Systematic Review and Meta-Analysis

Medicine®

OPEN

Dose-response association of resting heart rate and hypertension in adults

A systematic review and meta-analysis of cohort studies

Lijun Shen, MS[a], Yuming Wang, MD, PhD[a], Xuesong Jiang, BN[b], Yongcheng Ren, MD, PhD[c], Chengyi Han, MD, MPH[b,*], Yongguang Yang, MPH[a,*]

Abstract

Background: The association of resting heart rate (RHR) and hypertension in adults is unclear. We aimed to perform a meta-analysis of cohort studies to clarify the association.

Methods: We searched PubMed and Embase from their inception to November 3, 2017, for published articles. We used a random effects model to combine study-specific relative risks (RRs) and 95% confidence intervals (CIs). We used restricted cubic spline functions to assess the dose-response relationship.

Results: Nine cohort articles (12 independent studies) with 79,399 individuals and more than 26,380 incident cases of hypertension were included. The summary RR for hypertension was 1.09 (95% CI: 1.06–1.13) with each 10 bpm increment in RHR. The cubic spline model suggested that when compared with 55.5 beats per minute, the risk of hypertension significantly increased with increasing levels of RHR ($P_{nonlinearity}$ = 0.059).

Conclusion: We found a linear dose-response association between RHR and incident hypertension in adults.

Abbreviations: BMI = body mass index, bpm = beats per minute, CI = confidence interval, FPG: fasting plasma glucose, RHR = resting heart rate, RR = relative risk.

Keywords: heart rate, hypertension, keywords, meta-analysis, risk

1. Introduction

Resting heart rate (RHR), a sensitive, noninvasive and inexpensive indicator of cardiac function, has attracted widespread concern in recent years. Several dose-response meta-analyses ascertained that elevated RHR increased the risk of metabolic syndrome,[1] type 2 diabetes mellitus,[2] atrial fibrillation,[3] cardiovascular disease and all-cause mortality.[4,5] Hypertension, a major cardiovascular risk factor and a leading cause of global deaths, caused an estimated 9.4 (95% confidence interval [CI]: 8.6–10.1) million deaths and accounted for 7.0% (95% CI: 6.2–7.7) of disability adjusted life years in 2010.[6]

Cross-sectional or nest case-control studies have demonstrated that elevated RHR was associated with an increased risk of hypertension.[7,8] Among cohort studies, some studies suggested an increased risk of hypertension with elevated RHR,[9–13] whereas others found the association could be affected by sex and age.[14] Despite a dose-response meta-analysis[15] of RHR and risk of hypertension being published during the writing of the current paper, it missed an eligible cohort study[16] and included 2 noneligible cohort studies (one[17] with participants <10 years of age whose normal RHR were higher than adults and the other[18] about the association of RHR and elevated blood pressure [nonhypertension]). These shortcomings might have introduced a selection bias.

Hence, we conducted a systematic review and meta-analysis of cohort studies that examined the dose-response relationship of RHR and hypertension in adults.

2. Methods

2.1. Literature search strategy

We systematically searched for studies investigating the association of RHR and hypertension published in English until November 3, 2017 in the PubMed and Embase databases by

Editor: Leonardo Roever.

LS and YW contributed equally to this study.

This study was supported by the National Key R&D Program of China (SQ2018YFC010351)and Science and Technology People-benefit Program of Henan(182207310001).

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

[a] Henan Provincial Peoples Hospital, Zhengzhou, [b] The First Affiliated Hospital of Henan University of CM, Zhengzhou, [c] Huanghuai University, Zhumadian, Henan, China.

[*] Correspondence: Chengyi Han, 19 Renmin Road, Jinshui District, Zhengzhou, Henan 450003, China (e-mail: cyhan666666@126.com); Yongguang Yang, 7 Weiwu Road, Jinshui District, Zhengzhou, Henan 450003, China (e-mail: 657739174@qq.com).

How to cite this article: Shen L, Wang Y, Xuesong Jiang, Ren Y, Chengyi Han, Yongguang Yang. Dose-response association of resting heart rate and hypertension in adults: A systematic review and meta-analysis of cohort studies. Medicine 2020;99:10(e19401).

Received: 22 October 2019 / Received in final form: 27 January 2020 / Accepted: 1 February 2020

http://dx.doi.org/10.1097/MD.0000000000019401

using the terms (("hypertension" OR "high blood pressure" OR "high blood pressures") AND ("heart rate" OR "resting pulse")) in the title/abstract. The reference lists of relevant studies were also searched.

2.2. Study selection

Studies were included if they

1. were cohort study designs,
2. were performed on participants ≥18 years of age,
3. used a definite hypertension diagnostic method,
4. excluded participants with hypertension at baseline,
5. reported relative risks (RRs), odds ratios or hazard ratios with 95% CIs or data to calculate them, and
6. reported a quantitative measure of RHR, the number of cases, and the exposed person-years/participant numbers for the dose-response analysis.

We excluded studies that

1. involved cross-sectional study designs,
2. were reviews, comments, or letters,
3. reported RHR as a dichotomous variable, and
4. contained duplicate data.

If multiple articles were published from the same study, we included data from the study with the most informative reporting of RHR levels or the larger sample size. The year of study publication was used as the time variable. Two reviewers (L.S. and Y.W.) independently performed the literature search to identify studies. Discrepancies were resolved by discussion with a third reviewer (X.J.).

2.3. Data extraction

The following data were independently extracted by two reviewers (L.S. and Y.W.) for each included study: first author, place of study, publication time, follow-up time, sample size, age and sex of participants, number of cases and participants, RHR quantity, odds ratio (OR)/hazard ratio (HR)/relative risk (RR) and 95% CI, method of RHR measurement, and covariates.

2.4. Assessing the risk of bias

Two reviewers (L.S. and Y.W.) used the Newcastle-Ottawa Scale critically appraise the included studies.[19] The scoring system involved 3 columns: selection of study participants (4 items), intergroup comparability (1 item), and measurement of outcome (3 items). The total score was the sum of scores for each item, with >7, 4-7, and <4 representing high, moderate, and low quality, respectively.

2.5. Statistical analysis

Data are presented as RRs and 95% CIs. For cohort studies reporting HRs or ORs for hypertension, we assumed that the HRs and ORs were approximately RRs.[20] Heterogeneity of studies was estimated by the Q test. We selected the model to combine HRs, ORs, or RRs for hypertension according to the results of the Q test. If the number of cases in each category was missing, these data were inferred on the basis of the number of total cases and the reported effect size. If the exposed person-years or participant numbers were not reported in each category, groups were assumed to be of equal sizes.[21]

Generalized least squares regression was used to estimate the study specific dose-response association. The generalized least squares regression model estimates the linear dose-response coefficient by taking into account the covariance for each exposure category within each study because they are estimated relative to a common referent RHR exposure category.[22,23] The DerSimonian and Laird random effects model was used to pool the study-specific dose-response RR estimates.[24]

First, a linear association was assumed; study-specific RR estimates were calculated per RHR increments of 10 beats per minute (bpm) and then pooled. In addition, we examined possible nonlinear associations by modeling RHR using a restricted cubic spline with 2 knots located at the 33.3rd and 66.7th percentiles of the distribution.[25]

Only studies reporting risk estimates for at least 3 RHR exposure levels for incident hypertension were included in this analysis. The P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero.

To explore the sources of heterogeneity in RHR, we performed subgroup analyses by sex, study design, nationality, number of cases, follow-up time, measurement of RHR, and the covariates (smoking, alcohol drinking, physical activity, body mass index (BMI), fasting plasma glucose (FPG), and blood pressure) adjusted for in the analysis. We also performed a sensitivity analysis by excluding 1 study at a time to assess the stability of results and potential sources of heterogeneity.

Publication bias was evaluated by Egger test and Begg plotting. Sensitivity analyses involved removing some low-quality studies. Statistical significance was set at $P < .05$. Analyses involved the use of Stata 12.1 (Stata Corp, College Station, TX). All analyses were based on previous published studies; thus, no ethical approval, and patient consent were required.

3. Results

3.1. Search results and study characteristics

We identified 9 articles[9–12,16,26–29] (12 independent studies) in PubMed and Embase for the meta-analysis (Fig. 1). In total, the review included 79,399 individuals and more than 26,380 incident cases of hypertension. The details of the included studies are presented in Table 1. In all, 4 articles[9,10,12,29] did not distinguish between sex and 3 articles[11,16,28] described stratified analyses by sex. Overall, 1 study[26] was conducted in Italy, 2[9,16] in America, 3[12,27,29] in Japan, and 3[10,11,28] in China. Analyses of the quality of studies yielded the Newcastle-Ottawa Scale scores presented in Table S1, http://links.lww.com/MD/D891.

3.2. Dose-response association between RHR and incident hypertension

The summary RR for hypertension was 1.09 (95% CI: 1.06–1.13) with each 10 bpm increment in RHR, and there was low substantial heterogeneity ($I^2 = 53.4\%$; $P_{heterogeneity} = 0.015$) (Fig. 2).

We included 8 studies[9–12,28,29] in the nonlinear dose-response analysis; 4 studies[16,26,27] reporting only continuous risk estimates were excluded because the analysis required at least three categories of RHR. We found no evidence of a nonlinear association between RHR and hypertension ($P_{nonlinearity} =$

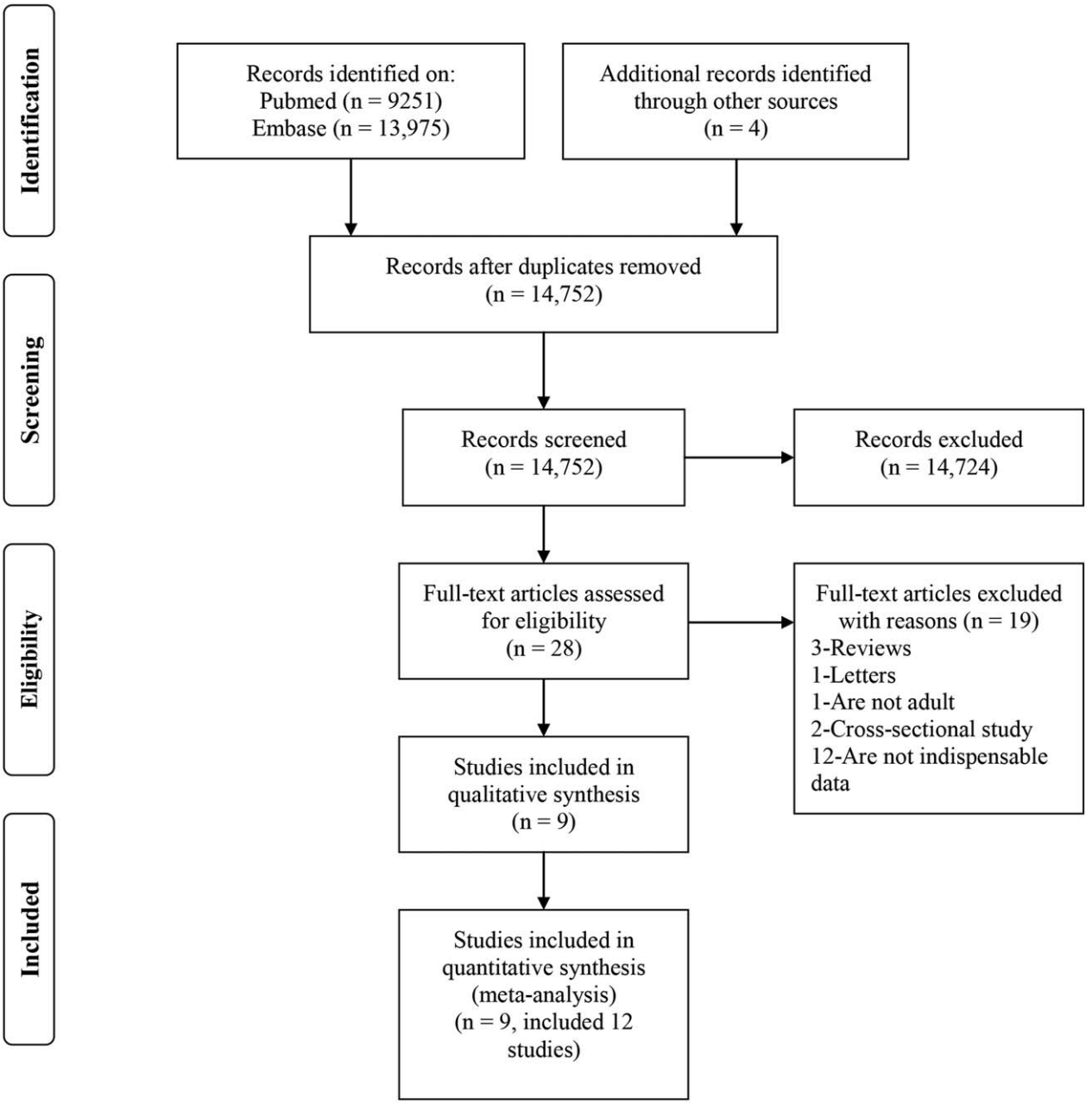

Figure 1. Flow diagram of studies in the meta-analysis.

0.059), so restricted cubic splines were adopted to model the linear dose-response association. The results from the cubic spline model suggested that when compared with 55.5 bpm, the risk of hypertension increased significantly with increasing levels of RHR (Fig. 3). Compared with 55.5 bpm, the risk of hypertension was 1.05 (95% CI, 1.03–1.07) at an RHR level of 60 bpm and 1.58 (95% CI, 1.32–1.88) at an RHR level of 100 bpm with the linear cubic spline model.

3.3. Subgroup and sensitivity analyses and publication bias

Results of the subgroup analyses are presented in Table 2. In general, the association was consistent in most analyses. The heterogeneity seemed to be lower in men and women populations ($I^2 = 0.0$, 10.6%), with a duration of follow up (years) < 5 and ≥ 5 ($I^2 = 0.0$, 14.6%), in American populations ($I^2 = 0.0$), in studies with cases of hypertension <500 ($I^2 = 0.0$), with electrocardiography measurements of RHR ($I^2 = 0.0$), and when the analyses were smoking-unadjusted ($I^2 = 0.0$), physical activity-adjusted ($I^2 = 0.0$), FPG-adjusted ($I^2 = 0.0$), and BMI-adjusted ($I^2 = 0.0$). No significant changes in heterogeneity occurred in other subgroup analyses.

No individual study had an excessive influence on the pooled effect in the sensitivity analysis. We found no evidence of publication bias by Egger test and Begg plotting ($P = .064$).

Table 1

Summary of the characteristics of cohort studies investigating the association of level of resting heart rate (RHR) and incident hypertension.

First author	Year	Country	Gender	Age (years)	Follow up (years)	Case	N	RHR (bpm)	RR (95%CI)	Adjusted variables	Assessment of RHR
Conti	1986	Italy	M		10	NA	590	Per 1	1.026 (0.999–1.054)	Age and smoking	Electrocardiography
Wendy	1994	American	M	44	4	201	1118	Per 10	1.06 (0.90–1.26)	Age, SBP, and DBP	Electrocardiography
Wendy	1994	American	W	46	4	257	1559	Per 10	1.00 (0.86–1.16)	Age, SBP, and DBP	Electrocardiography
Shao	2002	China	M		10	92	552	60.6	1.00	Age, SBP, DBP, BMI, and alcohol	Cardiac auscultation
						102	552	68	1.15 (0.80–1.66)		
						113	552	74	1.22 (0.87–1.70)		
						128	552	84.2	1.64 (1.20–2.36)		
Shao	2002	China	W			124	671	64	1.00	Age, SBP, and DBP	Cardiac auscultation
						137	672	71.4	0.98 (0.7–1.37)		
						148	672	76.3	1.10 (0.79–1.52)		
						173	671	84.7	1.34 (0.93–1.93)		
Inoue	2007	Japan	M/W	47	3	46	1033	≤58	1.00	Age, gender, current cigarette smoking, current drinking, habitual exercise, metabolic syndrome and proteinuria	Electrocardiogram
						79	1162	59–64	1.47 (1.01–2.16)		
						61	1012	65–70	1.28 (0.86–1.92)		
						81	1124	≥71	1.51 (1.03–2.21)		
Gu	2007	China	M	51	8.2	447	1760	≤75	1.00	age, gender, smoking, alcohol, education, region, BMI, and PA	NA
						480	1760	76–83	1.09 (0.96–1.24)		
						598	1760	≥84	1.27 (1.13–1.44)		
Gu	2007	China	W	51.9	8.2	418	1748	≤75	1.00	Age, gender, smoking, alcohol, education, region, BMI, and PA	NA
						416	1749	76–83	1.01 (0.88–1.16)		
						509	1748	≥84	1.19 (1.04–1.35)		
Shigetoh	2009	Japan	M/W	43.2	20	17	127	<60	1.00	Age, sex, BMI, and FPG	Electrocardiogram
						51	270	60–69	1.38 (0.33–5.73)		
						37	166	70–79	1.61 (0.35–7.36)		
						14	51	≥80	1.95 (0.35–8.36)		
Oda	2014	Japan	M	50.1	2.6	164	837	8.5	1.073 (0.906–1.271)	Age, smoking, alcohol drinking, physical activity, WC, SBP, DBP, TG, LHDL-C, and FPG,	Electrocardiogram
Wang	2014	China	M/W	46.3	3.5	2868	7610	≤66	1.00	Age, sex, married status, educational level, income of each family member, BMI, FPG, TG, HDL-C, LDL-C, TC and high-sensitivity C-reactive protein, current smoking status, current alcohol drinking status and family history of hypertension, SBP, and DBP	Electrocardiography
						3136	8122	67–71	1.06 (1.00–1.12)		
						3079	7663	72–77	1.08 (1.02–1.14)		
						3482	8112	78–88	1.16 (1.11–1.23)		
						743	1551	≥90	1.26 (1.17–1.36)		
						1,3308	33,058	Per 10	1.08 (1.06–1.10)		
Aladin	2016	American	M/W	49	4	3075	9054	<70	1.00	Age, sex, race, weight (kg), history of hyperlipidemia, diabetes mellitus, smoking status, history of coronary heart disease, family history of coronary heart disease, SBP, DBP, and METS	Manually
						3665	9604	70–85	1.06 (1.00–1.11)		
						1439	3215	>85	1.15 (1.08–1.23)		

BMI = body mass index, bpm = beats per minute, CI = confidence interval, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PA = physical activity, RR = relative risk, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

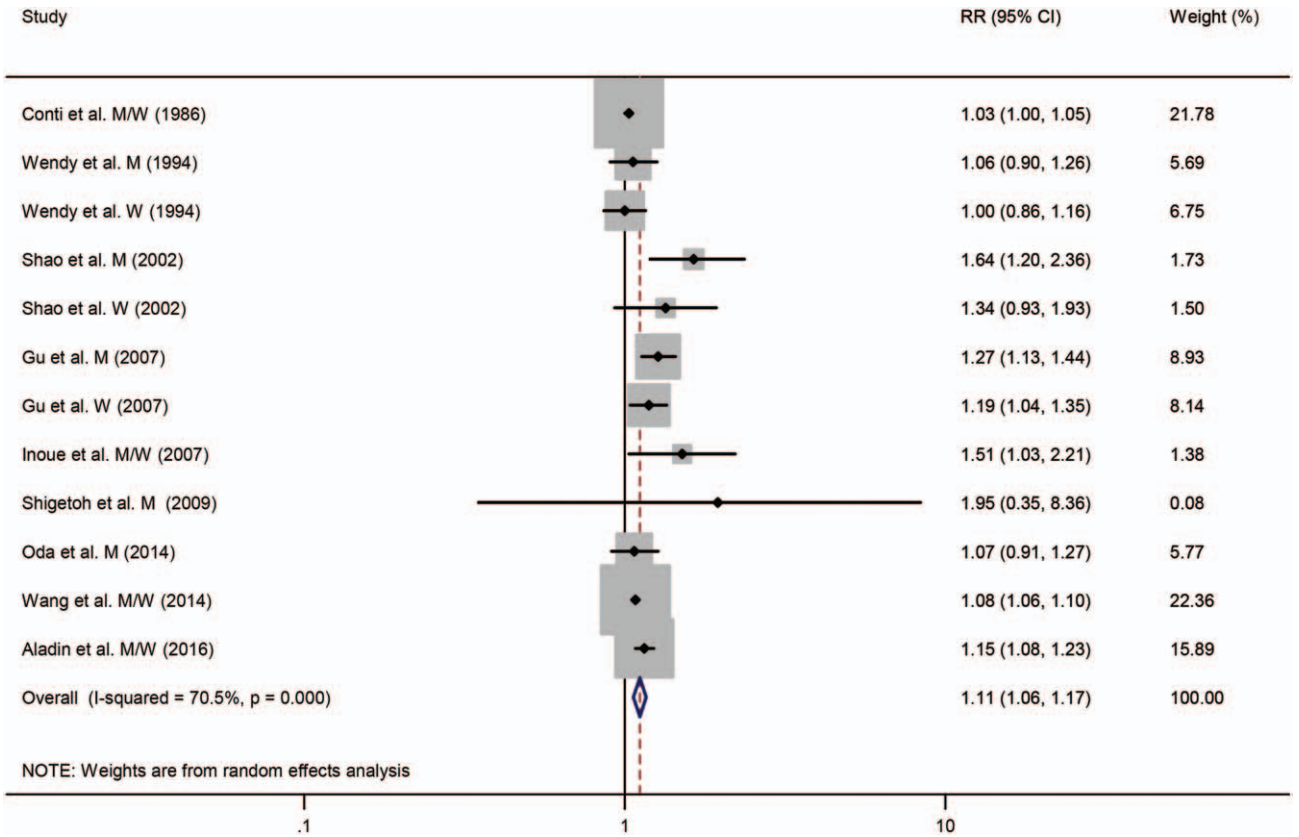

Figure 2. Risk of hypertension for per 10 bpm increment in resting heart rate.

4. Discussion

To our knowledge, this is the first meta-analysis of cohort studies to quantify the dose–response relationship between RHR and incident hypertension in adults. We found a linear, positive association between increments in RHR and risk of incident hypertension in adults, with a 9% increase in RR per 10 bpm increase in RHR. Compared with 55.5 bpm, those who met the guidelines-recommended minimum RHR levels of 60 bpm and maximum RHR levels of 100 bpm had 5% (RR, 1.05; 95% CI, 1.03–1.07) and 58% (RR, 1.58; 95% CI, 1.32–1.88) higher risk of hypertension, respectively.

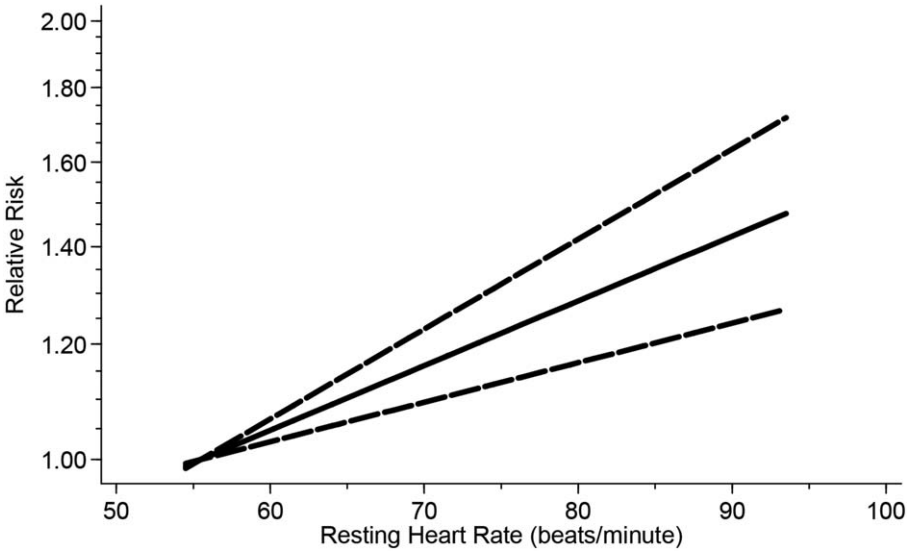

Figure 3. Linear dose–response association analysis of resting heart rate and incident hypertension modeled by using restricted cubic splines.

Table 2

Dose-response subgroup analysis of risk of hypertension per 10 bpm increment of RHR.

Characteristics	N	RR (95% CI)	I^2 (%)	*P*
All studies	12	1.09 (1.06–1.13)	53.4	.015
Gender				
Men	3	1.16 (1.09–1.23)	0.0	.392
Women	3	1.10 (1.02–1.18)	10.6	.327
Both	6	1.03 (1.01–1.05)	40.0	.139
Study design				
Retrospective	1	1.17 (0.96–1.42)	–	–
Prospective	11	1.07 (1.03–1.10)	65.0	.001
Duration of follow up (years)				
<5	6	1.03 (1.01–1.04)	0.0	.845
≥5	6	1.16 (1.10–1.21)	14.6	.321
Regin				
Italy	1	1.29 (0.94–1.64)	–	–
America	3	1.04 (1.02–1.06)	0.0	.853
China	5	1.12 (1.03–1.21)	81.8	<.001
Japan	3	1.14 (0.98–1.29)	0.0	.836
Case				
<500	7	1.11 (1.04–1.19)	0.0	.439
≥500	5	1.06 (1.02–1.09)	79.1	.001
Measurement of RHR				
Electrocardiography/Electrocardiogram	7	1.02 (1.02–1.03)	0.0	.539
Other	5	1.12 (1.05–1.20)	72.8	.005
Adjustment factors				
Smoking				
Yes	5	1.03 (1.01–1.05)	49.1	.097
No	7	1.13 (1.08–1.18)	0.0	.475
Alcohol drinking				
Yes	8	1.09 (1.03–1.15)	45.2	.078
No	4	1.11 (0.99–1.23)	63.6	.041
Physical activity				
Yes	2	1.13 (0.97–1.29)	0.0	.622
No	10	1.07 (1.03–1.10)	68.1	.001
Fasting plasma glucose				
Yes	3	1.02 (1.02–1.03)	0.0	.649
No	9	1.11 (1.05–1.17)	55.4	.022
Body mass index				
Yes	2	1.02 (1.02–1.03)	0.0	.490
No	10	1.11 (1.05–1.16)	50.1	.035
Blood pressure				
Yes	6	1.07 (1.00–1.14)	42.8	.120
No	6	1.11 (1.04–1.19)	59.1	.032

Bpm = beats per minute, CI = confidence interval, RHR = resting heart rate, RR = relative risk.

In contrast to a previous report,[15] we quantitatively assessed the risk of hypertension by dose-response analyses for people who met the guidelines-recommended minimum and maximum RHR. This study excluded two studies[17,18] and added one study[16] containing 458 cases among 2677 participants in our dose-response model. We observed a significant positive association between the RHR and hypertension, which was consistent with the previous meta-analysis. However, a recent study (The Rural Chinese Cohort Study)[14] did not identify a significant RR (1.02, 95% CI: 0.96–1.10) of hypertension per 10 bpm increase in men. Because of limited number of studies stratified by sex, further research is essential to confirm the possible relationship in men.

Several biological mechanisms could explain the association of RHR and hypertension. High RHR represents an imbalance in central nervous system activity, thereby leading to increased sympathetic and decreased parasympathetic tone. Increased sympathetic tone is also closely associated with high blood pressure or hypertension, which can be one possible mechanism.[30] High RHR or autonomic imbalance is also associated with subclinical inflammation represented by elevated C-reactive protein levels and leukocyte counts.[31,32] Therefore, inflammation may play an important role in the association of RHR and hypertension. One possible link between RHR and hypertension is leptin, an adipocytokine produced by adipose tissue that directly increases sympathetic outflow,[33] thereby increasing blood pressure and heart rate.[34,35] Elevated RHR might be a marker of chronic stress and anxiety, which may increase the risk of hypertension.[36] In a dose-response meta-analysis of cohort studies, the risk of hypertension gradually decreased with increasing exercise, which could be related to reduce sympathetic nerve activity, plasma norepinephrine levels, and total peripheral resistance and to improve endothelial function.[37–39] Because exercise training can also lower RHR, the risk of hypertension could be reduced with regular exercise via reduced RHR; thus, associations between RHR and hypertension may be worthy of further exploration.

5. Strengths and limitations

Our meta-analysis has several strengths. The broad search of relevant studies minimized meta-analysis. Last, the study quality was high and ranged from scores of 8 to 9, with the exception of one study with the lowest score being 6. Combining the evidence from all available studies increased the statistical power to detect an association between elevated RHR and hypertension. We conducted linear dose-response analyses and incorporated the recommended RHR levels to clarify the strength and shape of the dose-response relationship between RHR and hypertension. We also conducted a sensitivity analysis, which demonstrated that no individual study had an excessive influence on the pooled effect. These findings support a possible role for RHR in the development of hypertension.

Some potential limitations of this meta-analysis should be mentioned. RHR could be influenced by numerous factors.[40] However, most of the included studies adjusted for the main influencing factors in the multivariable regression models. Therefore, the effect of additional factors might be relatively limited. Heterogeneity among the included studies is unavoidable in all meta-analyses. To discover potential sources of heterogeneity, we performed various subgroup analyses and found that the association did not vary, suggesting that the finding is robust for hypertension.

5.1. Future directions

There is no cutoff at which harms are not achieved and more risks occur with increasing RHR. Future studies examining multiple aspects of RHR are needed to explore the optimal value of RHR for hypertension prevention.

6. Conclusions

This meta-analysis found an increased risk of hypertension with increasing RHR in adults. Elevated RHR may be used as an additional clinical indicator of hypertension in adults.

Author contributions

Conceptualization: Chengyi Han and Yongguang Yang
Data curation: Lijun Shen and Yuming Wang
Formal analysis: Yongcheng Ren
Supervision: Xuesong Jiang
Validation: Xuesong Jiang, Chengyi Han
Writing – original draft: Lijun Shen and Yuming Wang
Writing – review & editing: Chengyi Han and Yongguang Yang

References

[1] Liu X, Luo X, Liu Y, et al. Resting heart rate and risk of metabolic syndrome in adults: a dose-response meta-analysis of observational studies. Acta Diabetol 2017;54:223–35.
[2] Aune D, B OH, Vatten LJ. Resting heart rate and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis of cohort studies. Nutr Metab Cardiovasc Dis 2015;25:526–34.
[3] Liu X, Guo N, Zhu W, et al. Resting heart rate and the risk of atrial fibrillation. Int Heart J 2019;60:805–11.
[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:E53–63.
[5] Aune D, Sen A, o'Hartaigh B, et al. 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. Nutr Metab Cardiovasc Dis 2017;27:504–17.
[6] World Health Organization. A Global Brief on Hypertension: Silent Killer, Global Public Health Crisis: World Health Day 2013; 2018 Oct 3];: Available from: http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/.
[7] Yang HI, Kim HC, Jeon JY. The association of resting heart rate with diabetes, hypertension, and metabolic syndrome in the Korean adult population: The fifth Korea National Health and Nutrition Examination Survey. Clin Chim Acta 2016;455:195–200.
[8] Kim DI, Yang HI, Park JH, et al. The association between resting heart rate and type 2 diabetes and hypertension in Korean adults. Heart 2016;102:1757–62.
[9] Aladin AI, Al Rifai M, Rasool SH, et al. The Association of Resting Heart Rate and Incident Hypertension: the Henry Ford Hospital Exercise Testing (FIT) Project. Am J Hypertens 2016;29:251–7.
[10] Wang A, Liu X, Guo X, et al. Resting heart rate and risk of hypertension: results of the Kailuan cohort study. J Hypertens 2014;32:1600–5. discussion 5.
[11] Gu D, Wildman RP, Wu X, et al. Incidence and predictors of hypertension over 8 years among Chinese men and women. J Hypertens 2007;25:517–23.
[12] Inoue T, Iseki K, Iseki C, et al. Higher heart rate predicts the risk of developing hypertension in a normotensive screened cohort. Circ J 2007;71:1755–60.
[13] Thomas J, Semenya KA, Neser WB, et al. Risk factors and the incidence of hypertension in black physicians: the Meharry Cohort Study. Am Heart J 1985;110:637–45.
[14] Zhao Y, Qin P, Sun H, et al. Resting heart rate and its dynamic change and the risk of hypertension: The Rural Chinese Cohort Study. J Hum Hypert 2019;10.1038/s41371-019-0259-y.
[15] Shi Y, Zhou W, Liu X, et al. Resting heart rate and the risk of hypertension and heart failure: a dose-response meta-analysis of prospective studies. J Hypertens 2018;36:995–1004.
[16] Post WS, Larson MG, Levy D. Hemodynamic predictors of incident hypertension. The Framingham Heart Study. Hypertension 1994; 24:585–90.
[17] Hamer M, Kivimaki M, Batty GD. Pulse rate reactivity in childhood as a risk factor for adult hypertension: the 1970 British cohort study. J Hypertens 2016;34:1804–7.
[18] Dyer AR, Liu K, Walsh M, et al. Ten-year incidence of elevated blood pressure and its predictors: the CARDIA study. Coronary Artery Risk Development in (Young) Adults. J Hum Hypertens 1999;13:13–21.
[19] Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. Ottawa Health Research Institute, Ottawa, Canada).
[20] Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175:66–73.
[21] Bekkering GE, Harris RJ, Thomas S, et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol 2008;167:1017–26.
[22] Nicola O. Generalized least squares for trend estimation of summarized dose–response data. The Stata Journal 2006;6:40–57.
[23] Bagnardi V, Zambon A, Quatto P, et al. Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality. Am J Epidemiol 2004;159:1077–86.
[24] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[25] Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995;6:356–65.
[26] Conti S, Szklo M, Menotti A, et al. Risk factors for definite hypertension: cross-sectional and prospective analyses of two Italian rural cohorts. Prev Med 1986;15:403–10.
[27] Oda E, Aizawa Y. Resting heart rate predicts metabolic syndrome in apparently healthy non-obese Japanese men. Acta Diabetol 2014;51:85–90.
[28] Shao YC, Liu XQ, Mai JZ, et al. Relationship between the incident of hypertension and resting heart rate: the prospective cohort study. Acad J SUMs 2002;23:40–2.
[29] 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.
[30] Shibao C, Gamboa A, Diedrich A, et al. Autonomic contribution to blood pressure and metabolism in obesity. Hypertension 2007;49:27–33.
[31] Sajadieh A, Nielsen OW, Rasmussen V, et al. 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.

[32] Janszky I, Ericson M, Lekander M, et al. Inflammatory markers and heart rate variability in women with coronary heart disease. J Intern Med 2004;256:421–8.
[33] Haynes WG, Morgan DA, Walsh SA, et al. Receptor-mediated regional sympathetic nerve activation by leptin. J Clin Invest 1997;100:270–8.
[34] Dunbar JC, Hu Y, Lu H. Intracerebroventricular leptin increases lumbar and renal sympathetic nerve activity and blood pressure in normal rats. Diabetes 1997;46:2040–3.
[35] Shek EW, Brands MW, Hall JE. Chronic leptin infusion increases arterial pressure. Hypertension 1998;31:409–14.
[36] Cohen S, Herbert TB. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annu Rev Psychol 1996;47:113–42.
[37] Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159–219.
[38] Cleroux J, Kouame N, Nadeau A, et al. After effects of exercise on regional and systemic hemodynamics in hypertension. Hypertension 1992;19:183–91.
[39] Floras JS, Sinkey CA, Aylward PE, et al. Postexercise hypotension and sympathoinhibition in borderline hypertensive men. Hypertension 1989;14:28–35.
[40] Valentini M, Parati G. Variables influencing heart rate. Prog Cardiovasc Dis 2009;52:11–9.