**Name of Journal: *World Journal of Diabetes***

**Manuscript NO: 34545**

**Manuscript Type: ORIGINAL ARTICLE**

***Observational Study***

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

Prasada S *et al.* Heart rate and mortality in type 2 diabetes

**Sameer Prasada, Cameron Oswalt, Phyllis Yeboah, Georgia Saylor, Donald Bowden,** **Joseph Yeboah**

**Sameer Prasada, Cameron Oswalt,** Department of Medical School (Medical students), Wake Forest University, Winston Salem, NC 27157, United States

**Phyllis Yeboah**, Department of Internal Medicine, Wake Forest Baptist Health, Winston Salem, NC 27157, United States

**Georgia Saylor, Joseph Yeboah,** Department of Heart and Vascular Center of Excellence, Wake Forest Baptist Health, Winston Salem, NC 27157, United States

**Donald Bowden,** Department ofBiochemistry, Genomics and Personalized Medicine Research, Wake Forest University, Winston Salem, NC 27157, United States

**ORCID number**: Joseph Yeboah ([0000-0003-3655-469X](http://orcid.org/0000-0003-3655-469X)).

**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 J and Yeboah P helped write and edit the manuscript.

**Institutional review board statement:** The Diabetes Heart Study was approved by the Wake Forest University Institutional Review Board.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment in the Diabetes Heart Study (DHS).

**Conflict-of-interest** **statement:** No potential conflicts of interest relevant to this article were reported.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Joseph Yeboah, MD, MS,** Department ofHeart and Vascular Center of Excellence, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, United States. jyeboah@wakehealth.edu

**Telephone:** +1-336-7167015

**Fax:** +1-336-7169188

**Received:** May 4, 2017

**Peer-review started:** May 5, 2017

**First decision:** July 20, 2017

**Revised:** July 25, 2017

**Accepted: November 25, 2017**

**Article in press:**

**Published online:**

**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 +/- 9.2 years, 32.0 +/- 6.6 kg/m2, and 139.4 +/- 19.4 mmHg respectively. 56% were females, 85% were whites, 15% were blacks, 18% were smokers. The mean ± 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 human resourcewas 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

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

PrasadaS, Oswalt C, Saylor G, Bowden D, Yeboah J. Heart rate is an independent predictor of all-cause mortality in individuals with type 2 diabetes: The diabetes heart study. *World J Diabetes* 2017; In press

**INTRODUCTION**

Diabetes mellitus is a major health problem affecting 29.1 million (9.3%) Americans[1-3]. Type 2 diabetes mellitus comprises 90-95% of these diagnosed cases[1,2]. 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[1]. 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[4-7]. Resting heart rate is associated with increased cardiovascular risk in the general population[4-18]. Zhang *et al*[4] 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*[4] 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[19-25]. 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[26-30]. 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[25,27]. 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 ± SD and for categorical variables as frequency (percentage). Summary statistics of participants above and below the median heart rate [human resource (HR) = 69] was compared using chi-square test for categorical variables and students *t*-test for continuous variables. Kaplan-Meier analysis was use 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/m2, 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 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 ≥ 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 *P* = 0.045) (Figure 1 B). 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[29,30]. 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[4-18]. 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[21,22]. This neuronal death leads to conditions such as polyneuropathies 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*[24,25] 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*[20] 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*[24,25]. In our study a 1 standard deviation increase in resting heart rate 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[22] 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 valves 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.

***Peer-review***

This manuscript describes simple and interesting result that high resting heart rate predict mortality even in diabetics who frequently have cardiac autonomic neuropathy, a dysfunction in sympathetic and/or para-sympathetic nervous system.

**REFERENCES**

1 **Centers for Disease Control and Prevention.** National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services.

2 **Benjamin EJ**, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**: e146-e603 [PMID: 28122885 DOI: 10.1161/CIR.0000000000000485]

3 **World Health Organization.** Global report on diabetes. Geneva; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257\_eng.pdf

4 **Zhang D**, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ* 2016; **188**: E53-E63 [PMID: 26598376 DOI: 10.1503/cmaj.150535]

5 **Hansen TW**, Thijs L, Boggia J, Li Y, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Lind L, Sandoya E, Imai Y, Wang J, Ibsen H, O'Brien E, Staessen JA; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of ambulatory heart rate revisited in 6928 subjects from 6 populations. *Hypertension* 2008; **52**: 229-235 [PMID: 18574073 DOI: 10.1161/HYPERTENSIONAHA.108.113191]

6 **Legeai C**, Jouven X, Tafflet M, Dartigues JF, Helmer C, Ritchie K, Amouyel P, Tzourio C, Ducimetière P, Empana JP. Resting heart rate, mortality and future coronary heart disease in the elderly: the 3C Study. *Eur J Cardiovasc Prev Rehabil* 2011; **18**: 488-497 [PMID: 21450655 DOI: 10.1177/1741826710389365]

7 **Inoue R**, Ohkubo T, Kikuya M, Metoki H, Asayama K, Kanno A, Obara T, Hirose T, Hara A, Hoshi H, Totsune K, Satoh H, Kondo Y, Imai Y. Predictive value for mortality of the double product at rest obtained by home blood pressure measurement: the Ohasama study. *Am J Hypertens* 2012; **25**: 568-575 [PMID: 22318510 DOI: 10.1038/ajh.2012.3.]

8 **Wannamethee G**, Shaper AG, Macfarlane PW. Heart rate, physical activity, and mortality from cancer and other noncardiovascular diseases. *Am J Epidemiol* 1993; **137**: 735-748 [PMID: 8484365 DOI: 10.1093/oxfordjournals.aje.a116734]

9 **Hartaigh Bó**, Allore HG, Trentalange M, McAvay G, Pilz S, Dodson JA, Gill TM. Elevations in time-varying resting heart rate predict subsequent all-cause mortality in older adults. *Eur J Prev Cardiol* 2015; **22**: 527-534 [PMID: 24445263 DOI: 10.1177/2047487313519932.]

10 **Custodis F**, Roggenbuck U, Lehmann N, Moebus S, Laufs U, Mahabadi AA, Heusch G, Mann K, Jöckel KH, Erbel R, Böhm M, Möhlenkamp S. Resting heart rate is an independent predictor of all-cause mortality in the middle aged general population. *Clin Res Cardiol* 2016; **105**: 601-612 [PMID: 26803646 DOI: 10.1007/s00392-015-0956-7]

11 **Palatini P**, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. *Clin Exp Hypertens* 2004; **26**: 637-644 [PMID: 15702618 DOI: 10.1081/CEH-200031959]

12 **Ohira T**, Diez Roux AV, Prineas RJ, Kizilbash MA, Carnethon MR, Folsom AR. Associations of psychosocial factors with heart rate and its short-term variability: multi-ethnic study of atherosclerosis. *Psychosom Med* 2008; **70**: 141-146 [PMID: 18256350 DOI: 10.1097/PSY.0b013e318160686a]

13 **American Heart Association.** All about Heart Rate (Pulse); 2015. Available from: http://www.heart.org/HEARTORG/Conditions/More/MyHeartandStrokeNews/All-About-Heart-Rate-Pulse\_UCM\_438850\_Article.jsp#.WPQFZfnyuM8

14 **Seccareccia F**, Pannozzo F, Dima F, Minoprio A, Menditto A, Lo Noce C, Giampaoli S; Malattie Cardiovascolari Aterosclerotiche Istituto Superiore di Sanita Project. Heart rate as a predictor of mortality: the MATISS project. *Am J Public Health* 2001; **91**: 1258-1263 [PMID: 11499115 DOI: 10.2105/AJPH.91.8.1258]

15 **Fox K**, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; **50**: 823-830 [PMID: 17719466 DOI: 10.1016/j.jacc.2007.04.079]

16 **Boudoulas KD**, Borer JS, Boudoulas H. Heart Rate, Life Expectancy and the Cardiovascular System: Therapeutic Considerations. *Cardiology* 2015; **132**: 199-212 [PMID: 26305771 DOI: 10.1159/000435947]

17 **Lang CC**, Gupta S, Kalra P, Keavney B, Menown I, Morley C, Padmanabhan S. Elevated heart rate and cardiovascular outcomes in patients with coronary artery disease: clinical evidence and pathophysiological mechanisms. *Atherosclerosis* 2010; **212**: 1-8 [PMID: 20152981 DOI: 10.1016/j.atherosclerosis.2010.01.029]

18 **Johansen CD**, Olsen RH, Pedersen LR, Kumarathurai P, Mouridsen MR, Binici Z, Intzilakis T, Køber L, Sajadieh A. Resting, night-time, and 24 h heart rate as markers of cardiovascular risk in middle-aged and elderly men and women with no apparent heart disease. *Eur Heart J* 2013; **34**: 1732-1739 [PMID: 23306958 DOI: 10.1093/eurheartj/ehs449]

19 **Anselmino M**, Ohrvik J, Rydén L; Euro Heart Survey Investigators. Resting heart rate in patients with stable coronary artery disease and diabetes: a report from the euro heart survey on diabetes and the heart. *Eur Heart J* 2010; **31**: 3040-3045 [PMID: 20935002 DOI: 10.1093/eurheartj/ehq368]

20 **Bartáková V**, Klimešová L, Kianičková K, Dvořáková V, Malúšková D, Řehořová J, Svojanovský J, Olšovský J, Bělobrádková J, Kaňková K. Resting Heart Rate Does Not Predict Cardiovascular and Renal Outcomes in Type 2 Diabetic Patients. *J Diabetes Res* 2016; **2016**: 6726492 [PMID: 26824046 DOI: 10.1155/2016/6726492]

21 **Pop-Busui R**. Cardiac autonomic neuropathy in diabetes: a clinical perspective. *Diabetes Care* 2010; **33**: 434-441 [PMID: 20103559 DOI: 10.2337/dc09-1294]

22 **Manzella D**, Paolisso G. Cardiac autonomic activity and Type II diabetes mellitus. *Clin Sci* (Lond) 2005; **108**: 93-99 [PMID: 15476437 DOI: 10.1042/CS20040223]

23 **Stettler C**, Bearth A, Allemann S, Zwahlen M, Zanchin L, Deplazes M, Christ ER, Teuscher A, Diem P. QTc interval and resting heart rate as long-term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow-up. *Diabetologia* 2007; **50**: 186-194 [PMID: 17096116 DOI: 10.1007/s00125-006-0483-1]

24 **Hillis GS**, Hata J, Woodward M, Perkovic V, Arima H, Chow CK, Zoungas S, Patel A, Poulter NR, Mancia G, Williams B, Chalmers J. Resting heart rate and the risk of microvascular complications in patients with type 2 diabetes mellitus. *J Am Heart Assoc* 2012; **1**: e002832 [PMID: 23316296 DOI: 10.1161/JAHA.112.002832]

25 **Hillis GS**, Woodward M, Rodgers A, Chow CK, Li Q, Zoungas S, Patel A, Webster R, Batty GD, Ninomiya T, Mancia G, Poulter NR, Chalmers J. Resting heart rate and the risk of death and cardiovascular complications in patients with type 2 diabetes mellitus. *Diabetologia* 2012; **55**: 1283-1290 [PMID: 22286552 DOI: 10.1007/s00125-012-2471-y]

26 **Bowden DW**, Cox AJ, Freedman BI, Hugenschimdt CE, Wagenknecht LE, Herrington D, Agarwal S, Register TC, Maldjian JA, Ng MC, Hsu FC, Langefeld CD, Williamson JD, Carr JJ. Review of the Diabetes Heart Study (DHS) family of studies: a comprehensively examined sample for genetic and epidemiological studies of type 2 diabetes and its complications. *Rev Diabet Stud* 2010; **7**: 188-201 [PMID: 21409311 DOI: 10.1900/RDS.2010.7.188]

27 **Cox AJ**, Azeem A, Yeboah J, Soliman EZ, Aggarwal SR, Bertoni AG, Carr JJ, Freedman BI, Herrington DM, Bowden DW. Heart rate-corrected QT interval is an independent predictor of all-cause and cardiovascular mortality in individuals with type 2 diabetes: the Diabetes Heart Study. *Diabetes Care* 2014; **37**: 1454-1461 [PMID: 24574343 DOI: 10.2337/dc13-1257]

28 **Bowden DW**, Lehtinen AB, Ziegler JT, Rudock ME, Xu J, Wagenknecht LE, Herrington DM, Rich SS, Freedman BI, Carr JJ, Langefeld CD. Genetic epidemiology of subclinical cardiovascular disease in the diabetes heart study. *Ann Hum Genet* 2008; **72**: 598-610 [PMID: 18460048 DOI: 10.1111/j.1469-1809.2008.00446.x]

29 **Cox AJ**, Hsu FC, Freedman BI, Herrington DM, Criqui MH, Carr JJ, Bowden DW. Contributors to mortality in high-risk diabetic patients in the Diabetes Heart Study. *Diabetes Care* 2014; **37**: 2798-2803 [PMID: 24989706 DOI: 10.2337/dc14-0081]

30 **Cox AJ**, Hugenschmidt CE, Wang PT, Hsu FC, Kenchaiah S, Daniel K, Langefeld CD, Freedman BI, Herrington DM, Carr JJ, Stacey B, Bowden DW. Usefulness of biventricular volume as a predictor of mortality in patients with diabetes mellitus (from the Diabetes Heart Study). *Am J Cardiol* 2013; **111**: 1152-1158 [PMID: 23351459 DOI: 10.1016/j.amjcard.2012.12.044]

**P-Reviewer:** Tamemoto H, Zhao J, Koch TR, Huang J, Gómez-Sáez JM

**S-Editor:** Cui LJ **L-Editor: E-Editor:**

**Specialty type:** Endocrinology and metabolism

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): 0

**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/m2) | 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 x 1.73 m2) | 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.

Legend

≥ Median RHR(66bpm)

< Median RHR

Cardiovascular disease mortality

A B

 

Log-rank *P* = 0.0451

Log-rank *P* = 0.0223

**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: ≥ Median RHR (66 bpm); Blue line: < Median RHR.

.