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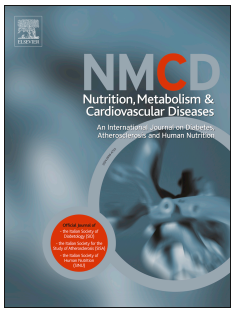

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D. Aune, B. ó Hartaigh, L.J. Vatten

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Resting heart rate and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies.

D. Aune[1,2], B. ó Hartaigh[3,4], L.J. Vatten[1].

Affiliations

[1] Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[2] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom

[3] Dalio Institute of Cardiovascular Imaging, Weill Cornell Medical College, New York, USA

[4] Department of Internal Medicine/Section of Geriatrics, Yale School of Medicine, New Haven, USA

Correspondence to: Dagfinn Aune, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, Paddington, London W2 1PG, UK.

Telephone: +44 20 7594 8478

Fax: +44 20 7594 0768

E-mail: d.aune@imperial.ac.uk

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Abstract

Background: High resting heart rate has been associated with increased risk of type 2 diabetes in several studies, but the available data are not consistent and it is unclear if there is a dose-response relationship between resting heart rate and type 2 diabetes risk. We aimed to clarify this association by conducting a systematic review and meta-analysis of published studies.

Methods and results: PubMed, Embase and Ovid Medline databases were searched for prospective studies published up until October 11th, 2013. Summary relative risks were estimated using a random effects model. Ten cohort studies with a total of 5,628 cases and 119,915 participants were included. The summary RR for high vs. low resting heart rate was 1.83 (95% CI: 1.28-2.60, I^2=88%, n=7), and in the dose-response analysis the summary RR was 1.20 (95% CI: 1.07-1.34, I^2=93%, n=9) for an increase of 10 beats per minute. The heterogeneity was to a large degree explained by two studies. There was evidence of nonlinear associations between resting heart rate ($p_{nonlinearity}$<0.0001) and risk of type 2 diabetes.

Conclusion: The current meta-analysis indicates a strong positive association between high resting heart rate and the risk of type 2 diabetes. As a non-invasive marker of type 2 diabetes risk, resting heart rate may have potential in the clinical setting, especially for interventions aimed at lowering the risk of type 2 diabetes. Additional studies are needed to clarify the mechanisms that may be responsible for the association between resting heart rate and type 2 diabetes.

Key words: Resting heart rate, type 2 diabetes, systematic review, meta-analysis.

Introduction

Several previous epidemiological studies have linked elevated resting heart rate to increased risk of cardiovascular disease and all-cause mortality (1;2). Resting heart rate is known to be a sensitive indicator of the autonomic nervous system,(3) and it is possible that an imbalance between parasympathetic and sympathetic activity might contribute towards the observed association between a raised resting heart rate and type 2 diabetes. Increased sympathetic tone not only elevates resting heart rate, but also amplifies insulin resistance,(4) which might suggest an intermediary role for impaired autonomic nervous activity in the relationship between resting heart rate and type 2 diabetes. Alternatively, metabolic syndrome, abdominal obesity and insulin resistance may activate the sympathetic nervous system, with elevated heart rate being a consequence rather than a cause of the metabolic alterations (5).

Despite this, the association between elevated resting heart rate and type 2 diabetes remains unclear (6-17). Some studies suggested an increased risk of type 2 diabetes with higher heart rate (6;7;10;12-17), whereas others found the association to be no longer significant after adjustment for potential confounding factors (8;9;11). These studies were, however, largely heterogeneous with regards to the strength of the association; some reported a 60-100% increase in the risk (6;7;13-15) and others up to a 5-fold increase (14) in risk with elevated heart rate.

Hence, we conducted a systematic review and meta-analysis of prospective studies that examined the relationship between resting heart rate and type 2 diabetes. Specifically we aimed to: 1) clarify the strength of the association, 2) determine whether there is a dose-response relationship, and 3) establish whether the association varies by adjustment for potential confounding factors and other study characteristics.

Methods

Search strategy

We searched the electronic databases PubMed, Embase and Ovid Medline databases up until October 11th 2013 for prospective studies of resting heart rate and type 2 diabetes risk. We used the following search terms for the search: ("resting heart rate" OR "heart rate" OR "resting pulse") AND "diabetes" with search fields "title/abstract" and "MeSH terms". No language restrictions were imposed. We also examined the reference lists of the studies included in the analysis in an effort to identify additional potentially relevant studies. All retrieved citations were screened by 2 independent reviewers (D.A. and B.H.) and any disagreements were resolved by consensus among authors.

Study selection

Studies were included in the analyses based on the following inclusion criteria: the study had to: 1) have a prospective cohort, case-cohort or nested case-control design from the general population (no studies of high-risk patients with hypertension or cardiovascular disease were included), 2) investigate the association between resting heart rate and risk of type 2 diabetes, 3) present estimates of the relative risk (RR), such as hazard ratios, risk ratios, or odds ratios with the 95% confidence intervals (95% CI), and 4) for the dose-response analysis, a quantitative measure of the heart rate and the total number of cases and person-years or participants had to have been available in the publication. We contacted the authors of two studies (6;7) to obtain more detailed results so the studies could be included in the dose-response analysis, and received more detailed data from one study (6).

Data extraction

We extracted the following data from each study: The first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, exposure, resting heart rate level, RRs and 95% CIs for the association and variables adjusted for in the analysis.

Statistical methods

We used random effects models to calculate summary RRs and 95% CIs for the highest vs. the lowest level of resting heart rate and also for the dose-response analysis (18). The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance and then un-weighted by a variance component which corresponds to the amount of heterogeneity in the analysis. A two-tailed $p<0.05$ was considered statistically significant. For the two studies which reported results separately for men and women (14) or by treatment group (10), we combined the results using a fixed-effects model to obtain an overall estimate which was used for the main analysis.

The method described by Greenland and Longnecker (19) was used for the dose–response analysis and study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs were computed across categories of resting heart rate. This method requires that the distribution of cases and person-years or non-cases and the level of resting heart rate and RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of person-years in studies that did not report these. For one study we divided the total number of participants by four to get the approximate number of participants for each quartile (11). For four studies (11-13;15) we multiplied the mean or median duration of follow-up by the number of participants in each

category to get an estimate of the number of person-years for each category. Importantly, because these estimated numbers are only used as starting points for the glst-iterations they do not affect the estimated dose-response slopes (we also repeated the analyses using slightly different numbers of person-years, but this led to identical results). The median or mean resting heart rate level in each category was assigned to the corresponding relative risk for each study. When resting heart rate was reported as ranges we estimated the midpoint for each category by calculating the average of the lower and upper bound. When the highest or lowest category was open-ended or had extreme upper cut-off points we assumed the open-ended interval length to be the same as the adjacent interval. A potential nonlinear dose-response relationship between resting heart rate and type 2 diabetes was examined using fractional polynomial models (20). We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity (20).

Study quality was assessed using the Newcastle-Ottawa scale which measures study quality based on representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome was not present at the start of the study, comparability of cohorts (adjustment or matching for two different risk factors), assessment of outcome, duration of follow-up, and adequacy of follow-up and gives a maximum of nine stars (21). We grouped studies with 0-3 stars, 4-6 stars, and 7-9 stars for the subgroup analysis.

We assessed heterogeneity between studies using the Q test and I^2 (22). I^2 is the amount of total variation that is explained by between study variation. I^2 values of approximately 25%, 50% and 75% are considered to reflect low, moderate and high heterogeneity, respectively. Subgroup analyses were conducted to investigate potential

sources of heterogeneity including duration of follow-up, gender, geographic location, number of cases, study quality, adjustment for confounding factors, and exclusion of subjects using hypertensive or cardiovascular disease medications or with diagnosed cardiovascular disease at baseline.

Publication bias was assessed with Egger's test (23) and the results were considered to indicate publication bias when $p<0.10$. We conducted sensitivity analyses excluding one study at a time to ensure that the results were not simply due to one large study or a study with an extreme result. Results from these sensitivity analyses are presented excluding the two studies with the largest negative and positive impact on the summary estimates. The statistical analyses were conducted using Stata, version 10.1 software (StataCorp, College Station, TX, USA).

Results

Main results

We identified 10 cohort studies of healthy general populations (6-15) that were included in the meta-analysis of resting heart rate and type 2 diabetes (Table 1, Figure 1) and these included a total of 5,628 cases and 119,915 participants. Two studies (16;17) of hypertensive patients and cardiovascular disease patients were excluded from the analysis. The summary RR for high vs. low resting heart rate was 1.83 (95% CI: 1.28-2.60, n=7) (Supplementary Figure 1), but there was substantial heterogeneity, I^2=88%, $p_{heterogeneity}$<0.0001. The summary RR ranged from 1.71 (95% CI: 1.20-2.44) when excluding the study by Nagaya et al. (14) to 1.99 (95% CI: 1.64-2.40) when excluding the study by Carnethon et al. (11). Heterogeneity was no longer significant when the latter study was excluded, I^2=30%, $p_{heterogeneity}$=0.21.

The summary RR for each 10 beats per minute increment in resting heart rate was 1.20 (95% CI: 1.07-1.34, n=9) (Figure 2a), but there was substantial heterogeneity, I^2=93%, $p_{heterogeneity}$<0.0001. The summary RR ranged from 1.14 (95% CI: 1.06-1.23) when the study by Nagaya et al. (14) was excluded to 1.23 (95% CI: 1.10-1.38) when the study by Carnethon et al. (11) was excluded. Heterogeneity was reduced when both of these outlying studies were excluded (11;14), but the summary estimate remained similar, summary RR=1.17 (95% CI: 1.09-1.26, I^2=59%, $p_{heterogeneity}$=0.02). There was no evidence of publication bias with Egger's test, p=0.42, although the number of studies was low. There was no substantial evidence of asymmetry in the funnel plot (Supplementary Figure 2). The nonlinear dose-response analysis requires at least three categories of resting heart rate, so studies that only reported a continuous estimate could not be included, so in total six studies were included in the nonlinear dose-response analysis (11-15). There was evidence of a nonlinear association between resting heart rate and risk of type 2 diabetes, $p_{nonlinearity}$<0.0001, with the slope

leveling off at higher levels (Figure 2b). Study quality as assessed by the Newcastle-Ottawa scale was in general high with a range from 5-9 stars out of 9 possible and a median of 7.5 stars (Supplemental Table 2) and there was no evidence of heterogeneity by study quality scores (Table 2).

Subgroup, sensitivity and meta-regression analyses

In subgroup and meta-regression analyses we found no significant heterogeneity between subgroups when studies were stratified by gender, duration of follow-up, geographic location, or study size (Table 2), although the associations did not always persist across subgroups. Further subgroup analyses according to whether studies had adjusted for confounding factors didn't reveal significant heterogeneity between strata, although associations were not always statistically significant. There was also no significant heterogeneity between subgroups of studies with or without exclusion of hypertensive medication users, cardiovascular medication users or persons with prevalent cardiovascular disease at baseline (Table 2). For one study reporting results from a randomized trial with three groups (placebo, metformin treatment, and lifestyle intervention) (10) we conducted a further sensitivity analysis using only the results from the placebo group in the meta-analysis, but the results remained similar, summary RR=1.20 (95% CI: 1.06-1.35, I^2=93%, $p_{heterogeneity}$<0.0001).

Discussion: To our knowledge this is the first meta-analysis on the relationship between resting heart rate and risk of type 2 diabetes. We found a high vs. low resting heart rate was associated with an 83% increase in the RR of type 2 diabetes. Moreover the dose-response analysis showed the RR increased 19% for every 10 beats per minute increment in resting heart rate. The association appeared to be nonlinear, and leveled off at higher values of resting heart rate.

Several biological mechanisms could explain the association between resting heart rate and type 2 diabetes. An elevated resting heart rate may reflect an imbalance in the autonomic nervous system favouring sympathetic activation. Indeed, sympathetic over-activity has been linked with reduced insulin sensitivity, high blood pressure, obesity, inflammation and the metabolic syndrome (12;24-27), all of which increases the risk of type 2 diabetes. Further, the pancreas is heavily innervated by parasympathetic nerve fibers, which stimulate β-cells of the pancreas to release insulin in response to increasing blood glucose levels. On the other hand sympathetic stimulation inhibits the secretion of insulin from pancreatic β-cells. Moreover, some evidence proposes that sympathetic activation might contribute to insulin resistance by inducing haemodynamic and cellular effects (28). Sympathetic activation causes vasoconstriction and decreases skeletal muscle blood flow, leading to impaired glucose uptake in skeletal muscle (29). Further, epinephrine causes hyperglycaemia by reducing the insulin-mediated glucose uptake in skeletal muscle cells, while β-adrenergic receptor blockade seems to abolish this effect (30). Sympathetic overactivity also stimulates the renin-angiotensin-aldosterone system, which increases heart rate and may be implicated in insulin resistance (31;32). In support of this are results from some randomized trials which have shown that patients treated with ACE inhibitors or angiotensin receptor blockers have a lower risk of type 2 diabetes compared to control patients (33-36), however, not all studies have been consistent (37).

Some evidence reported that chronic sympathetic overactivity may facilitate the development of obesity by downregulating the β-adrenoceptor-mediated thermogenic response (38;39). The relationship between sympathetic activation and insulin resistance may also be reciprocal. Elevated glucose levels, even in the non-diabetic range can damage peripheral nerve fibers, leading to increased sympathetic activity and reduced parasympathetic control (40-42). Thus, it is possible that an elevated resting heart rate could be a consequence, and equally, a marker of insulin resistance. In this meta-analysis, the association between resting heart rate was attenuated in subgroup analysis of the studies that adjusted for baseline glucose or HOMA-IR. These findings suggest that baseline glucose and/or insulin resistance accounts for part, though not all of the association, as the positive relationship between elevated resting heart rate and type 2 diabetes persisted in the studies with such adjustment. The potential mechanism that could explain the nonlinear association between resting heart rate and type 2 diabetes are yet to be fully clarified.

Some potential limitations of this meta-analysis should be mentioned. There was high heterogeneity both in the high vs. low analysis and the dose-response analysis, although this appeared to be largely explained by one (14) and two (11;14) studies , respectively. When both studies were excluded the heterogeneity was substantially reduced in the high vs. low analysis and it was lower in the dose-response analysis as well. In this meta-analysis it is possible that unmeasured or residual confounding may have influenced the association between elevated resting heart rate and type 2 diabetes. Indeed, high resting heart rate may be associated with other risk factors for type 2 diabetes including obesity, hypertension, smoking, and a sedentary lifestyle (12;43). Nevertheless, many of the studies included in this meta-analysis adjusted for known confounding factors such as age, BMI, smoking, and physical activity. The results persisted in most, but not all subgroup analyses, possibly due to few studies in some strata. However, more importantly we found no evidence of

heterogeneity between these subgroups with meta-regression analyses. Use of anti-hypertensive and cardiovascular disease medications can affect heart rate and could potentially have influenced the results, however, the results persisted in several subgroup analyses where persons using such medications and/or persons with cardiovascular disease at baseline had been excluded.

Publication bias may also have affected the results, albeit, in this study we found no evidence of publication bias with the statistical tests and there was no evidence of asymmetry when inspecting the funnel plots, although the number of studies was moderate.

Our meta-analysis has several strengths. Combining the evidence from all available studies increased the statistical power to detect an association between elevated resting heart rate and type 2 diabetes. We conducted high vs. low analyses, and linear and nonlinear dose-response analyses to clarify the strength and the shape of the dose-response relationship between resting heart rate and type 2 diabetes. We also conducted a number of subgroup and sensitivity analyses and the association persisted across most strata of study characteristics. Lastly the study quality was high and ranged from 5-9, with a median of 7.5 out of 9 stars.

In conclusion, the current meta-analysis found a positive association between resting heart rate and risk of type 2 diabetes. As a non-invasive marker, the resting heart rate may have potential in the clinical setting, particularly for interventions aimed at reducing the risk of type 2 diabetes. Additional studies are needed to disentangle the causal mechanisms that may be responsible for the association between resting heart rate and type 2 diabetes.

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Duality of interest: The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement: DA designed the project, and analyses and wrote the first draft of the paper. DA and BOH conducted the literature searches and study selection. DA, BH, LJV interpreted the data, revised the subsequent drafts for important intellectual content and approved the final version of the paper to be published.

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Reference List

1. Nauman J, Nilsen TI, Wisloff U, Vatten LJ. Combined effect of resting heart rate and physical activity on ischaemic heart disease: mortality follow-up in a population study (the HUNT study, Norway). J Epidemiol Community Health 2010;64:175-81.

2. Nauman J, Janszky I, Vatten LJ, Wisloff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA 2011;306:2579-87.

3. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. J Am Coll Cardiol 2008;51:1725-33.

4. Stern MP, Morales PA, Haffner SM, Valdez RA. Hyperdynamic circulation and the insulin resistance syndrome ("syndrome X"). Hypertension 1992;20:802-8.

5. Grassi G, Dell'Oro R, Facchini A, Quarti TF, Bolla GB, Mancia G. Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. J Hypertens 2004;22:2363-9.

6. Feskens EJ, Kromhout D. Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. Am J Epidemiol 1989;130:1101-8.

7. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. BMJ 1995;310:560-4.

8. Carnethon MR, Golden SH, Folsom AR, Haskell W, 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;107:2190-5.

9. Nilsson PM, Roost M, Engstrom G, Hedblad B, Berglund G. Incidence of diabetes in middle-aged men is related to sleep disturbances. Diabetes Care 2004;27:2464-9.

10. Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME. The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. Diabetes Care 2006;29:914-9.

11. Carnethon MR, Yan L, Greenland P et al. Resting heart rate in middle age and diabetes development in older age. Diabetes Care 2008;31:335-9.

12. Shigetoh Y, Adachi H, Yamagishi S et al. Higher heart rate may predispose to obesity and diabetes mellitus: 20-year prospective study in a general population. Am J Hypertens 2009;22:151-5.

13. Zhang X, Shu XO, Xiang YB et al. Resting heart rate and risk of type 2 diabetes in women. Int J Epidemiol 2010;39:900-6.

14. Nagaya T, Yoshida H, Takahashi H, Kawai M. Resting heart rate and blood pressure, independent of each other, proportionally raise the risk for type-2 diabetes mellitus. Int J Epidemiol 2010;39:215-22.

15. Grantham NM, Magliano DJ, Tanamas SK, Soderberg S, Schlaich MP, Shaw JE. Higher heart rate increases risk of diabetes among men: The Australian Diabetes Obesity and Lifestyle (AusDiab) Study. Diabet Med 2013;30:421-7.

16. Aksnes TA, Kjeldsen SE, Rostrup M, Storset O, Hua TA, Julius S. Predictors of new-onset diabetes mellitus in hypertensive patients: the VALUE trial. J Hum Hypertens 2008;22:520-7.

17. Bemelmans RH, Wassink AM, van der GY et al. Risk of elevated resting heart rate on the development of type 2 diabetes in patients with clinically manifest vascular diseases. Eur J Endocrinol 2012;166:717-25.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

19. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301-9.

20. Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. Stat Med 2000;19:1831-47.

21. Wells G, Shea B, O'Connell D. et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www ohri ca/programs/clinical_epidemiology/oxford asp Accessed 13 08 2014 2013.

22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.

23. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

24. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JF. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. Eur Heart J 2004;25:363-70.

25. Shibao C, Gamboa A, Diedrich A et al. Autonomic contribution to blood pressure and metabolism in obesity. Hypertension 2007;49:27-33.

26. Flanagan DE, Vaile JC, Petley GW et al. The autonomic control of heart rate and insulin resistance in young adults. J Clin Endocrinol Metab 1999;84:1263-7.

27. Mancia G, Bousquet P, Elghozi JL et al. The sympathetic nervous system and the metabolic syndrome. J Hypertens 2007;25:909-20.

28. Jamerson KA, Julius S, Gudbrandsson T, Andersson O, Brant DO. Reflex sympathetic activation induces acute insulin resistance in the human forearm. Hypertension 1993;21:618-23.

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

30. Deibert DC, DeFronzo RA. Epinephrine-induced insulin resistance in man. J Clin Invest 1980;65:717-21.

31. Ogihara T, Asano T, Ando K et al. Angiotensin II-induced insulin resistance is associated with enhanced insulin signaling. Hypertension 2002;40:872-9.

32. Perin PC, Maule S, Quadri R. Sympathetic nervous system, diabetes, and hypertension. Clin Exp Hypertens 2001;23:45-55.

33. Dahlof B, Devereux RB, Kjeldsen SE et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.

34. Hansson L, Lindholm LH, Niskanen L et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611-6.

35. Julius S, Kjeldsen SE, Weber M et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022-31.

36. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53.

37. Bosch J, Yusuf S, Gerstein HC et al. Effect of ramipril on the incidence of diabetes. N Engl J Med 2006;355:1551-62.

38. Valentini M, Julius S, Palatini P et al. Attenuation of haemodynamic, metabolic and energy expenditure responses to isoproterenol in patients with hypertension. J Hypertens 2004;22:1999-2006.

39. Julius S, Valentini M, Palatini P. Overweight and hypertension : a 2-way street? Hypertension 2000;35:807-13.

40. Van De BP, Hausberg M, Hoffman RP, Mark AL, Anderson EA. Hyperinsulinemia produces cardiac vagal withdrawal and nonuniform sympathetic activation in normal subjects. Am J Physiol 1999;276:R178-R183.

41. Vanninen E, Uusitupa M, Lansimies E, Siitonen O, Laitinen J. Effect of metabolic control on autonomic function in obese patients with newly diagnosed type 2 diabetes. Diabet Med 1993;10:66-73.

42. Emdin M, Gastaldelli A, Muscelli E et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: effects of weight loss. Circulation 2001;103:513-9.

43. Fernandes RA, Vaz Ronque ER, Venturini D et al. Resting heart rate: its correlations and potential for screening metabolic dysfunctions in adolescents. BMC Pediatr 2013;13:48.

Table 1: Prospective cohort studies of resting heart rate and type 2 diabetes risk

Author, publication year, country	Study name	Follow-up period	Study size, gender, age, number of cases	Study quality	Exposure and subgroup	Quantity	RR (95% CI)	Adjustment for confounders
Grantham NM et al, 2013, Australia	Australian Diabetes Obesity and Lifestyle study	1999-2000 – 2004-2005, 5 years follow-up	5817 men and women, age ≥25 years: 221 cases	8	Heart rate, all Heart rate, men Heart rate, women	<60 BPM 60-69 70-79 ≥80 <60 BPM 60-69 70-79 ≥80 <60 BPM 60-69 70-79 ≥80	1.00 1.55 (0.89-2.67) 1.44 (0.83-2.51) 1.89 (1.07-3.35) 1.00 2.01 (0.99-4.09) 1.54 (0.73-3.25) 2.02 (0.93-4.39) 1.00 1.03 (0.42-2.50) 1.25 (0.53-2.94) 1.72 (0.72-4.12)	Age, family history of diabetes, waist circumference, hip circumference, smoking status, education, physical activity, cholesterol, HDL cholesterol, triglycerides, hypertension, hypertension treatment, cardiovascular disease history, homeostasis model assessment of insulin sensitivity, urinary albumin creatinine ration, anxiety, total population also adjusted for sex
Nagaya T et al, 2010, Japan	Gifu Prefecture Center for Health Check and Promotion	1988-1991 – NA, 7.3 years follow-up	16828 men and 8368 women, age 30-59 years: 869/224 cases	8	Heart rate, men Heart rate, women	32-53 BPM 54-58 59-64 65-131 Per 8.9 BPM 36-57 BPM 58-62 63-67 68-137 Per 9.3 BPM	1.00 1.25 (1.00-1.56) 1.63 (1.32-2.01) 2.26 (1.84-2.78) 1.37 (1.29-1.45) 1.00 1.09 (0.72-1.64) 1.06 (0.70-1.62) 2.06 (1.43-2.96) 1.46 (1.31-1.62)	Age, BMI, smoking, drinking, exercise, education
Zhang X et al, 2010, China	Shanghai Women's Health Study	2000-2002 – NA, 4.9 years follow-up	47571 women, age 40-70 at baseline: 849 cases	7	Resting heart rate	≤68 BPM 69-72 73-76 77-80 >80	1.00 1.21 (0.99-1.47) 1.30 (1.05-1.62) 1.37 (1.12-1.69) 1.60 (1.28-2.00)	Age, education, occupation, family income, cigarette smoking, alcohol, BMI
Shigetoh Y et al, 2009, Japan	Tanashimaru – Seven Countries Study	1979 – 1999, 20 years follow-up	637 men and women, age >20 years: 8 cases	6	Heart rate	<60 BPM 60-69 70-79 ≥80	1.00 2.15 (0.68-6.76) 2.91 (0.89-9.53) 5.39 (1.34-21.8)	Age, sex, BMI, fasting plasma glucose

Carnethon MR et al, 2008, USA	Chicago Heart Association Detection Project in Industry	1992-2002, 10 years follow-up	14992 men and women, age 35-64 years: 1877 cases	8	Heart rate Heart rate	<68 BPM 68-74 75-83 ≥84 Per 12 BPM <68 BPM 68-74 75-83 ≥84 Per 12 BPM	1.00 1.07 (0.92-1.23) 1.07 (0.92-1.24) 1.19 (1.03-1.38) 1.07 (1.02-1.12) 1.00 1.04 (0.90-1.21) 1.02 (0.88-1.19) 1.02 (0.88-1.19) 1.00 (0.95-1.06)	Age, sex, cigarette smoking, education, years of Medicare eligibility, BMI + glucose
Carnethon MR et al, 2006, USA	Diabetes Prevention Programme	1996-2001, 3.2 years follow-up	2980 men and women, age ≥25 years: NA	5	Heart rate, placebo group Heart rate, metformin group Heart rate, lifestyle group	Per 11 BPM Per 11 BPM Per 11 BPM	1.09 (0.97-1.22) 1.17 (1.03-1.35) 1.19 (1.02-1.40)	Age, race, sex, baseline weight, weight change
Nilsson PM et al, 2004, Sweden	Malmø Preventive Project	1974-1984 – 1994-1996, 16.4 years follow-up	6599 men, age 35-51 years: 281 cases	7	Heart rate	Per 10 BPM	1.13 (0.99-1.30)	Age, sleep disturbances, systolic and diastolic blood pressure, antihypertensive medication, fasting whole blood glucose, BMI, change in BMI from baseline, follow-up time, diabetes heredity, smoking, physical activity, social class
Carnethon MR et al, 2003, USA	Atherosclerosis Risk in Communities Study	1987-1998, 8.3 years follow-up	8185 men and women, age 45-64 years: 1063 cases	8	Heart rate Heart rate	Per 9.7 BPM Per 9.7 BPM	1.18 (1.11-1.26) 1.06 (1.00-1.13)	Age, race, study center, education, alcohol, smoking, prevalent coronary heart disease, physical activity, BMI +baseline glucose
Perry IJ et al, 1995, United Kingdom	British Regional Heart Study	1978-1980 – 1991, 12.8 years follow-up	7097 men, age 40-59 years: 178 cases	9	Heart rate	Quintile 5 vs. 1	2.2 (1.1-4.2)	Age, BMI, coronary heart disease, physical activity, alcohol, systolic blood pressure, HDL cholesterol, smoking, uric acid
Feskens EJM et al, 1989, Netherlands	The Zutphen Study	1960-1985, 25 years follow-up	841 men, age 40-59 years: 58 cases	8	Heart rate	Quartile 4 vs. 1	2.0 (1.1-3.7)	Age, subscapular skinfold, cigarette use, alcohol, energy intake

BMI=Body Mass Index, HDL=high density lipoprotein

Table 2: Subgroup analyses of resting heart rate and type 2 diabetes risk, dose-response analysis

		Resting heart rate, per 10 bpm				
		n	RR (95% CI)	I^2 (95% CI)	P_h[1]	P_h[2]
All studies		9	1.20 (1.07-1.34)	92.9 (89.0-96.0)	<0.0001	
Duration of follow-up						
<10 yrs follow-up		5	1.21 (1.05-1.39)	93.3 (87.0-96.0)	<0.0001	0.75
≥10 yrs follow-up		4	1.18 (0.99-1.39)	78.9 (43.0-92.0)	0.003	
Gender[4]						
Men		4	1.27 (1.10-1.46)	73.4 (25.0-91.0)	0.01	0.11/ 0.50[3]
Women		3	1.37 (1.22-1.54)	48.8 (0-85.0)	0.14	
Men and women		5	1.08 (1.01-1.17)	72.2 (30.0-89.0)	0.006	
Geographic location						
Europe		2	1.20 (1.02-1.41)	40.2 (NC)	0.20	0.38
America		3	1.06 (0.99-1.13)	75.3 (18.0-93.0)	0.02	
Asia		3	1.41 (1.29-1.53)	32.2 (0-93.0)	0.23	
Australia		1	1.16 (0.99-1.36)			
Number of cases[4]						
Cases <500		4	1.22 (1.08-1.36)	28.5 (0-74.0)	0.24	0.68
Cases ≥500		4	1.19 (0.98-1.44)	97.2 (95.0-98.0)	<0.0001	
Study quality						
0-3 stars		0				0.78
4-6 stars		2	1.28 (0.91-1.80)	69.8 (NC)	0.07	
7-9 stars		7	1.19 (1.04-1.37)	94.5 (91.0-97.0)	<0.0001	
Adjustment for confounding factors						
Age	Yes	9	1.20 (1.07-1.34)	92.9 (89.0-96.0)	<0.0001	NC
	No	0				
Education	Yes	5	1.18 (1.00-1.40)	96.3 (94.0-98.0)	<0.0001	0.74
	No	4	1.19 (1.07-1.32)	43.7 (0-81.0)	0.15	

Body mass index, weight	Yes	7	1.19 (1.05-1.36)	94.6 (91.0-97.0)	<0.0001	0.76
	No	2	1.22 (1.07-1.40)	7.5 (NC)	0.30	
Glucose or HOMA-IS	Yes	5	1.08 (1.00-1.17)	65.0 (8.0-87.0)	0.02	0.11
	No	4	1.29 (1.12-1.50)	90.0 (77.0-96.0)	<0.0001	
Physical activity, fitness	Yes	4	1.19 (0.99-1.44)	94.4 (89.0-97.0)	<0.0001	0.99
	No	5	1.19 (1.05-1.35)	86.2 (70.0-94.0)	<0.0001	
Alcohol	Yes	4	1.28 (1.06-1.53)	94.2 (88.0-97.0)	<0.0001	0.22
	No	5	1.11 (1.01-1.22)	74.2 (36.0-90.0)	0.004	
Smoking	Yes	7	1.19 (1.04-1.37)	94.5 (91.0-97.0)	<0.0001	0.78
	No	2	1.28 (0.91-1.80)	69.8 (NC)	0.07	
Hypertension	Yes	2	1.14 (1.03-1.27)	0 (NC)	0.81	0.66
	No	7	1.22 (1.07-1.39)	94.7 (91.0-97.0)	<0.0001	
Exclusion of subjects						
Subjects using hypertensive medication were excluded	Yes	5	1.26 (1.08-1.46)	93.4 (88.0-97.0)	<0.0001	0.33
	No	4	1.12 (0.99-1.27)	72.5 (22.0-90.0)	0.01	
Subjects using cardiovascular disease medications were excluded	Yes	3	1.20 (0.99-1.46)	96.6 (93.0-98.0)	<0.0001	0.96
	No	6	1.20 (1.05-1.36)	82.4 (63.0-92.0)	<0.0001	
Subjects with prevalent cardiovascular disease at baseline were excluded	Yes	3	1.28 (1.08-1.53)	93.4 (84.0-97.0)	<0.0001	0.21
	No	6	1.11 (1.02-1.21)	69.7 (29.0-87.0)	0.006	
Subjects with prevalent cardiovascular disease at baseline or users of cardiovascular disease medications	Yes	4	1.22 (1.04-1.44)	94.9 (90.0-97.0)	<0.0001	0.66
	No	5	1.16 (1.02-1.33)	75.2 (39.0-90.0)	0.003	

n denotes the number of studies.

[1] P for heterogeneity within each subgroup,

[2] P for heterogeneity between subgroups with meta-regression analysis,

[3] P for heterogeneity between men and women (studies with genders mixed were excluded)

[4] The number of studies is not equal to the total because some studies reported both on men and women combined and separately or because of missing information regarding the number of cases

NC = not calculable

Figure 1. Flow-chart of study selection

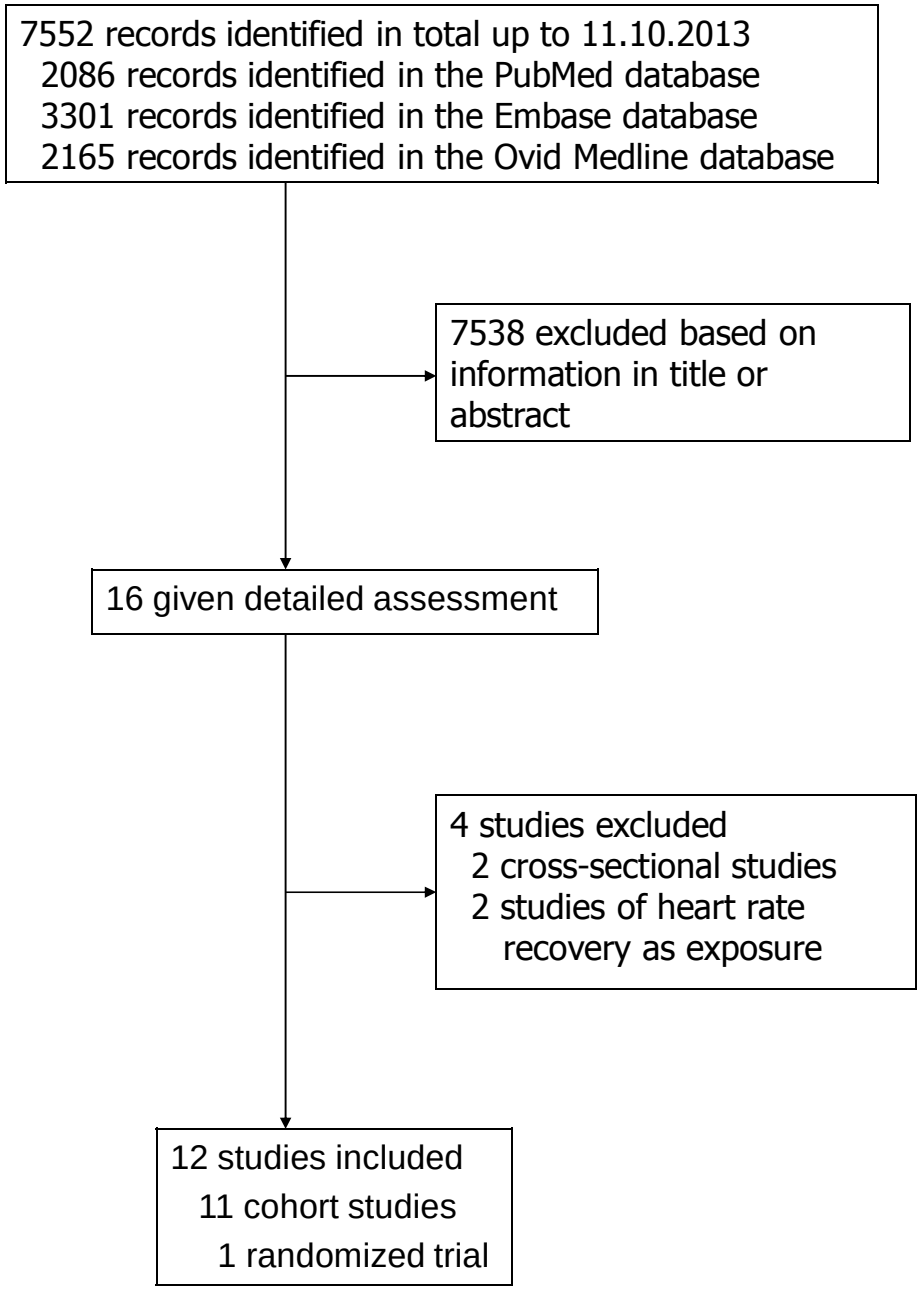
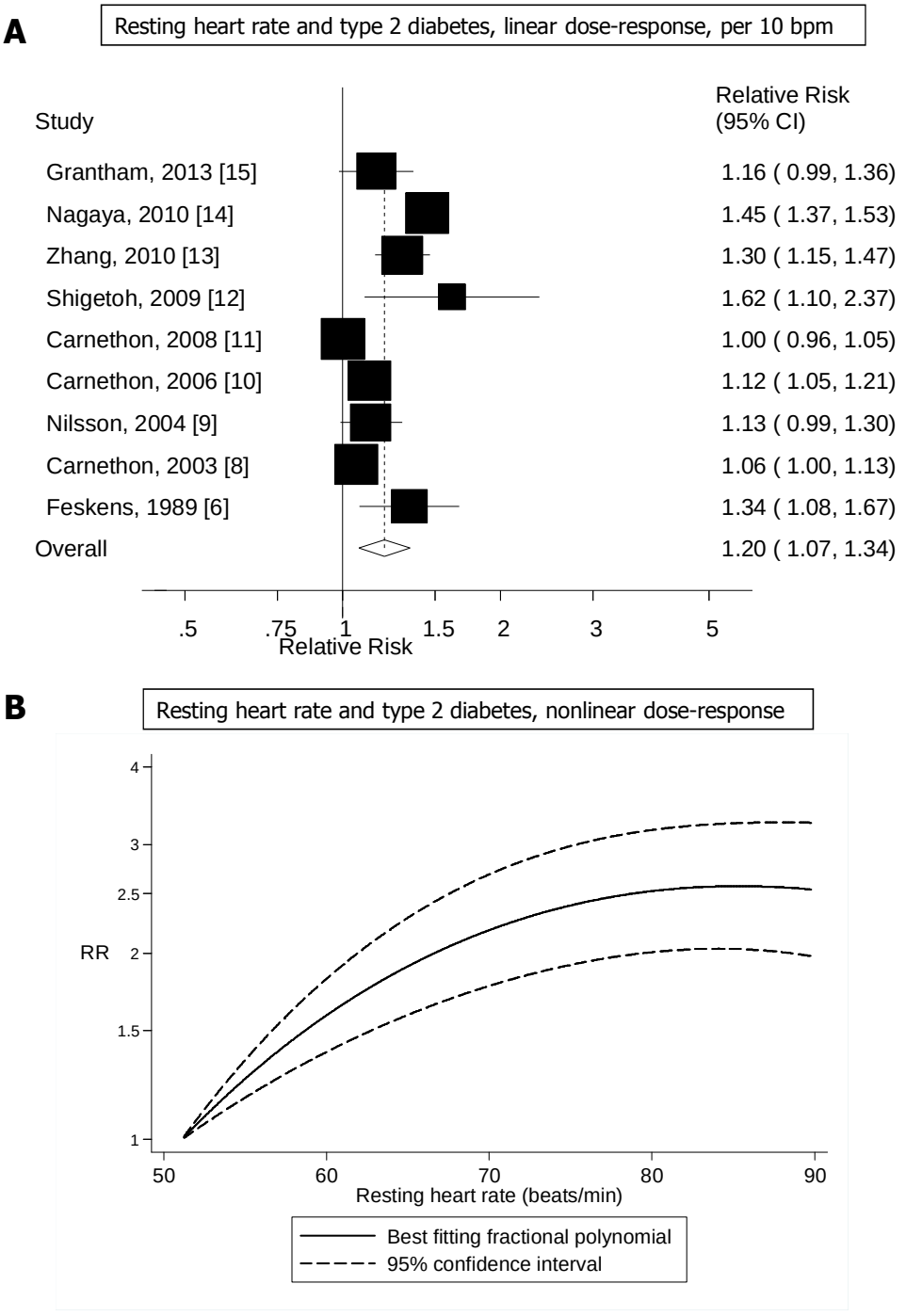


Figure 2. Resting heart rate and type 2 diabetes, linear (a) and nonlinear (b) dose-response analysis. The reference category in the nonlinear dose-response analysis was the lowest estimated midpoint among the included studies. References number 6, 11-15 were included in the nonlinear analysis.



Supplementary Table 1: Resting heart rate and type 2 diabetes, nonlinear dose-response

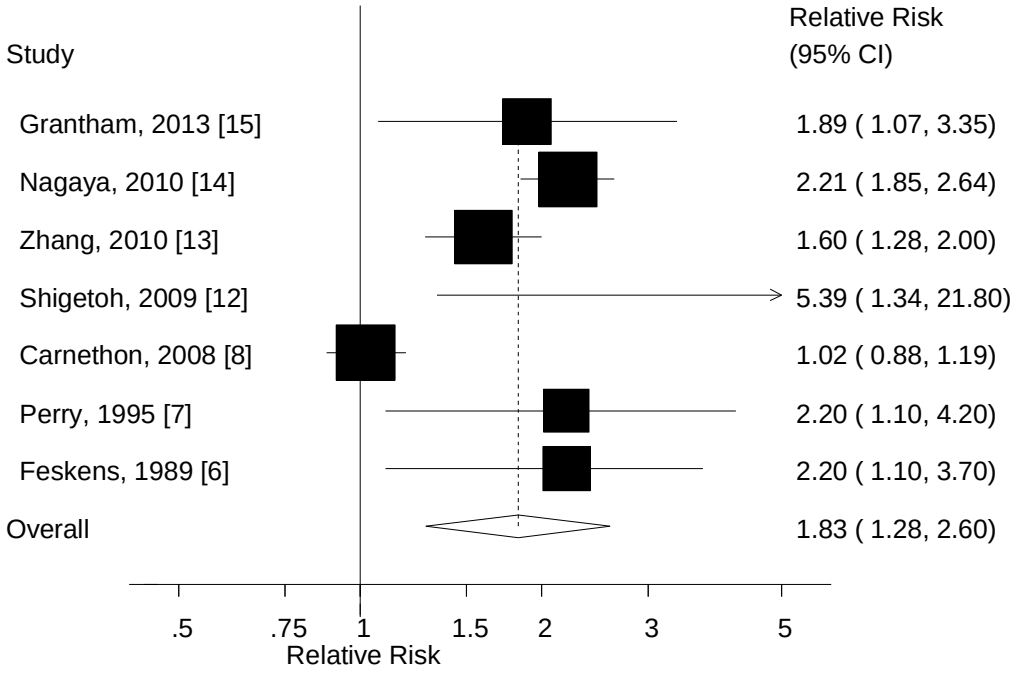
Beats per minute	RR (95% CI)
51[a]	1.00
55	1.26 (1.17-1.35)
60	1.59 (1.39-1.82)
65	1.91 (1.59-2.29)
70	2.18 (1.77-2.68)
75	2.39 (1.92-2.99)
80	2.52 (2.01-3.17)
85	2.57 (2.03-3.24)
90	2.53 (1.97-3.25)

[a] The reference category was the lowest estimated midpoint among the included studies.

Supplementary Table 2: Newcastle-Ottawa quality score for individual studies

Author, publication year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis (adjusted for age)	Comparability of cohorts on the basis of the design or analysis (adjusted for any other factor)	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
Grantham, 2013	1	1	1	1	1	1	1	1	0	8
Nagaya, 2010	1	1	1	1	1	1	1	1	0	8
Zhang, 2010	1	1	1	1	1	1	0	1	0	7
Shigetoh, 2009	1	1	1	0	1	1	0	1	0	6
Carnethon, 2008	1	1	1	1	1	1	1	1	0	8
Carnethon, 2006	0	1	1	0	1	1	0	1	0	5
Nilsson, 2004	1	1	1	0	1	1	1	1	0	7
Carnethon, 2003	1	1	1	1	1	1	1	1	0	8
Perry, 1995	1	1	1	1	1	1	1	1	1	9
Feskens, 1989	1	1	1	1	1	1	1	1	0	8

Supplementary Figure 1. Resting heart rate and type 2 diabetes, high vs. low analysis



Supplementary figure 2. Funnel plot of resting heart rate and type 2 diabetes