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Resting Heart Rate and Cognitive Decline: A Meta-Analysis of Prospective Cohort Studies

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Background and Purpose Several previous meta-analyses have identified an association between cognitive decline and heart rate variability, which reflects autonomic nerve activity. This systematic review and meta-analysis investigated the impact of increased resting heart rate (RHR) on the incidence of cognitive decline, including dementia.

Methods The PubMed, Embase, and PsycInfo databases were searched for relevant prospective cohort studies published before April 18, 2022. A methodological quality assessment of the included studies was conducted using the Newcastle–Ottawa Scale. Summary estimates of the incidence of cognitive decline, including dementia, were generated using a random-effects model. Potential publication bias was evaluated using Begg's funnel plots and Egger's regression tests.

Results The meta-analysis included 7 prospective cohort studies comprising 53,621 participants. A weak significant association was observed between RHR and the risk of cognitive decline, although the analysis indicated high heterogeneity among the studies (relative risk=1.18, 95% confidence interval=1.04–1.33, I^2=82.5%). Significant associations were determined between RHR and all combined types of dementia except for Alzheimer's disease and mild cognitive impairment. There was also a dose–response association between increased RHR and cognitive decline. The meta-estimate of the cognitive decline risk associated with a 10 beat-per-minute increase in RHR was 1.06, and it was 1.10 for dementia.

Conclusions This study found that a higher RHR was associated with an increased cognitive decline risk. Due to study limitations such as publication bias and high heterogeneity, additional studies are required to validate this finding.

Systematic review registration PROSPERO registration number CRD42021282912.

Keywords dementia; heart rate; meta-analysis; cognition.

INTRODUCTION

Dementia is a clinical syndrome characterized by cognitive decline, emotional instability, various neuropsychiatric symptoms, and impairment of daily living activities.[1] It currently affects approximately 50 million people worldwide, is recognized as a major global healthcare challenge, and its burden is growing in aging societies.[2] Developing preventive strategies is fundamental to decreasing the incidence and prevalence of dementia. Modifiable risk factors for cognitive decline and dementia are well established and include smoking status, little physical activity, sedentary lifestyle, poor diet, excessive alcohol consumption, midlife obesity, high blood pressure, midlife high cholesterol, and diabetes.[3] Depression, low social engagement, and low cognitive engagement have also been linked to dementia risk in late life.[4,5]

The resting heart rate (RHR) is a routine, noninvasive, and cost-effective vital-sign measurement, and a useful indicator of autonomic nervous system (ANS) function. A high RHR

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is maintained by decreased parasympathetic and increased sympathetic tones, and it indicates an imbalance in the ANS status.[6-8] Previous studies of the cerebral hemodynamics of neurodegenerative diseases have suggested that dysregulation of cerebral blood circulation could be an important factor in the pathogenesis of cognitive decline and dementia.[9,10] This supports the idea that autonomic dysfunction, including of the heart rate, could be involved in the etiology of dementia by affecting cerebral blood flow and circulation.

Few meta-analyses have examined the relationships between cognitive decline (including dementia) and heart rate variability, which reflects ANS activity.[11,12] The present meta-analysis was the first that we are aware of that has investigated the association between RHR and cognitive decline, including dementia.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PROSPERO protocol registration number: CRD42021282912).[13]

Literature search

A systematic literature search was performed on the PubMed, Embase, and PsycInfo databases by two reviewers, who worked independently. The last literature search was performed on April 18, 2022 (H.-B.K. and Y.H.J.) using the following common keywords associated with RHR and cognitive decline: "resting heart rate," "resting pulse rate," and "resting heart frequency" for exposure factors; and "cognition," "Alzheimer," and "dementia" for outcome factors. Additional articles were retrieved by manually reviewing the reference lists of identified articles. No restrictions were applied to the publication language.

Eligibility criteria

Two reviewers (H.-B.K. and Y.H.J.) independently assessed the eligibility of the studies, with disagreements settled through discussion with the third author (H.J.H.). The following inclusion criteria were applied for the meta-analysis: 1) observational studies with prospective cohort designs, 2) studies for which an association of "RHR" with "cognitive impairment" or "dementia" was reported, 3) studies in which RHR had been assessed before participants developed signs of cognitive decline, and 4) studies for which outcome measures were reported with adjusted relative risks (RRs) and 95% confidence intervals (CIs). Excluded studies were those not published in peer-reviewed journals, and those reported on as case reports, review articles, and abstracts presented at academic conferences.

Data extraction and assessment of methodological quality

A standardized tool was used independently by two reviewers to acquire the following data from the selected studies: first-author name, geographical region, study period, demographics (mean age or age range, and sex), sample size, ascertainment of exposure, outcome assessment, type of cognitive decline, confounding variables that were adjusted for, and adjusted RRs and 95% CIs. In case of insufficient or missing data, the reviewers contacted the corresponding author of the article. The Newcastle–Ottawa Scale (NOS) was used to establish the methodological quality of each included prospective cohort study.[14] The NOS is based on a star rating system from 0 to 9, in which a study can be awarded a maximum score of 4, 2, and 3 stars for selection, comparability, and exposure or outcome categories, respectively. Studies with scores of 0–3, 4–6, and 7–9 were considered to be of low, moderate, and high methodological quality, respectively.

Data synthesis and statistical analysis

The primary analysis examined the relationship between RHR and the incidence of cognitive decline, including dementia. A series of subgroup analyses were performed according to patient or study characteristics (mean age of participants, sex, disease type, geographical region, number of participants, follow-up duration, ascertainment of RHR, and ascertainment of cognitive decline), and according to confounding factors such as education level, cardiovascular risk, smoking status, alcohol consumption, APOE ε4 carrier status, and physical activity. The association between an RHR increase of 10 beats per minute (bpm) and cognitive decline was also investigated as a secondary analysis.

The RRs and 95% CIs of each comparison (which quantified the association between RHR and cognitive decline risk) were used to estimate the pooled RRs with corresponding 95% CIs. The Higgins I^2 test was used to assess the heterogeneity among studies,[15] with values of 0%–25%, 26%–50%, 51%–75%, and 76%–100% indicating insignificant, low, moderate, and high heterogeneity, respectively.[15] A random-effects model based on the DerSimonian and Laird method was used to pool study outcomes, given that the research methods and participant characteristics varied between the selected articles.[16] When the RR was measured using multiple adjustment models, the estimate that was adjusted for the most-confounding factors was selected. Meta-regression analysis was also employed to determine whether the heterogeneity of the studies could be explained by study-level covariates. Publication bias was evaluated using Begg's funnel plots and Egger's regression tests. An asymmetrical Begg's funnel plot or $p<0.05$, as determined using Egger's regression test, demonstrated the

presence of publication bias. All statistical analyses were performed using Stata SE (version 13.1, StataCorp, College Station, TX, USA).

RESULTS

Identification of relevant studies

Fig. 1 shows the study selection procedure. The PubMed, Embase, and PsycInfo databases were searched, which identified 9,906 articles, of which 4,439 were duplicates and therefore excluded. An additional 5,451 articles were excluded because they did not comply with the predetermined selection criteria based on their titles and Abstracts. The full texts of the remaining 16 articles were inspected, resulting in a further 10 articles being excluded due to them not meeting the inclusion criteria. One article was identified by a manual review of bibliographies. The present meta-analysis therefore involved seven prospective cohort studies.[17-23]

Characteristics of studies included in the final analysis

The general characteristics of the seven prospective cohort studies selected for the meta-analysis are listed in Table 1. These studies were published between 2010 and 2021 and involved 53,621 participants. Two studies[18,22] had follow-up periods shorter than 5 years, and five[17,19-22] had follow-up periods longer than 5 years. The mean age range of participants was 58.0–80.2 years. The mean proportion of female participants was 45.9%. Five studies[18-20,22,23] included both males and females in their populations, one study included only males[17] and one included only females.[21] Five studies were conducted in North America[17,19-22] and two were conducted in Europe.[18,23]

For diagnosing mild cognitive impairment (MCI) and dementia or measuring cognitive decline, six studies[17,19-23] employed various diagnostic tools, while one study[18] monitored the decrease in Mini-Mental State Examination scores from the baseline. Regarding the assessment of RHR, four studies[1] used bpm quartiles,[7,18,20,23] one[21] used bpm tertiles, one[19] used high bpm versus low bpm, and one[22] used a 10-bpm increase in RHR. All seven were rated as high quality (8 or 9 stars) on the NOS system (Table 2).

Association between RHR and cognitive decline risk

Fig. 2 presents the meta-estimate of the association between RHR and cognitive decline risk. The meta-analysis indicated a weak but significant association between RHR and cognitive decline risk, despite the high heterogeneity among the studies (RR=1.18, 95% CI=1.04–1.33, I^2=82.5%). Table 3 lists the results of the subgroup meta-analyses. Increased RHR was consistently related to cognitive decline based on sex, ascertainment of exposure factor, and follow-up duration, and

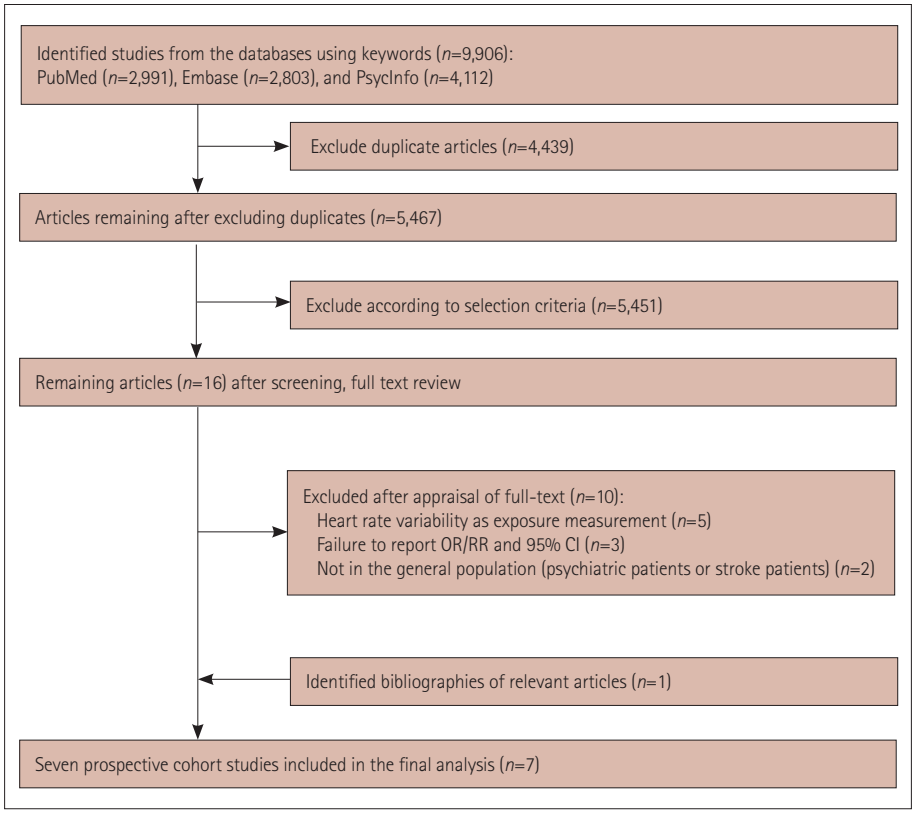

Fig. 1. Flow diagram of the identification of relevant studies. CI, confidence interval; OR, odds ratio; RR, relative risk.

Table 1. General characteristics of the studies included in the final analysis (*n*=7)

Study	Study type	Country	Years enrolled	Population (sex, age)	Type of cognitive decline	Definition of RHR (longest vs shortest category)	RR (95% CI)	Adjusted variables
Young et al., 2010[17]	Prospective cohort study	USA	1991–1999	Total 3,741 (males, 71–93 years)	AD+vascular dementia	RHR quartiles determined using 12-lead ECG	1.54 (1.01–2.37)	Age, education level, APOE ε4 carrier status, prevalent stroke, physical activity, hypertension, diabetes, smoking status, medication use (digoxin, beta blockers or calcium-channel blockers), and baseline CASI score
Leong et al., 2013[18]	Prospective cohort study	Germany	NA	4,699 cases and 23,161 controls (males and females, mean 66 years)	A decrease of ≥3 points from baseline to follow-up on MMSE	Categorized by quartiles (<60, 60–66, 67–74, and ≥75 bpm)	2.18 (1.09–4.37)	Demographics, cardiovascular comorbidities, tobacco use, alcohol consumption, pharmacotherapy, physical activity level, ethnicity, education level, depressive symptoms, dietary habits, BP, anthropometrics, renal function, serum lipid concentrations, left ventricular hypertrophy, and baseline MMSE score
Besser et al., 2016[19]	Prospective cohort study	USA	2005–2015	53 cases and 140 controls (males and females, ≥40 years)	AD (presence of moderate to frequent neuritic plaques, and Braak stages III and IV)	High vs. low bpm	0.97 (0.93–1.00)	BMI, BP, history of hypertension, diabetes, and hypercholesterolemia, age at death, sex, education level, and presence of at least one APOE ε4 allele
Wang et al., 2019[20]	Prospective cohort study	USA	1996–2013	1,350 cases and 12,370 controls (males and females, 44–66 years)	Incident dementia (prior discharge records using ICD-9 codes)	Quartiles (<60, 60–69, 70–79, and ≥80 bpm)	1.28 (1.04–1.57)	Age, sex, race/center, education level, BMI, smoking status, alcohol consumption, physical activity, systolic BP, pulse pressure, use of hypertension medication, diabetes, HDL cholesterol, total cholesterol, cholesterol-lowering medications, history of prevalent coronary heart disease, use of AV-node-blocking medications, and APOE ε4 genotype
Haring et al., 2020[21]	Prospective cohort study (Women's Health Initiative Memory Study and its ancillary MRI substudies [WHIMS-MRI 1 and WHIMS-MRI 2])	USA	1996–2017	91 cases and 701 controls (females, average 69.1 years)	MCI or probable dementia based on fourth edition of DSM	Tertiles (51–66, 67–70, and 71–92 bpm)	2.02 (1.18–3.47)	Age, education level, depression, physical activity, alcohol consumption, presence of APOE ε4 allele, mean systolic BP, antihypertensive medication use, and incident CVD

Table 1. General characteristics of the studies included in the final analysis (*n*=7) (continued)

Study	Study type	Country	Years enrolled	Population (sex, age)	Type of cognitive decline	Definition of RHR (longest vs shortest category)	RR (95% CI)	Adjusted variables
Singleton et al., 2021[22]	Prospective cohort study	USA	2010–2013	502 cases and 4,666 controls (males and females, average 67.1 years)	MCI or dementia	10-bpm increase in RHR	MCI=1.06 (0.96–1.16) Dementia=1.17 (1.02–1.36)	Age, sex, race, history of CVD, smoking status, education level, BMI, systolic BP, creatinine, total cholesterol, HDL lipoprotein cholesterol, and treatment assignment
Imahori et al., 2021[23]	Prospective cohort study	Sweden	2001–2016	289 cases and 1,858 controls (males and females, average 70.6 years)	Incident dementia	Quartiles (<60, 60–69, 70–79 and ≥80 bpm)	1.55 (1.06–2.27)	Age, sex, education level, smoking status, physical activity, BMI, total cholesterol, hypertension, diabetes, use of beta blockers, nondihydropyridine calcium-channel blocker, and digoxin, APOE ε4 genotype, and CVD

AD, Alzheimer's disease; APOE, apolipoprotein E; AV, atrioventricular; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CASI, Cognitive Abilities Screening Instrument; CI, confidence interval; CVD, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECG, electrocardiogram; HDL, high-density lipoprotein; ICD-9, International Classification of Diseases, 9th revision; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; OR, odds ratio; RHR, resting heart rate; RR, relative risk.

was adjusted for education level, cardiovascular risk, smoking status, alcohol consumption, APOE ε4 carrier status, and physical activity.

Regarding disease type, the RHR was positively associated with dementia, but not with Alzheimer's disease (AD) or MCI. A significant association was not observed in the subgroup analysis for studies conducted in Europe. The association was also only observed in large-scale studies (>5,000 participants). In the subgroup analysis of ascertainment of cognitive decline, the association was present only in studies that used The Diagnostic and Statistical Manual of Mental Disorders to assess outcomes.

Dose–response relationship between higher RHR and cognitive decline risk

Three prospective cohort studies[18,20,22] were selected to analyze the dose–response relationship between RHR and cognitive decline (Supplementary Fig. 1 in the online-only Data Supplement), and three prospective cohort studies[20,22,23] were selected to analyze the same relationship between RHR and dementia (Supplementary Fig. 2 in the online-only Data Supplement). The summary RR between a 10-bpm increase in RHR and cognitive decline was 1.06 (95% CI=1.03–1.09, I^2=2.9%, $p_{heterogeneity}$=0.357), and between a 10-bpm increase in RHR and dementia was 1.10 (95% CI=1.05–1.15, I^2=0.0%, $p_{heterogeneity}$=0.504) without significant heterogeneity.

Publication bias

Publication bias was identified in the meta-analysis based on an asymmetrical Begg's funnel plot and a significant Egger's regression test (p=0.001) (Supplementary Fig. 3 in the online-only Data Supplement). It was possible that small-scale observational studies identifying negative or no associations were not published in peer-reviewed articles, and therefore not selected in the present meta-analysis.

DISCUSSION

The present meta-analysis suggested that increased RHR tended to be associated with increased cognitive decline risk. Furthermore, dose–response relationships were identified between RHR and both cognitive decline and dementia.

This association between RHR and cognitive decline can be explained by considering RHR as an ANS dysfunction biomarker. RHR reflects the balance between the sympathetic and parasympathetic nervous systems. A higher RHR can be a sign of decreased parasympathetic and increased sympathetic activity, which is typical of patients with cognitive decline in neurodegenerative diseases.[24-26] Higher RHR has also been associated with higher levels of inflammatory markers

Table 2. Methodological quality of studies included in the final analysis based on the Newcastle–Ottawa Scale* to assess the quality of case–control and cohort studies (*n*=7)

Cohort studies	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at the start of the study	Control of important and additional factors	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Young et al., 2010[17]	1	1	1	1	2	1	1	0	8
Leong et al., 2013[18]	1	1	1	1	2	1	0	1	8
Besser et al., 2016[19]	1	1	1	1	2	1	1	1	9
Wang et al., 2019[20]	1	1	1	1	2	1	1	0	8
Haring et al., 2020[21]	1	1	1	1	2	1	1	0	8
Singleton et al., 2021[22]	1	1	1	1	2	1	0	1	8
Imahori et al., 2021[23]	1	1	1	1	2	1	1	1	9

*Each study can be awarded a maximum of 1 star for each numbered item within the selection and exposure categories, and a maximum of 2 stars for the comparability category.

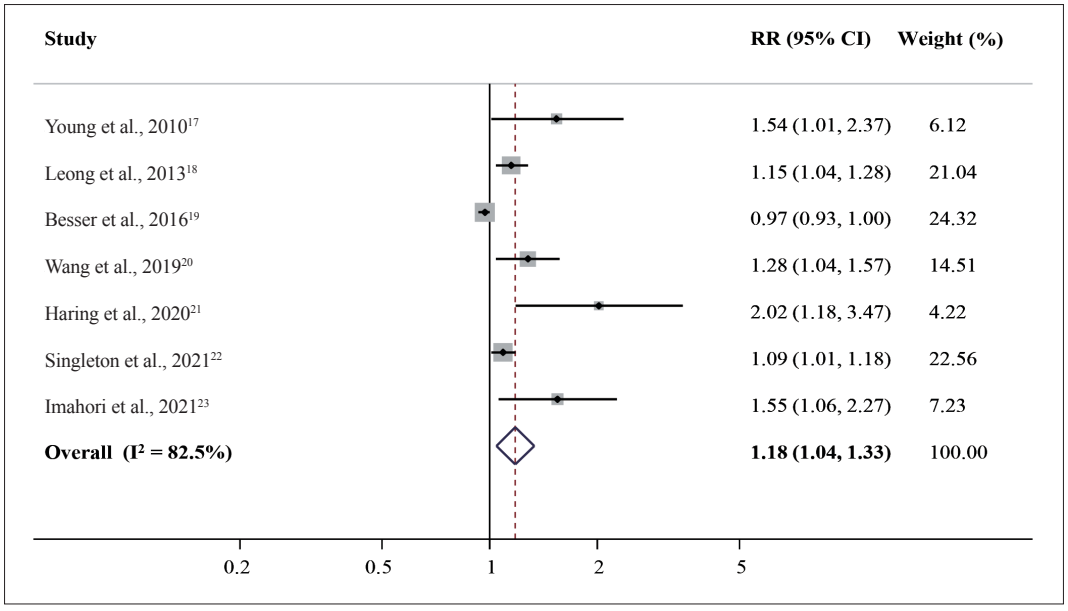

Fig. 2. Forest plot of the association between resting heart rate and cognitive decline (*n*=7). CI, confidence interval; RR, relative risk.

such as high-sensitivity C-reactive protein, IL-6, and fibrinogen.[27] Inflammation has been correlated with cognitive decline, and it is therefore possible that inflammation alters the balance of sympathetic and parasympathetic stimulations.[20] Previous studies have demonstrated that cognitive and autonomic processes are linked via the central autonomic network (CAN), which modulates both cognitive functions and the autonomic regulation of cardiovascular functions.[28] The CAN consists of a complex network of cortical and subcortical regions, including the insula, hippocampus, and prefrontal cortex, and projects to the preganglionic neurons in the ANS.[28,29] The insula is a key hub within the CAN that plays a major role in generating sympathetic outflow, as demonstrated in several animal and human studies. In rodent models, electrically and chemically stimulating the insula increased heart rates and blood pressure.[30] Similarly, structural neuroimaging indicated that the gray-matter volume of the insula was negatively correlated with parasympathetic heart rate variability.[31]

Another important component of the CAN is the hippocampus. Retroviral tracing techniques have established its connections to the sympathetic system,[32] and stress response tests in rodents induced an increase in hippocampal electroencephalographic activity that paralleled an increase in heart rate variability. The former increase was related to sympathetic activation/parasympathetic withdrawal, and it was reduced by inhibiting hippocampal glutamatergic transmission.[33,34] In

Table 3. Association between RHR and cognitive decline in the subgroup meta-analysis according to various factors

Factor	No. of studies	Q statistic	RR (95% CI)	Heterogeneity, I^2 (%)	*p* (for heterogeneity)	*p* (between groups)
All[17-23]	7	34.32	1.18 (1.04–1.33)	82.5	<0.001	
Disease type						0.38
All types of dementia[17,20,22,23]	4	3.01	1.25 (1.12–1.39)	0.3	0.39	
Alzheimer's disease[19]	1		0.97 (0.93–1.00)	NA		
MCI[22]	1		1.06 (0.97–1.16)	NA		
Cognitive decline[18,21]	2	4.04	1.43 (0.83–2.44)	75.3	0.044	
Sex						0.13
Female[21]	1	NA	2.02 (1.18–3.47)	NA	NA	
Male[17]	1	NA	1.54 (1.01–2.37)	NA	NA	
Both[18–20,22,23]	5	24.38	1.09 (1.00–2.22)	83.6	<0.001	
Mean age						0.59
<70 years [18,20–22]	4	6.79	1.17 (1.05–1.31)	55.8	0.08	
>70 years[17,19,23]	3	10.17	1.27 (0.87–1.85)	80.3	0.006	
Region						0.81
USA[17,19–22]	5	23.40	1.16(1.00–1.33)	82.9	<0.001	
Europe[18,23]	2	2.20	1.26 (0.96–1.65)	54.5	0.14	
Sample size						0.68
Small (<5,000)[17,19,21,23]	4	17.10	1.40 (0.96–2.06)	82.5	0.001	
Large (>5,000)[18,20,22]	3	2.32	1.13 (1.06–1.21)	13.6	0.314	
Ascertainment of RHR						0.45
12-lead ECG[17,20,23]	3	1.11	1.37 (1.16–1.61)	0.0	0.57	
Trained observer[21]	1		2.02 (1.18–3.47)	NA		
Ascertainment of cognitive decline						0.11
DSM[17,21,23]	3	0.74	1.64 (1.27–2.11)	0.0	0.69	
Others[18–20]	3	15.11	1.10 (0.94–1.30)	86.8	0.001	
Follow-up duration						0.87
Shorter (<5 years)[18, 22]	2	0.66	1.11 (1.04–1.18)	0.0	0.42	
Longer (≥5 years)[17,19,20,21,23]	5	23.35	1.34 (1.03–1.75)	82.9	<0.001	
Sensitivity analysis (adjustment)						0.34
Education level[17-23]	7	34.32	1.18 (1.04–1.33)	82.5	<0.001	
Cardiovascular risk[17-23]	7	34.32	1.18 (1.04–1.33)	82.5	<0.001	
Smoking status[17,18,20,22,23]	5	6.93	1.18 (1.07–1.30)	42.3	0.14	
Alcohol consumption[18,20,21]	3	4.59	1.27 (1.05–1.54)	56.4	0.10	
APOE ε4 carrier status[17,19–21,23]	5	23.35	1.34 (1.03–1.75)	82.9	<0.001	
Physical activity[18,20,21,23]	4	6.30	1.31 (1.10–1.57)	52.4	0.10	

CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECG, electrocardiogram; MCI, mild cognitive impairment; NA, not applicable; RHR, resting heart rate; RR, relative risk.

humans, functional neuroimaging studies have demonstrated hippocampus activation during sympathetic stress. Parasympathetic heart rate variability is also negatively correlated with hippocampal activity and with the gray-matter volume of the parahippocampal gyrus.[31] These findings support the relationship between RHR and cognitive decline, and may also suggest a relationship between RHR and neurodegeneration via the heart–brain axis.[34] On the other hand, our subgroup study indicated that increased RHR might be associated with types of dementia other than AD (Table 3). This suggests that RHR is related to cognitive decline in neurodegenerative diseases such as Lewy body disease and multiple-system atrophy. However, further research is needed to confirm this.

The present meta-analysis was the first to summarize the evidence of the association between RHR and cognitive decline, including dementia. All of the studies included in the analysis adjusted for confounding variables, and were selected based on their high methodological quality. However, our meta-analysis also had some important limitations. First, the reliability of the calculated meta-estimates was impacted by

the small number of available prospective cohort studies and relatively small patient sample. Second, high heterogeneity was found in the primary analysis and also in most of the subgroup analyses. The two factors that contributed most to the heterogeneity were sex and ascertainment of cognitive decline. Third, most of the studies assessed RHR only once at baseline and once during the follow-up period. This small number of measurements might not fully capture the variability of RHR and its long-term effects on cognitive decline. Fourth, several pivotal factors related to RHR and cognitive decline might not have been included. For example, anxiety disorder,[35] stressful events,[36] and concurrent use of medications such as β-blockers or calcium-channel blockers can affect RHR,[37] but they were not adjusted for in the selected studies. Since many variables affect the clinical meaning of RHR, ranging from organic diseases to psychological situations such as anxiety, it is difficult to conclude that RHR is the causative factor of cognitive decline.

In conclusion, the evidence from the present meta-analysis indicates that increased RHR can be a risk factor for cognitive decline, including dementia. Our study suggests that people with a high RHR may need to be monitored for cognitive decline or dementia. Large-scale prospective cohort studies are required to determine if increased RHR directly causes cognitive decline.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.6.619.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Jung YH, Lee S, Kim WJ, Lee JH, Kim MJ, Han HJ. Effect of integrated cognitive intervention therapy in patients with mild to moderate Alzheimer's disease. *Dement Neurocogn Disord* 2020;19:86-95.
2. Patterson C. World Alzheimer report 2018 [Internet]. London: Alzheimer's Disease International; 2018 [cited 2021 Oct 15]. Available from: https://www.alzint.org/resource/world-alzheimer-report-2018/.
3. Lincoln P, Fenton K, Alessi C, Prince M, Brayne C, Wortmann M, et al. The Blackfriars Consensus on brain health and dementia. *Lancet* 2014;383:1805-1806.
4. Prince M, Albanese E, Guerchet M, Prina M. World Alzheimer report 2014. Dementia and risk reduction: an analysis of protective and modifiable risk factors [Internet]. London: Alzheimer's Disease International; 2014 [cited 2021 Oct 18]. Available from: https://www.alzint.org/resource/world-alzheimer-report-2014/.
5. Peters R, Booth A, Rockwood K, Peters J, D'Este C, Anstey KJ. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. *BMJ Open* 2019;9:e022846.
6. Wulsin LR, Horn PS, Perry JL, Massaro JM, D'Agostino RB Sr. The contribution of autonomic imbalance to the development of metabolic syndrome. *Psychosom Med* 2016;78:474-480.
7. Licht CM, de Geus EJ, Penninx BW. Dysregulation of the autonomic nervous system predicts the development of the metabolic syndrome. *J Clin Endocrinol Metab* 2013;98:2484-2493.
8. Licht CM, Vreeburg SA, van Reedt Dortland AK, Giltay EJ, Hoogendijk WJ, DeRijk RH, et al. Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal axis activity is associated with metabolic abnormalities. *J Clin Endocrinol Metab* 2010;95:2458-2466.
9. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC; Alzheimer's Disease Neuroimaging Initiative. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun* 2016;7:11934.
10. Hajjar I, Marmerelis V, Shin DC, Chui H. Assessment of cerebrovascular reactivity during resting state breathing and its correlation with cognitive function in hypertension. *Cerebrovasc Dis* 2014;38:10-16.
11. Cheng YC, Huang YC, Huang WL. Heart rate variability in patients with dementia or neurocognitive disorders: a systematic review and meta-analysis. *Aust N Z J Psychiatry* 2022;56:16-27.
12. da Silva VP, Ramalho Oliveira BR, Tavares Mello RG, Moraes H, Deslandes AC, Laks J. Heart rate variability indexes in dementia: a systematic review with a quantitative analysis. *Curr Alzheimer Res* 2018;15:80-88.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
14. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa: Ottawa Hospital Research Institute; 2011 [cited 2021 Oct 18]. Available from: https://www.ohri.ca//Programs/clinical_epidemiology/oxford.asp.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-1558.
16. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1:97-111.
17. Young K, Abbott R, Petrovitch H, Chen R, White L, Ross G, et al. Resting heart rate and cognitive function: the Honolulu-Asia Aging Study. Proceedings of the American Geriatrics Society (AGS) 2010 Annual Scientific Meeting; 2010 May 12-15; Orlando, FL, USA: AGS; 2010; p. S65.
18. Leong DP, O'Donnell MJ, Teo K, Smyth A, Joseph P, Gao P, et al. Resting heart rate and decline in cognitive function: observations from the ONTARGET/TRANSCEND studies. *Eur Heart J* 2013;34(suppl_1):

2737.
19. Besser LM, Alosco ML, Ramirez Gomez L, Zhou XH, McKee AC, Stern RA, et al. Late-life vascular risk factors and Alzheimer disease neuropathology in individuals with normal cognition. *J Neuropathol Exp Neurol* 2016;75:955-962.
20. Wang S, Fashanu OE, Zhao D, Guallar E, Gottesman RF, Schneider ALC, et al. Relation of elevated resting heart rate in mid-life to cognitive decline over 20 years (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2019;123:334-340.
21. Haring B, Liu J, Rapp SR, Shimbo D, Padula CB, Mozhui K, et al. Heart rate, brain imaging biomarkers and cognitive impairment in older (≥63 years) women. *Am J Cardiol* 2020;129:102-108.
22. Singleton MJ, Soliman E, Hughes T, Shantha G, Bhave P, Beaty E, et al. Association of resting heart rate with incident dementia and mild cognitive impairment: SPRINT. *J Am Coll Cardiol* 2021;77(18_Supplement_1):1657.
23. Imahori Y, Vetrano DL, Xia X, Grande G, Ljungman P, Fratiglioni L, et al. Association of resting heart rate with cognitive decline and dementia in older adults: a population-based cohort study. *Alzheimers Dement* 2021 Dec 3 [Epub]. Available from: https://doi.org/10.1002/alz.12495.
24. Collins O, Dillon S, Finucane C, Lawlor B, Kenny RA. Parasympathetic autonomic dysfunction is common in mild cognitive impairment. *Neurobiol Aging* 2012;33:2324-2333.
25. Kim DH, Lipsitz LA, Ferrucci L, Varadhan R, Guralnik JM, Carlson MC, et al. Association between reduced heart rate variability and cognitive impairment in older disabled women in the community: Women's Health and Aging Study I. *J Am Geriatr Soc* 2006;54:1751-1757.
26. Aharon-Peretz J, Harel T, Revach M, Ben-Haim SA. Increased sympathetic and decreased parasympathetic cardiac innervation in patients with Alzheimer's disease. *Arch Neurol* 1992;49:919-922.
27. Whelton SP, Narla V, Blaha MJ, Nasir K, Blumenthal RS, Jenny NS, et al. Association between resting heart rate and inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin-6, and fibrinogen) (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol* 2014;113:644-649.
28. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann Behav Med* 2009;37:141-153.
29. Tahsili-Fahadan P, Geocadin RG. Heart–brain axis: effects of neurologic injury on cardiovascular function. *Circ Res* 2017;120:559-572.
30. Ruggiero DA, Mraovitch S, Granata AR, Anwar M, Reis DJ. A role of insular cortex in cardiovascular function. *J Comp Neurol* 1987;257:189-207.
31. Wei L, Chen H, Wu GR. Heart rate variability associated with grey matter volumes in striatal and limbic structures of the central autonomic network. *Brain Res* 2018;1681:14-20.
32. Westerhaus MJ, Loewy AD. Central representation of the sympathetic nervous system in the cerebral cortex. *Brain Res* 2001;903:117-127.
33. Aitake M, Hori E, Matsumoto J, Umeno K, Fukuda M, Ono T, et al. Sensory mismatch induces autonomic responses associated with hippocampal theta waves in rats. *Behav Brain Res* 2011;220:244-253.
34. Nicolini P, Mari D, Abbate C, Inglese S, Bertagnoli L, Tomasini E, et al. Autonomic function in amnestic and non-amnestic mild cognitive impairment: spectral heart rate variability analysis provides evidence for a brain-heart axis. *Sci Rep* 2020;10:11661.
35. Latvala A, Kuja-Halkola R, Rück C, D'Onofrio BM, Jernberg T, Almqvist C, et al. Association of resting heart rate and blood pressure in late adolescence with subsequent mental disorders: a longitudinal population study of more than 1 million men in Sweden. *JAMA Psychiatry* 2016;73:1268-1275.
36. Eriksson P, Schiöler L, Söderberg M, Rosengren A, Torén K. Job strain and resting heart rate: a cross-sectional study in a Swedish random working sample. *BMC Public Health* 2016;16:228.
37. Yayla Ç, Gayretli Yayla K, Ertem AG, Açar B, Ünal S, Gökaslan S. Drugs that affect the resting heart rate. *Angiology* 2017;68:174.