, 10.4 years, 7.4%, 69.8 bpm, 32.0 kg/m<sup>2</sup>, and 139.4 mmHg respectively (Table 1). The majority of participants were European Americans (84.6%) and there were more women (55.9%) in the study. Of the 1315 participants, 652 (49.6%) had below median RHR and 663 (50.4%) had above median RHR (Table 1). Participants with resting heart rate below the median were older and had higher prevalence of prior CVD. Those with resting heart rate greater than the median had higher BMI, diastolic blood pressure, HbA1c, glucose, triglyceride and total cholesterol levels.

### **Resting heart rate and all-cause mortality**

After a median follow-up time of 8.5 years (maximum follow-up time of 14.0 years), 258 participants (19.6%) were deceased. As shown in Figure 1A, participants with resting heart rate  $\geq$  median had significantly less mortality event-free survival compared with those with resting HR  $<$  median (Log rank  $P = 0.022$ ). Table 2 shows the CVD mortality risk associated with 1 standard deviation increase in resting heart rate in the 4 models. In the full Cox regression model, each 1-SD increase in RHR was associated with a 20% increase in risk for all-cause mortality [HR 1.20 (95%CI: 1.05-1.37),  $P = 0.01$ ; Table 2] after controlling for age, sex, ethnicity, BMI, hemoglobin A1c, diabetes duration, systolic blood pressure, hypertension, total cholesterol level, triglyceride level, current smoking status, eGFR, and baseline CVD history. An interaction term of resting heart rate and either sex or race was not significant in our full model.

### **Resting heart rate and cvd mortality**

After the same follow-up period (median follow-up 8.5 years; maximum follow-up 14.0 years), 111 participants (8.4%) died from CVD causes. Participants with resting heart rate  $>$  median had a lower CVD mortality event-free survival compared with those  $<$  median (Log rank

**Table 1 Baseline characteristics of participants in the diabetes heart study**

Characteristics	All (n = 1315)	< Median RHR (n = 652)	≥ Median HR (n = 663)	P value
Age (yr)	61.4 (9.2)	62.2 (9.3)	60.6 (9.1)	0.0015
Caucasian (%)	1113 (84.6)	557 (85.4)	556 (83.9)	
African American (%)	202 (15.4)	95 (14.6)	107 (16.1)	
Women (%)	735 (55.9)	323 (49.5)	412 (62.1)	
BMI (kg/m <sup>2</sup> )	32.0 (6.6)	31.0 (6.5)	33.0 (6.5)	< 0.0001
Current smoker (%)	234 (17.9)	98 (15.1)	136 (20.6)	0.1336
Ex-smoker (%)	541 (41.3)	296 (45.7)	245 (37.2)	0.0223
Diabetes duration (yr)	10.4 (7.04)	10.0 (7.0)	10.7 (7.1)	0.0953
Systolic BP (mmHg)	139.4 (19.4)	139.1 (19.1)	139.7 (19.7)	0.5661
Diastolic BP (mmHg)	73.4 (10.4)	72.6 (10.1)	74.2 (10.6)	0.0044
Hypertension (%)	1116 (84.9)	543 (83.3)	573 (86.4)	0.1118
Prior CVD (%)	397 (30.7)	218 (33.7)	179 (27.6)	0.0161
HbA1c (%)	7.4 (1.9)	7.1 (1.67)	7.7 (2.1)	< 0.0001
Glucose (g/L)	1.4 (0.6)	1.3 (0.5)	1.5 (0.7)	< 0.0001
Total cholesterol (g/L)	1.8 (0.5)	1.8 (0.4)	1.9 (0.5)	0.0006
HDL (g/L)	0.44 (0.1)	0.4 (0.1)	0.4 (0.1)	0.7662
LDL (g/L)	1.0 (0.4)	1.0 (0.3)	1.05 (0.4)	0.2616
Triglycerides (g/L)	1.8 (1.2)	1.7 (1.1)	2.0 (1.3)	< 0.0001
eGFR (mL/min × 1.73 m <sup>2</sup> )	67.9 (20.5)	68.2 (20.0)	67.7 (20.9)	0.6865
RHR (bpm)	69.8 (11.9)	60.2 (5.6)	79.3 (8.4)	< 0.0001

RHR: Resting heart rate; BMI: Body mass index; CVD: Cardiovascular diseases; HDL: High density lipoprotein; LDL: Low density lipoprotein; eGFR: Estimated glomerular filtration rate.

**Table 2 Association between 1- standard deviation of resting heart rate with mortality in the diabetes heart study in cox proportional hazard models after a median follow-up of 8.5 years**

Models	Hazard ratio	95%CI	P value
All-cause mortality (model)			
1	1.16	1.03-1.31	0.0151
2	1.26	1.12-1.42	0.0020
3	1.15	1.01-1.32	0.0355
4	1.20	1.05-1.37	0.0079
Cardiovascular mortality (model)			
1	1.19	0.98-1.43	0.0688
2	1.29	1.07-1.54	0.0073
3	1.14	0.93-1.40	0.2164
4	1.19	0.97-1.47	0.0975

Model 1: Unadjusted; Model 2: Adjusted for age, sex, ethnicity; Model 3: Model 2 + body mass index, hemoglobin A1c, diabetes duration, systolic blood pressure, hypertension, total cholesterol level, triglyceride level, current smoking status, estimated glomerular filtration rate; Model 4: Model 3 + baseline cardiovascular diseases history.

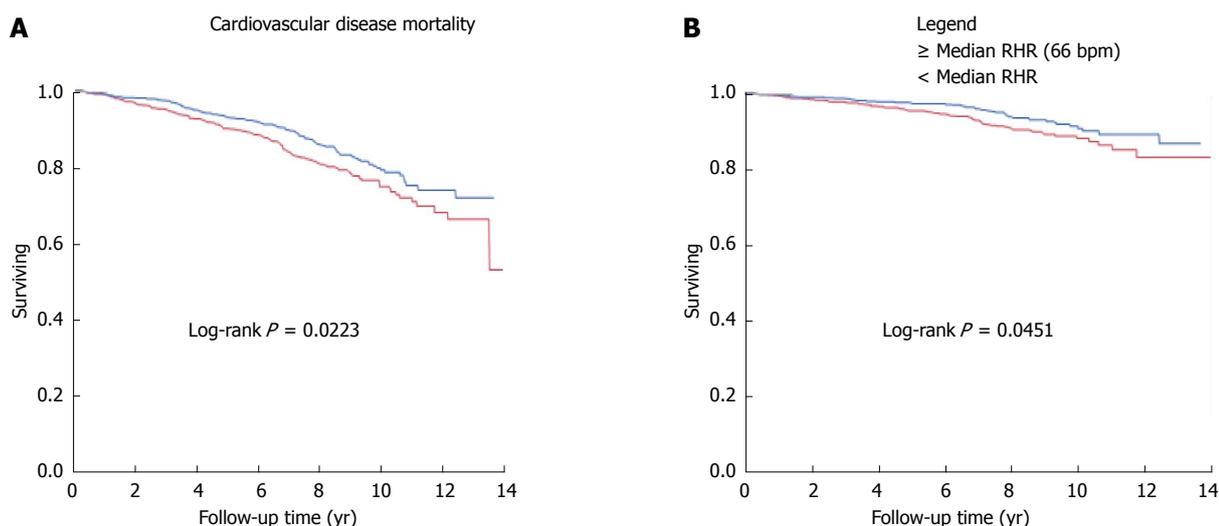
$P = 0.045$ ) (Figure 1B). Resting heart rate showed trends similar to that if all-cause mortality but some of the models did not attain statistical significance likely because of the lower number of CVD mortality that occurred during the follow up (Table 2).

## DISCUSSION

The goal of this study was to assess the association between resting heart rate and mortality in type-2 diabetics, a high risk group with very high prevalence of cardiac autonomic dysfunction<sup>[29,30]</sup>. Our study showed that despite the high prevalence of cardiac autonomic

dysfunction in type-2 diabetics, resting heart rate predicts mortality similar to that found in the general population.

Current data is consistent with an association between resting heart rate and mortality in the general population<sup>[4-18]</sup>. In the absence of medication use and cardiac arrhythmias, resting heart rate variability is controlled by a balance between sympathetic and parasympathetic systems. Persistently high resting heart rates are seen in stressful situations, chronic illness, physical inactivity, etc., all of which have been associated with higher mortality and morbidity in the general population. In diabetes mellitus, however, complex cascades of pathways are activated by hyperglycemia resulting in neuronal ischemic and cellular death<sup>[21,22]</sup>. This neuronal death leads to conditions such as poly-neuropathies and cardiac autonomic neuropathy. Symptoms of cardiac autonomic neuropathy include resting tachycardia, exercise intolerance, postural hypotension and diabetes cardiomyopathy. Thus resting tachycardia may represent a stressful state in both diabetic and non-diabetic individuals but the pathophysiology may be different. Hillis *et al.*<sup>[24,25]</sup> used data from the Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation study of about 11140 patients with type-2 diabetes mellitus, recruited from 215 centers in 20 countries, to show that resting heart rate was associated with all-cause mortality, macrovascular and microvascular complications. However, Bartáková *et al.*<sup>[20]</sup> used a smaller cohort of 421 type 2 diabetes mellitus (T2DM) patients to show that resting heart rate was not associated with advanced cardiovascular events and all-cause mortality. The present study findings are consistent with the findings by Hillis *et al.*<sup>[24,25]</sup>. In our study a 1 standard deviation increase in resting heart rate



**Figure 1 Result of Kaplan Meier curves.** A: Kaplan Meier curves showing the Mortality free- survival of Type-Diabetics with resting heart rate (RHR) above and below the median (Median RHR = 69 bpm) in the Diabetes Heart Study; B: Kaplan Meier curves showing the Cardiovascular disease Mortality free- survival of Type-Diabetics with RHR above and below the median (Median RHR = 69 bpm) in the Diabetes Heart Study; Red line:  $\geq$  Median RHR (66 bpm); Blue line:  $<$  Median RHR.

was associated with a 20% increase in CVD/ all-cause mortality.

In our study, the mean BMI of participants with resting heart rate greater than the median was higher than those with resting heart rate less than the median suggesting that factors such as obesity, physical inactivity/deconditioning, and endocrine abnormalities such as thyroid function may play a significant role in the increased risk observed. We adjusted for BMI in our final models but data on physical activity and thyroid function were not collected in the DHS so it is unclear if adequate adjustment for these variables will change our estimates in this analysis. Nonetheless, this suggests that targeting factors such as obesity, physical activity and other factors that leads to reduced resting heart rate may help reduced the high mortality risk seen in persons' with diabetes mellitus. Additionally Aggressive control of hyperglycemia to minimize the prevalence of cardiac autonomic dysfunction<sup>[22]</sup> which may manifest as resting tachycardia and reduction of stress among others, all of which leads to reduce resting heart rate in the general population may all be beneficial targets for reducing mortality in patients with type-2 diabetes mellitus.

### Limitations

This study is an observational study and therefore despite the effort to adjust for all possible confounders available to us, our results may still be due to residual confounding. We did not have adequate documentation of medications that influence resting heart rate in the Diabetes Heart Study and therefore could not eliminate nor adjust for them in our full model. This may have affected our results and findings. Our study results and findings should therefore be interpreted with this limitation in mind. The DHS only included whites and blacks and therefore our results may not be extended to other race/ethnicities. The number of events especially CVD mortality that occurred during the follow up was

small hence the non-significant p values seen in Table 2.

In conclusion, heart rate is an independent predictor of all-cause and CVD mortality in this population with type 2 diabetes. In this study, a 1-SD increase in HR was associated with a 20% increase in risk suggesting that additional prognostic information may be available from this ubiquitously collected vital sign.

## ARTICLE HIGHLIGHTS

### Research background

Individuals with type 2 diabetes mellitus have a significantly higher risk of morbidity and mortality compared with those without diabetes mellitus. Cardiovascular diseases still remains the number one cause of death in persons with diabetes mellitus. Current efforts at reducing this risk include tight glycemic control, control of cardiovascular risk factors and weight reduction among others. Despite these measures, morbidity and mortality in diabetes mellitus still remains high. There is therefore the need for identifying other non-traditional risk factors to further reduce this risk. Resting heart rate has been associated with mortality in the general population. However the association of resting heart rate and mortality risk in diabetes mellitus is unclear.

### Research motivation

There are several ways (pharmacological and non-pharmacological) that resting heart rate can be reduced. Establishing an association between resting heart rate and mortality in individuals with diabetes mellitus provides a whole new avenue and pathway for further reducing the high mortality risk associated with the disease.

### Research objectives

This study used a large population of individuals with diabetes mellitus.

### Research methods

Heart rate was collected from baseline resting electrocardiogram and mortality (all-cause and CVD) was obtained from state and national death registry. Kaplan-Meier (K-M) and Cox proportional hazard analyses were used to assess the association.

### Research results

The results show that a 1 standard deviation increase in resting heart rate is associated with a 20% increase in the risk mortality.

### Research conclusions

Resting heart rate is a risk factor for all-cause and cardiovascular disease mortality in individuals with diabetes mellitus and may provide additional prognostic information.

### Research perspectives

Resting heart rate is a cheap ubiquitous vital sign that is obtained during every doctor's visit. The information gleaned from this vital sign maybe be useful to guide therapy choices which will ultimately reduce mortality in this population.

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