Nutrition, Metabolism & Cardiovascular Diseases (2017) 27, 504–517

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

SYSTEMATIC REVIEWS AND META-ANALYSES

Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality – A systematic review and dose–response meta-analysis of prospective studies

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Received 8 December 2016; received in revised form 6 April 2017; accepted 13 April 2017
Available online 21 April 2017

KEYWORDS
Coronary heart disease;
Sudden cardiac death;
Heart failure;
Atrial fibrillation;
Stroke;
Cardiovascular disease;
Cancer;
All-cause mortality

Abstract *Background and aim:* Epidemiological studies have reported increased risk of cardiovascular disease, cancer and all-cause mortality with greater resting heart rate, however, the evidence is not consistent. Differences by gender, adjustment for confounding factors, as well as the potential impact of subclinical disease are not clear. A previous meta-analysis missed a large number of studies, and data for atrial fibrillation have not been summarized before. We therefore aimed to clarify these associations in a systematic review and meta-analysis of prospective studies.

Methods and results: PubMed and Embase were searched up to 29 March 2017. Summary RRs and 95% confidence intervals (CIs) were calculated using random effects models. Eighty seven studies were included. The summary RR per 10 beats per minute increase in resting heart rate was 1.07 (95% CI: 1.05–1.10, I^2 = 61.9%, n = 31) for coronary heart disease, 1.09 (95% CI: 1.00–1.18, I^2 = 62.3%, n = 5) for sudden cardiac death, 1.18 (95% CI: 1.10–1.27, I^2 = 74.5%, n = 8) for heart failure, 0.97 (95% CI: 0.92–1.02, I^2 = 91.4%, n = 9) for atrial fibrillation, 1.06 (95% CI: 1.02–1.10, I^2 = 59.5%, n = 16) for total stroke, 1.15 (95% CI: 1.11–1.18, I^2 = 84.3%, n = 35) for cardiovascular disease, 1.14 (95% CI: 1.06–1.23, I^2 = 90.2%, n = 12) for total cancer, and 1.17 (95% CI: 1.14–1.19, I^2 = 94.0%, n = 48) for all-cause mortality. There was a positive dose–response relationship for all outcomes except for atrial fibrillation for which there was a J-shaped association.

Conclusion: This meta-analysis found an increased risk of coronary heart disease, sudden cardiac death, heart failure, atrial fibrillation, stroke, cardiovascular disease, total cancer and all-cause mortality with greater resting heart rate.

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http://dx.doi.org/10.1016/j.numecd.2017.04.004
0939-4753/

Introduction

Cardiovascular disease and cancer remain the two most common causes of death worldwide and accounted for 25.5 million deaths in 2013 [1]. Resting heart rate is known to be a sensitive indicator of the autonomic nervous system, and elevations in resting heart rate has been associated with increased risk of cardiovascular disease, cancer and total mortality in several previous studies [2,3]. It is plausible that an imbalance between parasympathetic and sympathetic activity (in favour of the latter) might contribute to the associations observed between a raised resting heart rate and increased chronic disease risk [2,3]. A recent meta-analysis suggested an association between high resting heart rate and increased risk of type 2 diabetes [4], an established risk factor for cardiovascular disease, several cancers and all-cause mortality [5]. Moreover, elevations in resting heart rate may increase myocardial oxygen consumption, fatigue, and fracture of elastic fibres within the arterial wall, further advancing the formation of atherosclerotic lesions as a consequence [2].

In spite of these conjectures, epidemiological data regarding the association between resting heart rate and cardiovascular disease, cancer and all-cause mortality have not been entirely consistent with some studies reporting a significant positive association between resting heart rate and coronary heart disease [6–20], sudden cardiac death [8,21–24], heart failure [19,25–31], stroke [15,19,20,32–35], cardiovascular disease [3,7,9,12,13,15,17,19,20,28,33,34,36–50], total cancer [3,10,11,46,51,52], and mortality [3,7,9–13,17,19,20,23,28,31,36–38,40–43,46–49,53–73], however, other studies reported no association [9,11,16,23,32–34,36,37,45,54,55,72,74–80] or associations only in men [53,60,81], while a few studies on atrial fibrillation suggested inverse [82,83], U-shaped [71], positive [48] or no associations [84–86].

The magnitude of the risk estimates has varied considerably between studies (hazard ratios ranging from 1.1 to 4.8 for mortality) and it is possible that part of this variation may be due to differences in the range of heart rate, gender, or detail of adjustment for confounding factors in each study. Although a recent meta-analysis reported a positive association between resting heart rate and mortality and cardiovascular disease [87] it either missed or excluded 19 studies on resting heart rate and all-cause mortality [3,7,16,31,32,40,46–48,53,54,56,59,61–64,66,68,70–72,78,80], and in addition 7 studies have since been published [31,47–49,71–73]. Altogether these additional studies included more than 84,000 deaths and almost one million participants. Another meta-analysis on resting heart rate and heart failure [29] only conducted analyses of the highest versus lowest category and questions therefore remain with regard to the strength or shape of the dose–response relationship between resting heart rate and heart failure. Therefore to provide a more up-to-date and complete assessment of the available evidence in relation to a range of different health outcomes we conducted a systematic review and meta-analysis of prospective studies examining the relationship between resting heart rate and risk of coronary heart disease, sudden cardiac death, heart failure, atrial fibrillation, stroke, cardiovascular disease, total cancer, and all-cause mortality. We specifically aimed to clarify 1) the direction, strength and shape of the dose–response relationship between resting heart rate and these outcomes, 2) whether potential confounding could explain the associations, 3) as well as potential sources of heterogeneity in the results.

Methods

Search strategy and inclusion criteria

We searched the PubMed and Embase from inception to 25.10.2016 and the search was later updated to 29.03.2017. The search terms used for the PubMed search are found in Supplementary Table 1 and a similar search was conducted in Embase. Prospective studies of resting heart rate and risk coronary heart disease, sudden cardiac death, heart failure, atrial fibrillation, stroke, cardiovascular disease, total cancer and overall mortality were included. Cross-sectional studies were not included because of the difficulty in drawing causal inferences from such studies and case–control studies were excluded because of the greater potential for selection bias in such studies. For all outcomes except all-cause mortality both studies of incidence and mortality were included. Adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) had to be available in the publication. We followed standard criteria (Moose criteria) for reporting meta-analyses [88]. Additional details are found in the Supplementary Methods. A list of the excluded studies and the exclusion reason is found in Supplementary Table 2.

Data extraction

Main study characteristics and results were extracted from each study, including name of first author, publication year, country, the name of the study, follow-up period, sample size and number of cases/deaths, gender, age, the resting heart rate level, RRs and 95% CIs and variables adjusted for in the analysis and outcome. Data were extracted by one author (DA) and checked for accuracy by a second author (AS).

Statistical methods

We calculated summary relative risks of cardiovascular disease, cancer and mortality for the highest vs. the lowest level and for the dose–response analysis of resting heart rate (per 10 beats per minute, bpm) using the random-effects model by DerSimonian and Laird [89] which takes into account heterogeneity. The average of the natural logarithm of the RRs was estimated and the RRs from each study were weighted using random effects weighting. A two-tailed p-value <0.05 was considered statistically significant.

Dose–response analyses were conducted using the method by Greenland and Longnecker [90] to calculate

RRs and 95% CIs from the natural logarithm of the risk estimates across categories of exposure. For each category of resting heart rate we used the mean or median if reported and the midpoint of the upper and lower bound was estimated for the remaining studies. When extreme categories were open-ended or had extreme ranges we used the width of the adjacent interval to calculate an upper or lower cut-off value. A potential nonlinear dose–response relationship was examined using fractional polynomial models and the best-fitting second-order fractional polynomial regression model defined as the one with the lowest deviance was determined [91].

Heterogeneity between studies was evaluated using Q and I^2 statistics [92]. I^2 values of approximately 25%, 50%, and 75% were considered to indicate low, moderate and high heterogeneity, respectively. To explore potential sources of heterogeneity we conducted subgroup analyses by study characteristics such as duration of follow-up, gender, geographic location, number of cases, study quality and adjustment for confounding factors. Study quality was assessed using the Newcastle–Ottawa scale, which awards a score from 0 to 9 based on the selection, comparability, and outcome assessment [93].

Publication bias was assessed using Egger's test [94] and Begg's test [95] and by inspection of the funnel plots for analyses with 6 or more studies. We used the trim and fill method of Duval to assess the possible impact of publication bias on the results [96]. To explore the robustness of the findings we conducted sensitivity analyses excluding one study at a time from the analyses. All statistical analyses were conducted using Stata, version 12.0 software (StataCorp, Texas, US).

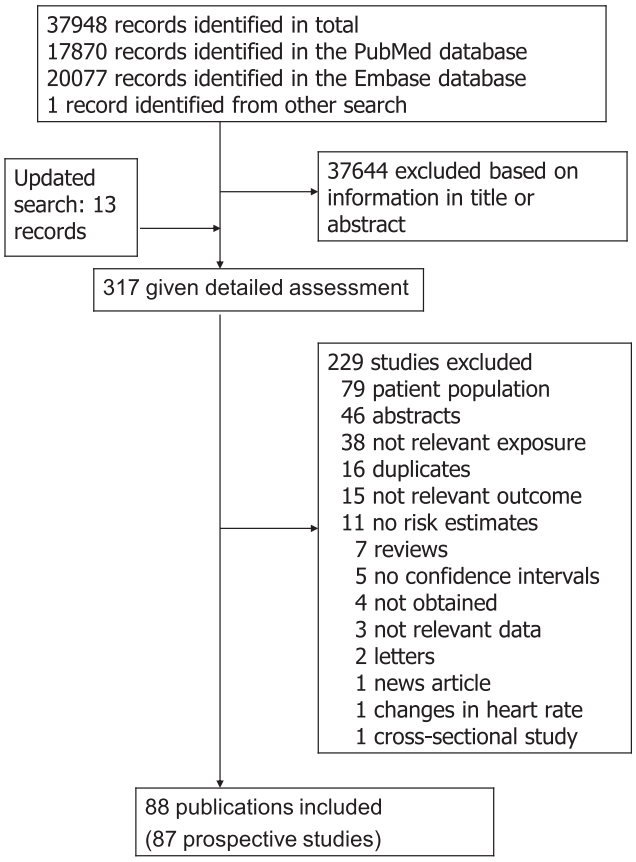

Figure 1 Flow-chart of study selection.

Results

Eighty eight publications [3,6–86,97–102] with data from 87 prospective studies were included in the analyses (Fig. 1, Supplementary Tables 3–9). Thirty five studies were from Europe, 22 studies were from the US, and 27 studies were from Asia (including a pooled analysis of 12 Asian cohort studies [19]), one study was from Australia, and two studies were international studies (Supplementary Tables 3–9).

Coronary heart disease

Fourty two prospective studies (31 publications, 31 risk estimates) [6–21,23,32–34,40,45,54,55,70,74,97] were included in the dose–response analysis of resting heart rate and coronary heart disease and included >26,950 cases among 1,225,633 participants (Supplementary Table 3). The summary RR for a 10 beat per minute increase in resting heart rate was 1.07 (95% CI: 1.05–1.10, I^2 = 61.9%, $p_{heterogeneity} < 0.0001$) (Fig. 2a), and 1.30 (95% CI: 1.19–1.42, I^2 = 71.9%, $p_{heterogeneity} < 0.0001$) [7–9,11,13–20,22,23,33,34,45,54,55,70] (Supplementary Fig. 1) when comparing high vs. low resting heart rate. There was no evidence of publication bias with Egger's test, p = 0.61 or with Begg's test, p = 0.63 (Supplementary Fig. 2). Although the test for nonlinearity was significant, $p_{nonlinearity} < 0.0001$, the association was approximately linear when inspected visually (Fig. 2b, Supplementary Table 10).

Sudden cardiac death

Five prospective studies [8,21,23,24,75] were included in the dose–response analysis of resting heart rate and sudden cardiac death and included 746 cases among 35,897 participants (Supplementary Table 3). The summary RR for a 10 beat per minute increase in resting heart rate was 1.09 (95% CI: 1.00–1.18, I^2 = 62.3%, $p_{heterogeneity}$ = 0.03) (Supplementary Fig. 3) and 2.15 (95% CI: 1.50–3.09, I^2 = 47.3%, $p_{heterogeneity}$ = 0.13 (Supplementary Fig. 4) [8,22–24] for a high vs. low heart rate. There was no evidence of a nonlinear association between resting heart rate and sudden cardiac death, $p_{nonlinearity}$ = 0.30 (Supplementary Fig. 5, Supplementary Table 10).

Heart failure

Twenty one prospective studies (8 publications, 8 risk estimates, including one combined analysis of three cohort studies [29] and a pooled analysis [19]) [19,25–29,31,81] were included in the analysis of resting heart rate and heart failure and included >4338 cases among 164,143 participants (Supplementary Table 4). The summary RR for a 10

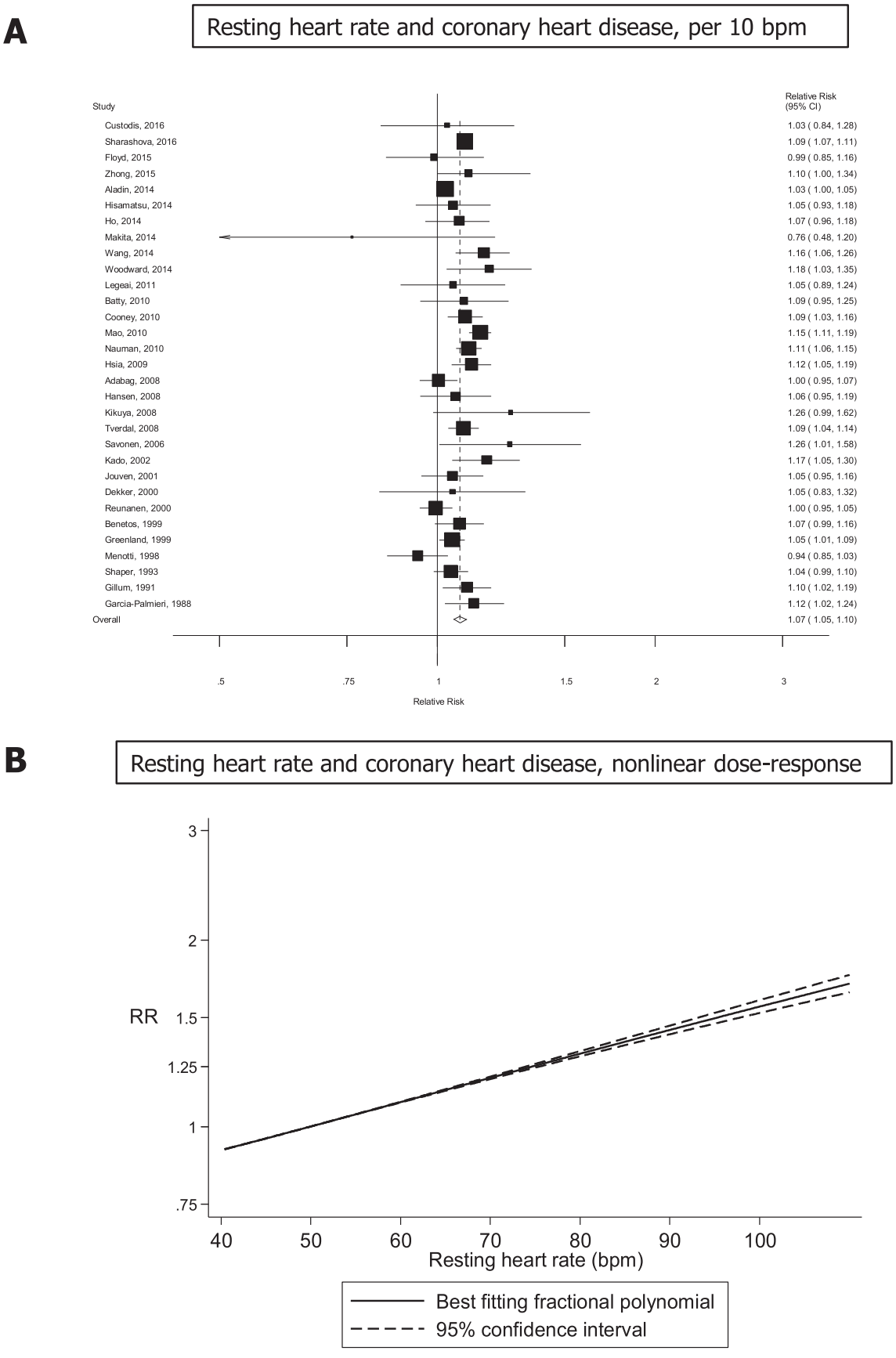

Figure 2 Resting heart rate and coronary heart disease.

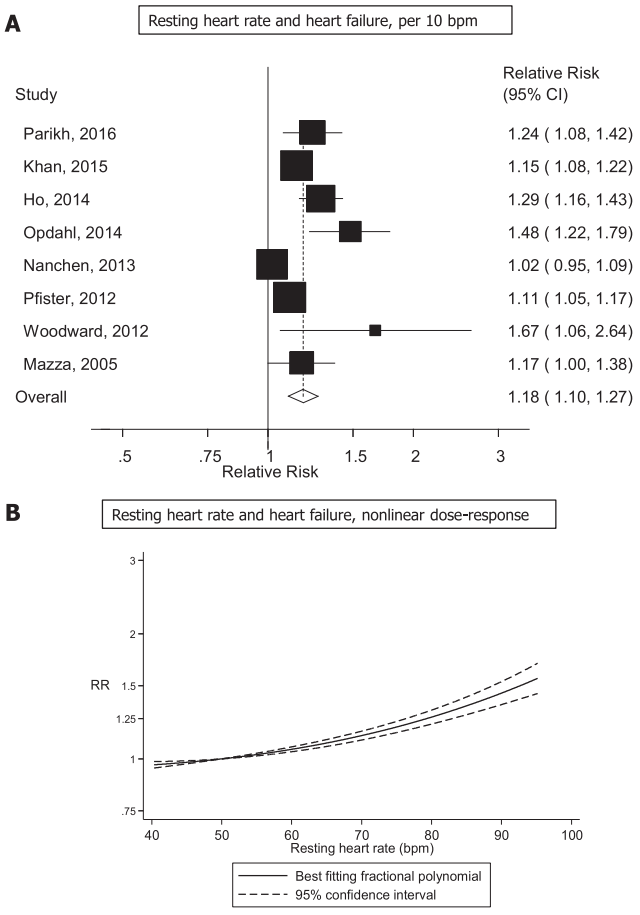

Figure 3 Resting heart rate and heart failure.

beat per minute increase in resting heart rate was 1.18 (95% CI: 1.10–1.27, I^2 = 74.5%, $p_{heterogeneity}$ < 0.0001) (Fig. 3a) and 1.46 (95% CI: 1.20–1.77, I^2 = 64.6%, $p_{heterogeneity}$ = 0.009) (Supplementary Fig. 6) [19,25–27,81] for high vs. low resting heart rate. There was some suggestion of publication bias, Egger's test, p = 0.10, and Begg's test, p = 0.11, and there was some indication of asymmetry in the funnel plot with small negative studies missing (Supplementary Fig. 7). Three studies were added with the trim and fill method, however, the association remained significant, summary RR = 1.12 (95% CI: 1.04–1.21). Although the test for nonlinearity was significant, $p_{nonlinearity}$ < 0.0001, the association appeared to be approximately linear (Fig. 3b, Supplementary Table 10).

Atrial fibrillation

Nine prospective studies (six publications) [48,71,82–84,86] were included in the dose–response analysis of resting heart rate and atrial fibrillation and included 20,474 cases among 649,188 participants (Supplementary Table 5). The summary RR per 10 bpm increase in resting heart rate was 0.97 (95% CI: 0.92–1.02, I^2 = 91.4%, $p_{heterogeneity}$ < 0.0001) (Supplementary Fig. 8) and 1.09 (95% CI: 0.91–1.30, I^2 = 68.0%, $p_{heterogeneity}$ = 0.01) (Supplementary Fig. 9) [48,71,83–85] for high vs. low resting heart rate. There was no evidence of publication bias with Egger's test, p = 0.11, or with Begg's test, p = 0.92 (Supplementary Fig. 10). The test for nonlinearity was significant, p < 0.0001, and there was some indication of a slight J-shaped association between heart rate and atrial fibrillation (Supplementary Fig. 11, Supplementary Table 10).

Stroke

Twenty seven prospective studies (16 risk estimates, 16 publications) [9,11,13–16,19,20,28,32–34,45,55,74,98] were included in the dose–response analysis of resting heart rate and stroke and included 10,753 cases among 969,150 participants (Supplementary Table 6). The summary RR for a 10 beat per minute increase in resting heart rate was 1.06 (95% CI: 1.02–1.10, I^2 = 59.5%, $p_{heterogeneity}$ = 0.001) (Fig. 4a) and the summary RR for high vs. low resting heart rate was 1.17 (95% CI: 1.03–1.32, I^2 = 47.7%, $p_{heterogeneity}$ = 0.03) (Supplementary Fig. 12) [9,11,13–16,19,20,33,34,45,55]. There was no evidence of publication bias with Egger's test, p = 0.42 or with Begg's test, p = 0.50 (Supplementary Fig. 13). The test for nonlinearity was significant, $p_{nonlinearity}$ < 0.0001, and the association was slightly stronger at the lower range compared to the higher range of resting heart rate (Fig. 4b, Supplementary Table 10).

Cardiovascular disease

Fourty six prospective studies (35 risk estimates, 35 publications) [3,7,9,13,15,17,19,20,28,32–34,36–50,54,55,74,98,100–103] were included in the dose–response analysis of resting heart rate and cardiovascular disease and included 33,489 cases among 1,565,028 participants (Supplementary Table 7). The summary RR for a 10 beat per minute increase in resting heart rate was 1.15 (95% CI: 1.11–1.18, I^2 = 84.3%, $p_{heterogeneity}$ < 0.0001) (Fig. 5a) and 1.52 (95% CI: 1.37–1.70, I^2 = 83.8%, $p_{heterogeneity}$ = <0.0001, n = 25) (Supplementary Fig. 14) [3,7,9,13,15,17,19,20,33,34,37–40,43,44,46–50,54,55,77,102] for high vs. low resting heart rate. There was indication of publication bias with Begg's test, p = 0.06, but not with Egger's test, p = 0.10 (Supplementary Fig. 15). Eight studies were added with the trim and fill method and the association remained statistically significant, summary RR 1.11 (95% CI: 1.07–1.14). Although the test for nonlinearity was significant, $p_{nonlinearity}$ < 0.0001, the association appeared to be approximately linear across the range of resting heart rate (Fig. 5b, Supplementary Table 10).

Total cancer

Twelve prospective studies [3,10,11,16,36,37,46,51,52,54,55,100] were included in the dose–response analysis of resting heart rate and total cancer and included 10,938 cases among 615,790 participants (Supplementary Table 8). The summary RR for a 10 beat per minute increase in resting heart rate was 1.14 (95% CI: 1.06–1.23, I^2 = 90.2%, $p_{heterogeneity}$ < 0.0001) (Fig. 6a) for total cancer and for high vs. low resting heart rate was 1.43 (95% CI: 1.12–1.82, I^2 = 87.2%, $p_{heterogeneity}$ < 0.0001, n = 9) (Supplementary

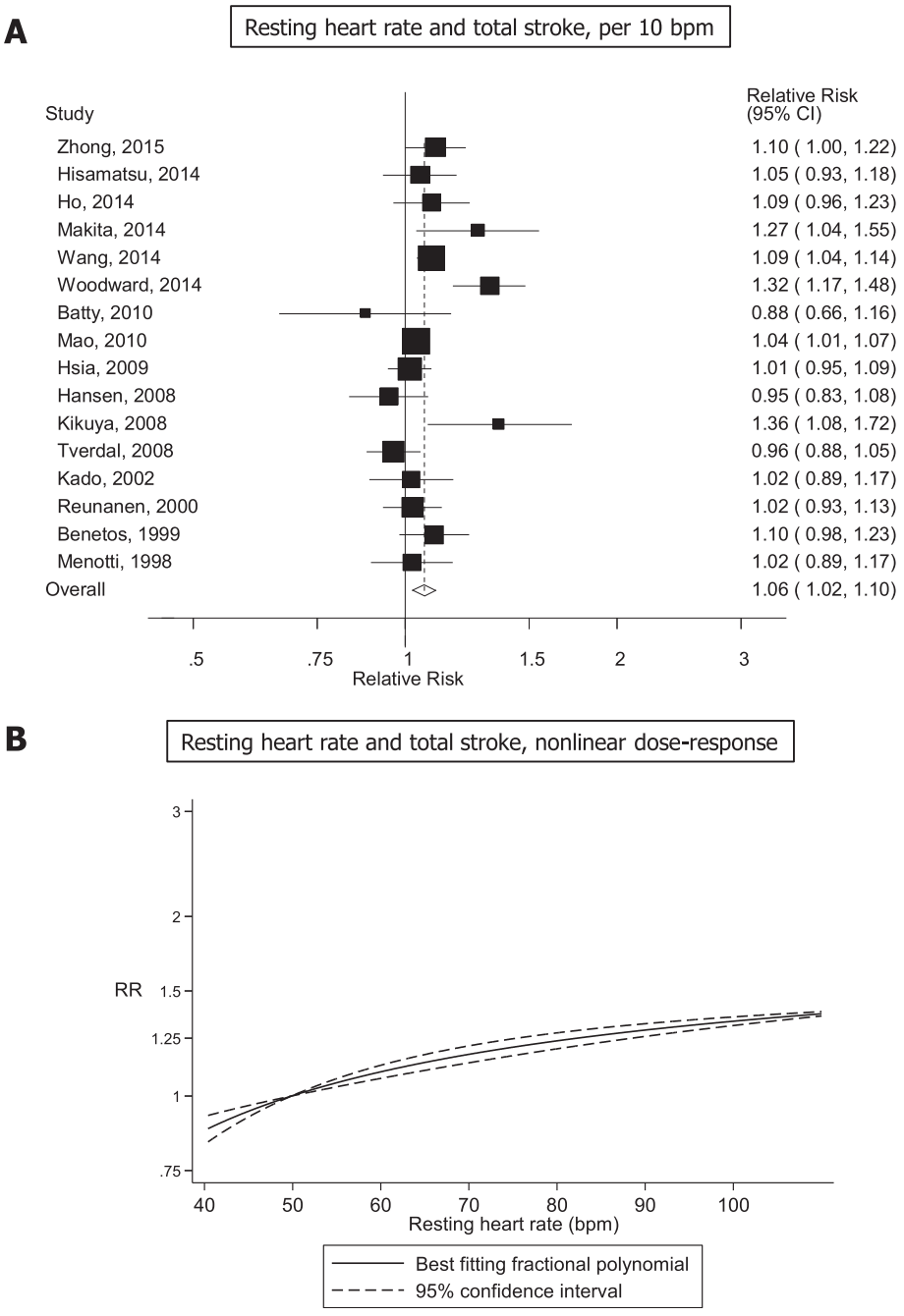

Figure 4 Resting heart rate and total stroke.

Fig. 16) [3,11,16,37,46,51,52,54,55]. There was no evidence of publication bias with Egger's test, p = 0.89 or with Begg's test, p = 0.37 (Supplementary Fig. 17). Although the test for nonlinearity was significant, $p_{nonlinearity} < 0.0001$, the association was approximately linear (Fig. 6b, Supplementary Table 10).

All-cause mortality

Fifty nine prospective studies (48 risk estimates, 48 publications) [3,7,9–13,16,17,19,20,28,31,32,36–38,40–43,46–49,53–56,59,61–68,70–73,78,80,98,100–102] were included in the analysis of resting heart rate and all-cause mortality and included >134,183 deaths among 1,810,695 participants (Supplementary Table 9). The summary RR for a 10 beat per minute increase in resting heart rate was 1.17 (95% CI: 1.14–1.19, I^2 = 94.0%, $p_{heterogeneity} < 0.0001$) for all-cause mortality (Fig. 7a). The summary RR for high vs. low resting heart rate was 1.69 (95% CI: 1.52–1.87, I^2 = 91.6%, $p_{heterogeneity} < 0.0001$, n = 39) (Supplementary Fig. 18) [3,7,9,11–13,16,17,19,20,31,37,38,40,43,46–48,54–56,58–62,64,65,67,68,70–72,77–80,102]. There was evidence of publication bias with Begg's test, p = 0.02, but not with Egger's test, p = 0.93 (Supplementary Fig. 19).

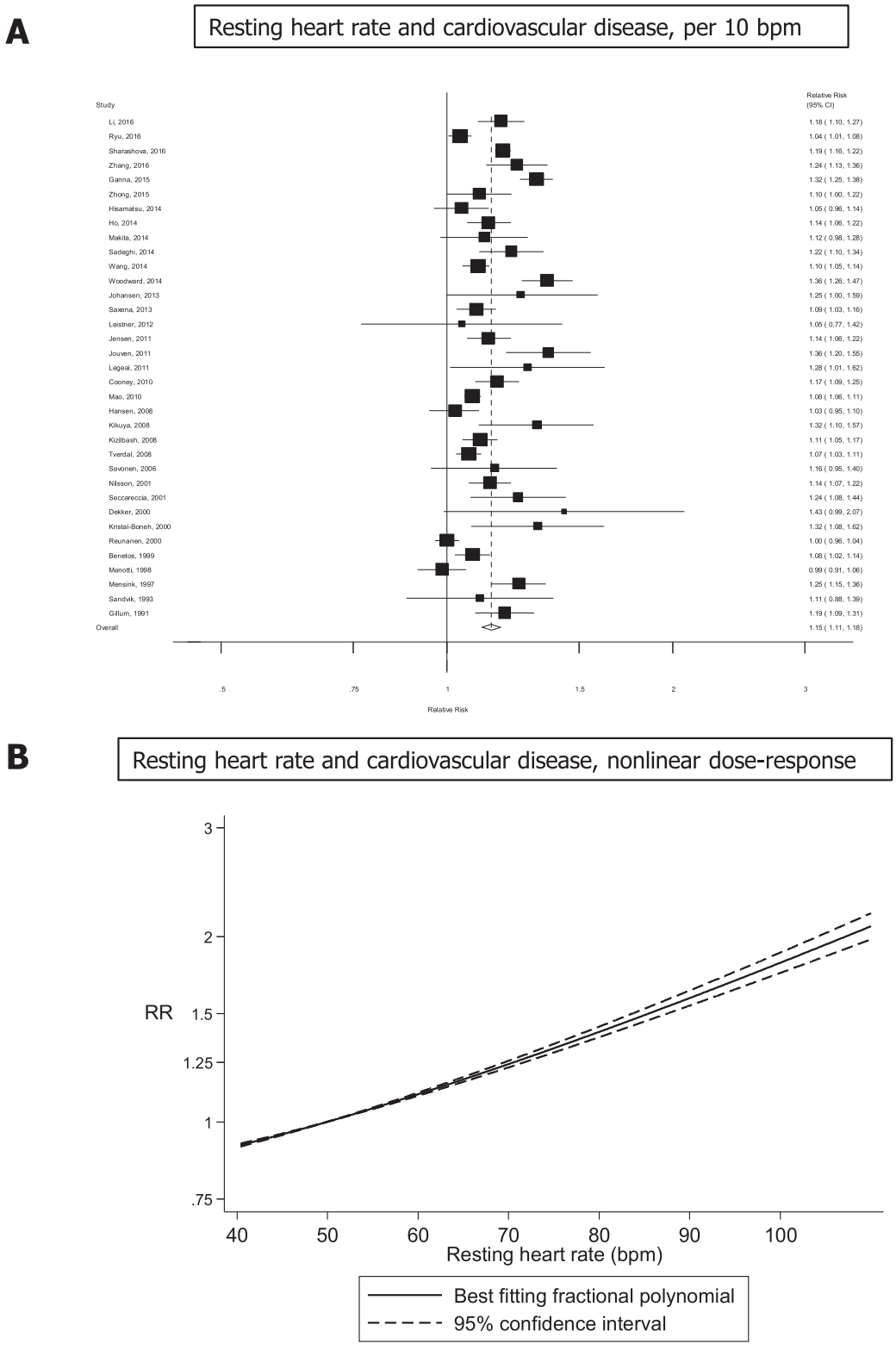

Figure 5 Resting heart rate and cardiovascular disease.

Eleven studies were added with the trim and fill method and the summary RR became 1.13 (95% CI: 1.11–1.16). Although the test for nonlinearity was significant, $p_{nonlinearity} < 0.0001$, the association was approximately linear (Fig. 7b, Supplementary Table 10).

Subgroup and sensitivity analyses

With meta-regression analyses there was indication of heterogeneity between studies when stratified by duration of follow-up for coronary heart disease ($p = 0.02$), heart

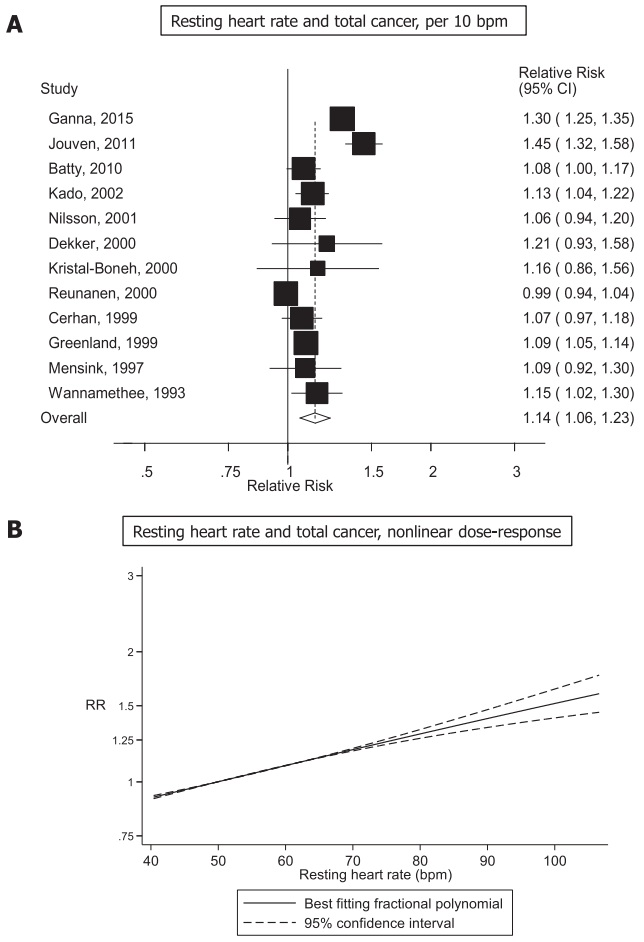

Figure 6 Resting heart rate and total cancer.

failure (p = 0.08), cardiovascular disease (p = 0.05), and mortality (p = 0.001) with weaker associations among studies with longer duration of follow-up (Supplementary Tables 11 and 12). There was suggestion of heterogeneity for coronary heart disease (p = 0.09), heart failure (p = 0.01) and stroke (p = 0.05), when stratified by geographic location, with stronger associations among Asian studies than among European and American studies, and for stroke the positive association was restricted to the Asian studies (Supplementary Table 11). For mortality (p = 0.006) there was heterogeneity by number of deaths with a weaker association among studies with ≥1000 deaths than among studies with <500 deaths (Supplementary Table 12). There was heterogeneity by adjustment for: smoking for stroke (p = 0.002) and cardiovascular disease (p = 0.004), systolic blood pressure for coronary heart disease (p = 0.05), total cancer (p = 0.04), and mortality (p = 0.003), cholesterol for total cancer (p = 0.04), and mortality (p = 0.03), with weaker associations among studies with such adjustment than in studies without such adjustment (Supplementary Tables 11 and 12).

The results persisted in influence analyses when excluding one study at a time (Supplementary Figs. 20–26).

Discussion

In this meta-analysis of prospective studies there was a positive association between resting heart rate and risk of cardiovascular disease, total cancer and all-cause mortality. In the linear dose–response analysis we found increases in the relative risk of 7% for coronary heart disease, 9% for sudden cardiac death, 18% for heart failure, 6% for total stroke, 15% for cardiovascular disease, 14% for total cancer and 17% for all-cause mortality for each 10 beats per minute increase in resting heart rate, respectively, but there was no association between heart rate and atrial fibrillation. Although the test for nonlinearity was significant in most analyses, there was a clear dose–response relationship and little evidence of a threshold effect with the exception of atrial fibrillation, for which there was some indication of a J-shaped association with increased risk at very low and high resting heart rate. The present findings further support as well as extend prior studies that examined changes in resting heart rate whereby increasing resting heart rate over time increased risk of coronary heart disease and mortality [36,68,104,105]. The findings are also consistent with a previous meta-analysis of resting heart rate and cardiovascular disease and mortality [87] in finding an increased risk, however, the current meta-analysis found a stronger association with a 17% increase in the RR per 10 bpm increase in resting heart rate compared to 9% for the same increment in the previous meta-analysis. The current meta-analysis on all-cause mortality included 57 studies and >134,000 deaths and 1.8 million participants compared to 37 studies and 78,000 deaths and 1.25 million participants in the previous meta-analysis, thus the 20 additional studies included in this analysis could have contributed to a stronger association in the present meta-analysis. Our results are also consistent with a previous meta-analysis of resting heart rate and heart failure which only conducted a high versus low analysis [29], however, the current analysis provides clear evidence of a dose–response relationship between increasing heart rate and heart failure risk.

Our meta-analysis may have some limitations. Although meta-analyses gain increased statistical power by combining studies from different populations, it also results in significant heterogeneity. There was high heterogeneity in most of the analyses, but this appeared driven more by differences in the strength of the association, rather than a disparity in the presence or absence of an association. Also, we cannot exclude the possibility that some of the heterogeneity may be due to differences by gender, ethnicity, duration of follow-up, and differences in the detail of adjustment for confounding factors. We conducted several subgroup and sensitivity analyses to investigate potential sources of heterogeneity, and found heterogeneity by duration of follow-up and number of cases or deaths. There was a weaker association among studies with a longer follow-up, compared to studies with a short follow-up. The reason for this difference is not entirely clear, but it is possible that regression dilution bias may have attenuated the associations among studies with a longer follow-up. It is also possible that the

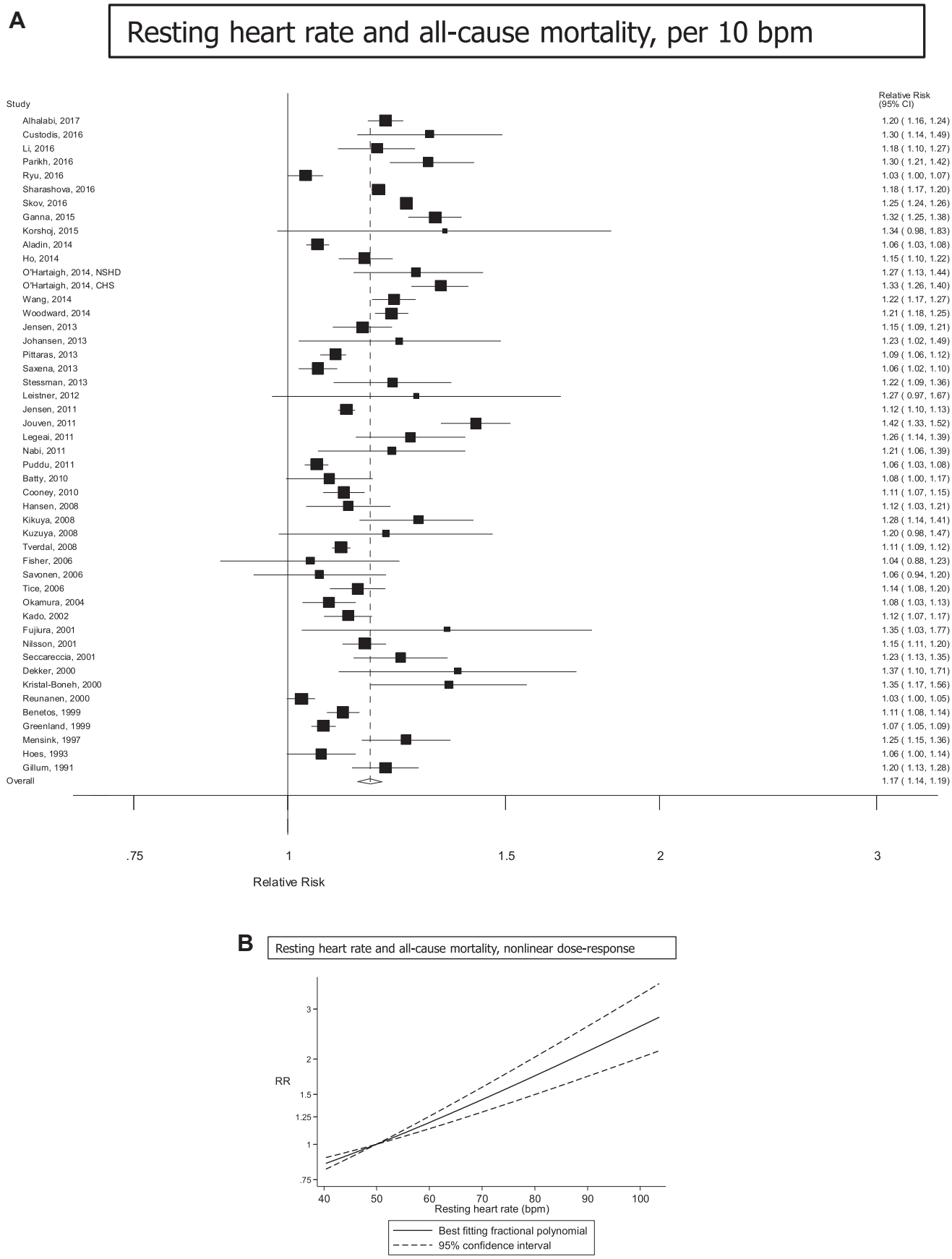

Figure 7 Resting heart rate and all-cause mortality.

association between high heart rate and mortality and cardiovascular disease is attenuated with age because of changes in biology or due to increased prevalence of undiagnosed chronic conditions in old age that may lower the heart rate, but increase mortality risk, including cardiovascular disease, sinus node dysfunction or hypothyroidism [106–108].

The association between resting heart rate and all-cause mortality was stronger in men than in women ($p_{heterogeneity} = 0.03$), and associations for cardiovascular disease and cancer also appeared to be stronger among men than women, although between subgroup heterogeneity was not significant in the latter analyses. It's not clear if any difference might be due to sex hormones as studies on the relation between sex hormones and resting heart rate have been mixed [109,110].

Significant heterogeneity was observed by geographic location for coronary heart disease, heart failure, and stroke, with stronger associations reported among the Asian studies than among the European and American studies, and for stroke the association was confined to Asian studies. Although the reason for this difference is unclear, rates of stroke tend to be higher and comprise a larger portion of the cardiovascular diseases in Asia compared with western countries. Nonetheless, risk estimates for overall cardiovascular disease as well as all-cause mortality appeared similar between geographic locations, thus it is possible that the differences for coronary heart disease, heart failure and stroke may be an artifact due to a more limited number of studies or as a consequence of a not entirely overlapping group of studies in the separate analyses.

There was also some evidence of heterogeneity by adjustment for confounding factors. However, the results persisted in most subgroups of studies with such adjustment suggesting that confounding only partly may explain the observed associations. Some of the studies may have over-adjusted by including potential intermediate factors in the models, including fasting glucose or diabetes, blood pressure or hypertension, triglycerides and cholesterol, however, most of the associations persisted even in subgroups with such adjustment. Resting heart rate is correlated with both BMI and smoking. Notably, smoking is reported to have an unfavourable effect on arterial stiffness, and with time may influence the resting heart rate [111,112]. However, we found that the associations persisted in studies that adjusted for these factors. Physical activity is also known to influence the resting heart rate, however, most of the associations persisted in the subgroup that adjusted for physical activity. Residual confounding by other risk factors cannot be entirely excluded.

As a meta-analysis of published literature the analysis may have been affected by publication bias, and we found some indication of publication bias in the analyses of heart failure, cardiovascular disease and all-cause mortality. However, when using the trim and fill method as a sensitivity analysis, the associations were only slightly attenuated, but all remained significant. Measurement error and regression dilution bias may have affected the results in light of intra-individual variation and changes in resting heart rate during follow-up. However, such errors would most likely lead to an underestimation of the association between resting heart rate and cardiovascular disease, cancer and mortality.

Resting heart rate is considered a sensitive indicator of autonomic nervous system activity and an increase likely reflects sympathetic overactivity. This imbalance is known to stimulate the renin–angiotensin–aldosterone system, leading to increased release of angiotensin 2, which has an adverse effect on the cardiovascular system by promoting the development and progression of atherosclerosis [113]. Chronic activation of the sympathetic system can produce a state of insulin resistance [114,115] which is associated with hypertriglyceridemia, low HDL-cholesterol, and hyperuricemia [116]. Indeed, a faster resting heart rate has been associated with increased risk of type 2 diabetes [4], and both insulin resistance and diabetes increases the risk of cardiovascular disease, cancer and all-cause mortality [5]. Elevated heart rate may additionally be involved in the formation of atherosclerotic lesions due to increased myocardial oxygen consumption, fatigue, and fracture of elastic fibres within the arterial wall [117]. Further, a high resting heart rate may provoke coronary vasoconstriction in subjects with atherosclerosis [118] and may be accompanied with greater arterial stiffening [119,120]. Increased resting heart rate has been shown to be positively related to progression of coronary atherosclerosis in humans [121,122] and this may contribute to coronary heart disease mortality by increasing case fatality, particularly as the current meta-analysis found an increased risk of sudden cardiac death with increasing heart rate. It has further been speculated that a high resting heart rate may lead to low-grade inflammation or be a consequence of subclinical conditions that may cause inflammation. Nevertheless, the positive association between elevated resting heart rate and heart failure, cardiovascular disease and all-cause mortality persisted in two studies after adjusting for various inflammatory markers [123,124], suggesting an independent association. Albeit, the precise pathophysiological mechanisms that could explain the association between high resting heart rate and cancer risk are not fully understood, it has been speculated that the association might be explained by residual confounding by smoking or physical activity, or that it perhaps is mediated by psychological stress [51,52], but further clarification of the mechanisms at play is needed. Resting heart rate may also be a marker of subclinical disease, and elevated glucose levels, even in the non-diabetic range, can damage peripheral nerve fibres, leading to increased sympathetic activity and reduced parasympathetic control [125–127]. However, although there was some indication of heterogeneity between subgroup analyses stratified by duration of follow-up for coronary heart disease, heart failure, cardiovascular disease, and all-cause mortality with slightly weaker associations among studies with 10 or more compared to less than 10 years of follow-up, most of the associations persisted, thus it seems less likely that subclinical disease explains the entire association between

resting heart rate and cardiovascular disease, cancer and all-cause mortality. Further, in support of a causal interpretation of the available evidence is the results of a genome-wide association study which found that a genetic risk score consisting of 64 loci associated with resting heart rate was associated with increased mortality. For each 5 bpm increase in the genetically predicted resting heart rate there was a 20% increase in mortality [128].

Strengths of this analysis include the large number of studies, cases and deaths, which provided increased statistical power to detect even moderate associations, the detailed dose–response analyses and the numerous subgroup and sensitivity analyses which showed that the results persisted among most subgroups of study characteristics and were robust to the influence of any single study. In addition, the quality of the studies were in general high and the results persisted in the subgroup of the studies with the highest study quality. Any further studies should clarify the association between resting heart rate and less common causes of death and further clarify the underlying mechanisms.

In conclusion we found positive associations between greater resting heart rate and risk of coronary heart disease, sudden cardiac death, heart failure, stroke, cardiovascular disease, total cancer, and mortality, and a J-shaped association with atrial fibrillation. As resting heart rate is an easily measured risk factor, and can be modified by lifestyle changes and medical treatment, the present findings suggest lowering resting heart rate may be a potential target to reduce risk of cardiovascular disease and premature mortality.

Conflict of interest

None of the authors have any conflict of interest to declare with regard to this manuscript.

Contribution statement

MrAune had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Aune, Tonstad, Vatten.

Acquisition, analysis, or interpretation of data: Aune, Sen, ó'Hartaigh, Janszky, Romundstad, Tonstad, Vatten.

Drafting of the manuscript: Aune.

Critical revision of the manuscript for important intellectual content: Aune, Sen, ó'Hartaigh, Janszky, Romundstad, Tonstad, Vatten.

Statistical analysis: Aune.

Obtained funding: Aune, Tonstad, Vatten.

Study supervision: Tonstad, Vatten.

Funding/support

This project has been funded by Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) and by "Olav og Gerd Meidel Raagholt's Stiftelse for Medisinsk Forskning".

Role of the sponsors

The sponsors of the study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgements

The authors thank Darren C. Greenwood for the Stata code for the nonlinear dose–response analysis.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2017.04.004.

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