Association of resting heart rate with cognitive decline and dementia in older adults: A population-based cohort study

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Abstract

Introduction: Resting heart rate (RHR) predicts future risk for cardiovascular disease (CVD). However, longitudinal studies investigating the relationship of RHR with cognitive decline are scarce.

Methods: This population-based cohort study included 2147 participants (age ≥ 60) in SNAC-K who were free of dementia and regularly followed from 2001–2004 to 2013–2016. RHR was assessed with electrocardiogram. Dementia was diagnosed following the Diagnostic and Statistical Manual of Mental Disorders 4th Revision criteria. Global cognitive function was assessed using Mini-Mental State Examination (MMSE). Data were analyzed using Cox and linear mixed-effects models.

Results: RHR ≥ 80 (vs. 60–69) bpm was associated with a multi-adjusted hazard ratio of 1.55 (95% confidence interval 1.06–2.27) for dementia. The association remained significant after excluding participants with prevalent and incident CVDs. Similarly, RHR ≥ 80 bpm was associated with a multi-adjusted β-coefficient of –0.13 (–0.21 to –0.04) for MMSE score.

Discussion: Higher RHR is associated with increased risk for dementia and faster cognitive decline independent of CVDs in a general population of elderly people.

KEYWORDS
cardiovascular disease, dementia, heart rate, risk factor

1 BACKGROUND

The global burden of dementia has increased rapidly, with 43.8 million people affected in 2016.1 The number of people living with dementia is expected to reach 131 million by 2051, with 68% residing in low- and middle-income countries.2 Dementia has a devastating impact on the quality of life of older adults, their families, and society at large. Currently, there is no cure for dementia, but growing evidence suggests that the onset of dementia could be delayed through managing modifiable risk factors.3 Evidence has also been accumulating that cardiovascular diseases (CVDs) are associated with the development of dementia, including Alzheimer's disease, possibly because of common risk factors, atherosclerotic changes of arteries, arterial stiffness, micro-embolism, and cerebral hypoperfusion.4–6

Abundant evidence has consistently shown that an elevated resting heart rate (RHR) predicts future CVD events beyond traditional CVD risk factors.7,8 A limited number of studies also show that a high RHR
is associated with cognitive decline and dementia in the general population of middle-aged adults and in patients with ischemic stroke. However, this association has not been investigated in the general population of older adults. Besides, whether an increased RHR is independently associated with cognitive decline or the association is merely explained by the underlying CVDs has yet to be explored. This is important because an elevated RHR is associated with a higher risk of several CVDs such as ischemic heart disease (IHD), atrial fibrillation (AF), heart failure (HF), and stroke, and these CVDs are known risk factors for dementia. Therefore, a higher RHR may be linked with dementia only through an indirect pathway of these CVDs, and thus not an independent risk factor for dementia.

The aim of this population-based cohort study was to investigate the association of elevated RHR with incident dementia in a general population of older adults. We hypothesized that an elevated RHR was associated with an increased risk for dementia and global cognitive decline in older adults and that their association could be present independent of cardiovascular risk factors and CVDs. We sought to test our hypotheses by examining the associations of RHR with cognitive decline and dementia among older adults with and without prevalent and incident CVDs.

2 METHODS

2.1 Study population

Study participants were from the population-based Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), as previously described. Briefly, SNAC-K targeted men and women aged ≥60 years and living at home or in an institution in the Kungsholmen district of central Stockholm, Sweden, between 2001 and 2004 (baseline), among the 5111 persons who were invited from a random sample of the population stratified by 11 age groups (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and ≥99 years). 321 were found to be ineligible and 200 died before the examination. Of the remaining 4590 eligible persons, 3363 (response rate 73%) underwent the baseline examination. Follow-up examinations were conducted every 6 years for the younger-old cohort (60, 66, and 72 years) and every 3 years for the older-old cohort (78, 81, 84, 87, 90, 93, 96, and 99 years).

Of the 3363 participants at baseline, we first excluded 814 participants who had missing information on baseline RHR or Mini-Mental State Examination (MMSE) score. These participants were older (mean age, 86.1 vs. 71.1, P < 0.001), less educated (university degree, 13.3% vs. 38.7%, P < 0.001), and more likely to be female (76.3% vs. 61.2%, P < 0.001) and live in institutions (22.4% vs. 0.4%, P < 0.001). Then, we excluded 27 participants with prevalent dementia, 11 with a baseline MMSE score < 24, 181 with non-sinus rhythm on echocardiogram (ECG), and 183 with missing covariates, leaving 2147 participants who were free of dementia at baseline and undertook at least one follow-up examination for the current analyses (Figure S1 in supporting information).

All phases of SNAC-K were approved by the Regional Ethical Review Board in Stockholm, Sweden. Written informed consents were obtained from all participants, or in the case of cognitively impaired persons, from proxies.

2.2 Data collection and assessments

At baseline, data were collected through face-to-face interviews, clinical examinations, and laboratory tests by trained staff following standard procedures. Information on age, sex, education (elementary school, high school, or university), and smoking status (never, former, or current smokers) was collected via interviews. Physical activity was assessed through a self-administered questionnaire by asking how often respondents engaged in light exercises such as walking, biking, and light aerobics (every day, several times per week, a few times per month, less frequent, or never). Body mass index (BMI) was calculated by dividing weight in kilograms by squared height in meters. A peripheral blood sample was obtained. Serum total cholesterol was measured...
and APOE alleles were genotyped at the university laboratory. Participants were categorized as ε4 carriers when they have at least one ε4 allele. Diagnosis of hypertension, diabetes, and CVDs (IHD, AF, HF, and cerebrovascular diseases) were made based on the comprehensive information on participants’ self-report, anamnestic data, clinical and laboratory data, medications, and registers from the Swedish National Patient Register as previously described at every study visit. Participants were asked to provide a list of currently used medications, and the use of medications was classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The use of beta blockers, digoxin, and non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) was identified using ATC codes (C07, C01AA05, and C08D). Ivalbradine had not been approved at baseline (2001–2004).

2.3 | Assessment of ECG

RHR was obtained from a standard 12-lead ECG at baseline. ECG was recorded using MAC500 (GE Healthcare) by trained technicians based on the standard procedure. RHR was categorized into < 60, 60–69 (reference), 70–79, and ≥80 beats per minute (bpm) according to previous studies.9,15

2.4 | Cognitive assessments and diagnosis of dementia

At baseline and each follow-up visit, global cognitive function was assessed using MMSE, and dementia diagnosis was made based on Diagnostic and Statistical Manual of Mental Disorders 4th Revision (DSM-IV) criteria following a three-step procedure.16,17 Briefly, the examining physician made a preliminary diagnosis of dementia based on interviews, clinical examination, and cognitive testing. Then, the second physician who was blind to the first diagnosis independently made a second preliminary diagnosis. Any discrepancies between the two diagnoses were resolved by a neurologist external to the data collection (LF or GG). In case the participants died before the study visit and did not have a diagnosis of dementia, the diagnosis of dementia was ascertained by physicians via thoroughly reviewing the information from the Swedish Cause of Death Register, clinical chart, and medical records.

3 | STATISTICAL ANALYSIS

The baseline characteristics of participants who were included in and excluded from the analytical samples were compared using a Chi-squared test for categorical variables and a t-test for continuous variables. The association between RHR and incident dementia was assessed using a Cox proportional hazards model. Follow-up time was defined as the interval between the date of the baseline examination and the date of the following events, depending on whichever came first: the first dementia diagnosis, death, or the last study visit. RHR was used as both a categorical (60–69 bpm as the reference group) and continuous variable (per 10 bpm increment in RHR). The proportional hazards assumption was verified for categorical RHR by visual inspection of survival curves and by tests of Schoenfeld residuals. We further conducted a complementary analysis using MMSE score as an outcome to support our findings concerning dementia as the primary outcome, because MMSE is a screening tool for dementia. The association between RHR and change in MMSE score was assessed using linear mixed-effects models with random intercepts and slopes. Interaction terms between RHR and follow-up time were included in all models to estimate the effect of RHR on changes in MMSE score over time.

We reported the main results from three models. Model 1 was adjusted for age, sex, and education. Model 2 was further adjusted for behavioral risk factors assessed at baseline (smoking, physical activity, and BMI). Model 3 was additionally adjusted for vascular risk factors at baseline (total cholesterol, hypertension, and diabetes), CVDs (IHD, AF, HF, and cerebrovascular disease at baseline), medications that reduce RHR (beta blockers, digoxin, and non-dihydropyridine calcium channel blockers), and APOE ε4 alleles. We examined the statistical interactions of RHR with age, sex, each of the CVDs, and APOE genotype on the risk of dementia.

Furthermore, to examine the contribution of underlying CVDs to the association of RHR with dementia and change in MMSE score, we repeated the analyses while excluding participants with at least one of the four CVDs (IHD, AF, HF, and cerebrovascular disease) at baseline. Next, we further excluded participants who had developed at least one CVD during follow-up to see the effect of incident CVDs on these associations. We also investigated the association of RHR with dementia and change in MMSE score among participants with at least one CVD. In addition, to explore the effect of higher and lower RHR, we examined an association of RHR with incident dementia and MMSE score changes using categorical RHR with six levels (< 50, 50–59, 60–69, 70–79, 80–89, and 90+ bpm). Finally, we conducted a sensitivity analysis using the inverse probability weighting method to evaluate the potential impact of selection bias due to dropouts on the main results.

Stata version 16.0 (StataCorp) was used for all the analyses.

4 | RESULTS

The baseline characteristics of study participants according to RHR groups are presented in Table 1. The mean age of the 2147 participants was 70.6 (standard deviation [SD], 8.9) years, and 62% were women. Participants included in the analytical sample were younger and had fewer chronic diseases and a higher MMSE score than those excluded (P < 0.05, Table S1 in supporting information). The average MMSE score of all participants was 29.0 (SD, 1.2). The average RHR was 65.7 bpm (SD, 10.9). Participants without underlying CVDs at baseline had a slightly higher RHR than those with at least one CVD (66.1 ± 10.8 vs. 63.9 ± 11.2 bpm, P < 0.01; Figure S2 in supporting information). Participants in higher RHR groups were older, less educated, more likely to be current smokers and physically inactive, and to have hypertension (Table 1). The prevalence of CVDs was not significantly different among RHR groups, but those in higher RHR groups were less likely to use beta blockers. The MMSE score at baseline was similar among different RHR groups.
| Characteristics                  | Total sample (n = 2147) | RHR < 60 bpm (n = 674) | RHR 60–69 bpm (n = 776) | RHR 70–79 bpm (n = 467) | RHR ≥80 bpm (n = 230) | P-values |
|---------------------------------|-------------------------|------------------------|-------------------------|-------------------------|-----------------------|----------|
| Age (years), mean (SD)          | 70.6 (8.9)              | 69.5 (8.8)             | 70.7 (8.9)              | 71.6 (9.0)              | 71.7 (9.1)            | 0.0003   |
| Female sex, n (%)               | 1333 (62.1)             | 363 (53.9)             | 523 (67.4)              | 304 (65.1)              | 143 (62.2)            | <0.001   |
| Education, n (%)                |                         |                        |                         |                         |                       |          |
| Elementary                      | 265 (12.3)              | 65 (9.6)               | 100 (12.9)              | 64 (13.7)               | 36 (15.7)             | 0.006    |
| High school                     | 1033 (48.1)             | 311 (46.1)             | 377 (48.6)              | 221 (47.3)              | 124 (53.9)            |          |
| University                       | 849 (39.5)              | 298 (44.2)             | 299 (38.5)              | 182 (39.0)              | 70 (30.4)             |          |
| Smoking status, n (%)           |                         |                        |                         |                         |                       |          |
| Never                           | 954 (44.4)              | 289 (42.9)             | 341 (43.9)              | 225 (48.2)              | 99 (43.0)             | 0.048    |
| Former smoker                   | 860 (40.1)              | 299 (44.4)             | 304 (39.2)              | 165 (35.3)              | 92 (40.0)             |          |
| Current smoker                  | 333 (15.5)              | 86 (12.8)              | 131 (16.9)              | 77 (16.5)               | 39 (17.0)             |          |
| Light physical activity, n (%)  |                         |                        |                         |                         |                       |          |
| Every day                       | 811 (37.8)              | 249 (36.9)             | 309 (39.8)              | 165 (35.3)              | 88 (38.3)             | 0.03     |
| Several times/week              | 858 (40.0)              | 293 (43.5)             | 309 (39.8)              | 176 (37.7)              | 80 (34.8)             |          |
| 2–3 times/month                 | 252 (11.7)              | 75 (11.1)              | 88 (11.3)               | 57 (12.2)               | 32 (13.9)             |          |
| Less frequent                   | 129 (6.0)               | 34 (5.0)               | 41 (5.3)                | 36 (7.7)                | 18 (7.8)              |          |
| Never                           | 97 (4.5)                | 23 (3.4)               | 29 (3.7)                | 33 (7.1)                | 12 (5.2)              |          |
| **BMI (kg/m²), mean (SD)**      | 26.0 (3.9)              | 25.9 (3.6)             | 26.0 (4.0)              | 26.2 (4.1)              | 26.0 (4.2)            | 0.76     |
| **SBP (mmHg), mean (SD)**       | 144.5 (19.5)            | 142.1 (19.7)           | 145.7 (19.9)            | 144.0 (18.5)            | 148.1 (18.6)          | 0.0001   |
| **DBP (mmHg), mean (SD)**       | 82.8 (10.3)             | 81.2 (9.9)             | 83.0 (10.2)             | 83.1 (9.8)              | 85.9 (11.7)           | <0.0001  |
| **TC (mmol/l), mean (SD)**      | 6.1 (1.1)               | 5.9 (1.0)              | 6.1 (1.1)               | 6.1 (1.2)               | 6.1 (1.1)             | 0.003    |
| Medical history, n (%)          |                         |                        |                         |                         |                       |          |
| Diabetes                        | 158 (7.4)               | 49 (7.3)               | 46 (5.9)                | 39 (8.4)                | 24 (10.4)             | 0.10     |
| Hypertension                    | 1508 (70.2)             | 436 (64.7)             | 567 (73.1)              | 328 (70.2)              | 177 (77.0)            | <0.001   |
| Heart failure                   | 86 (4.0)                | 32 (4.8)               | 28 (3.6)                | 15 (3.2)                | 11 (4.8)              | 0.49     |
| Atrial fibrillation             | 68 (3.2)                | 31 (4.6)               | 20 (2.6)                | 9 (1.9)                 | 8 (3.5)               | 0.05     |
| Ischemic heart disease          | 234 (10.9)              | 97 (14.4)              | 78 (10.1)               | 32 (6.9)                | 27 (11.7)             | 0.001    |
| Cerebrovascular disease         | 86 (4.0)                | 25 (3.7)               | 38 (4.9)                | 14 (3.0)                | 9 (3.9)               | 0.39     |
| Use of beta blockers, n (%)     | 400 (18.6)              | 185 (27.5)             | 138 (17.8)              | 56 (12.0)               | 21 (9.1)              | <0.001   |
| Use of calcium blockers*, n (%) | 32 (1.5)                | 5 (0.7)                | 17 (2.2)                | 6 (1.3)                 | 4 (1.7)               | 0.14     |
| Use of digoxin, n (%)           | 15 (0.7)                | 6 (0.9)                | 2 (0.3)                 | 6 (1.3)                 | 1 (0.4)               | 0.17     |
| MMSE score, mean (SD)           | 29.0 (1.2)              | 29.1 (1.1)             | 29.0 (1.2)              | 29.1 (1.1)              | 28.8 (1.3)            | 0.08     |
| APOE ε4 allele carrier, n (%)   | 628 (29.3)              | 204 (30.3)             | 216 (27.8)              | 139 (29.8)              | 69 (30.0)             | 0.75     |

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; MMSE, Mini-Mental State Examination; RHR, resting heart rate; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol.

*Use of non-dihydropyridine calcium channel blockers.

During a total of 19,344 person-years of follow-up (median per person, 11.4 years), 289 participants were diagnosed with dementia (incidence 14.9 per 1000 person-years). Participants with RHR ≥80 bpm, compared to those with RHR 60–69 bpm, had an average 55% increased risk for developing dementia in the fully adjusted model (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.06, 2.26; Table S2, Model 3). There was no evidence of interactions of RHR with age, sex, HF, AF, IHD, cerebrovascular disease, or APOE genotype (P for all interactions > 0.10). The association of high RHR with dementia remained significant after excluding participants with at least one of the four CVDs at baseline (HF, AF, IHD, or cerebrovascular disease). Further exclusion of participants who developed any of the four CVDs during follow-up did not change the results materially (Table 2). We repeated our analyses among participants with CVDs at baseline, and no significant association between RHR and dementia was found in this group (Table S2 in supporting information).

Regarding cognitive function, the MMSE score declined over time during the follow-up period in all RHR groups (Table 3). However,
participants with RHR 70–79 and +80 bpm had a greater decline compared to those with RHR 60–69 bpm (Table 3). The associations remained significant even after excluding prevalent CVDs at baseline and incident CVDs developed during the follow-up period (Table 3). Participants with CVDs showed steeper cognitive decline than the total population and CVD-free participants (Table S3 in supporting information).

Sensitivity analyses were also performed by using RHR category with six levels including higher (90+ bpm) and lower RHR (< 50 bpm) and examining an association of RHR with incident dementia and changes in MMSE score. Participants with RHR < 50 bpm showed a higher HR of dementia in Models 1 and 2, suggesting a J-shaped association, although this association became non-significant in Model 3. RHR ≥90 bpm was not significantly associated with dementia potentially due to low sample size (Table S4 in supporting information). Regarding the MMSE, higher (90+ bpm) and lower (< 50 bpm) RHR was not associated with a greater cognitive decline compared to those with RHR 60–69 bpm (Table S5 in supporting information). Finally, applying the inverse probability weighting to dropouts did not change the results materially (Table S6 in supporting information).

5 | DISCUSSION

In this population-based prospective cohort study of Swedish older adults, we found that RHR ≥80 bpm was associated with an increased risk for incident dementia independent of vascular risk factors and underlying CVDs over 12 years. This association remained significant after excluding participants with prevalent and incident CVDs, which are known risk factors for dementia. Similarly, participants with RHR ≥70 bpm experienced a faster decline in general cognitive function compared to those with RHR 60–69 bpm, supporting our findings of association with incident dementia.

Previously, three prospective cohort studies investigated the association between RHR and cognitive function. The ARIC study of middle-aged adults who were free from prevalent stroke and AF (n = 13,172,
average age 58 years) showed that an RHR $\geq$ 80 bpm (vs. $<$ 60 bpm) was associated with an increased risk of incident dementia during the 18 years of follow-up and that RHR $\geq$ 70 bpm was associated with a steeper cognitive decline after the adjustment for various CVD risk factors and prevalent coronary heart disease,9 which were quite similar to our results. These results suggest that higher RHR is an independent risk factor for cognitive decline both in the middle-aged population and the elderly. By contrast, data from the Women’s Health Initiative Memory Study of post-menopausal women who were free of prevalent CVDs and cardiovascular risk factors (n = 493, age $\geq$ 63 years, average age 69 years) failed to show an association of high RHR with cognitive impairment after a 15-year follow-up owing partially to insufficient statistical power, although high RHR was associated with an increase in ischemic brain lesions on magnetic resonance imaging.18 Of note, this study used the tertiles of RHR (51–66, 66–71, and 71–92 bpm) with the lowest tertile as a reference. Participants with RHR $<$ 60 bpm might include those with conduction disease, thus they might not be appropriate as the reference group in older adults. Finally, data from the ProFESS trial of 20,165 post-ischemic stroke patients showed that an increased RHR was associated with a lower MMSE score during the follow-up.10 To the best of our knowledge, ours is the first study to investigate the associations of RHR with cognitive decline and dementia in a general population of older adults. Notably, our study showed that an increased RHR was associated with an increased risk of accelerated cognitive decline and dementia, even among individuals without prevalent and incident CVDs.

Several pathways may explain the association of elevated RHR with cognitive decline and dementia. First, an elevated RHR is associated with an increased risk for various CVDs, including stroke, HF, and IHD, which are also risk factors for dementia.11,20–23 Alternatively, an elevated RHR may occur secondary to CVDs because activation of sympathetic nervous system may act as a marker of underlying CVDs. Therefore, the association of higher RHR with dementia might be explained by these underlying CVDs through subsequent cerebral hypoperfusion, microembolism, and cerebrovascular damage. Elevated RHR is also associated with vascular risk factors for both CVDs and dementia, such as hypertension, diabetes, and obesity, possibly driven by sympathetic hyperactivity.7,24 This further suggests that
an elevated RHR, CVDs, and cognitive decline may share a common pathway.\textsuperscript{19,24,25} However, the association remained after the adjustment for vascular risk factors and even after excluding those with prevalent and incident CVDs, suggesting that the association of elevated RHR with dementia and cognitive decline may partially reflect pathophysiological pathways independent from vascular risk factors and CVDs. Nevertheless, we cannot rule out the possibility that subclinical or undiagnosed CVDs may contribute to this association. Interestingly, among participants with CVDs, elevated RHR was not associated with dementia, although it was associated with steeper cognitive decline. This might be partially explained by the competing risk of death occurring before the transition from cognitive decline to incident dementia. Whereas 28% of CVD-free participants died during follow-up, 58% of those with prevalent CVDs died. Abundant evidence suggests that elevated RHR is associated with high mortality.\textsuperscript{26} Therefore, high mortality in participants with elevated RHR and prevalent CVDs might preclude the occurrence of dementia in our population, resulting in the diluted association between elevated RHR and dementia in participants with CVDs. Nevertheless, a steep decline in MMSE score in participants with elevated RHR and CVDs suggests an important role of CVDs in cognitive decline. Second, elevated RHR could result in endothelial dysfunction and arterial stiffness, possibly through pulsatile stress and shear stress on arterial walls.\textsuperscript{27,28} Increased arterial stiffness has been associated with cognitive decline and cerebral small vessel diseases through small vessel damage caused by augmented pulse pressure.\textsuperscript{29–31} Third, the impaired autonomic tone might play an important role in this association. RHR reflects the net effect of sympathetic and parasympathetic nerve activities well, and impaired autonomic tone has been linked with worse cognitive function.\textsuperscript{32} Furthermore, the impaired autonomic tone has been linked with worse cognitive performance independent of cardiovascular risk factors.\textsuperscript{33} Fourth, elevated RHR might reflect a low level of physical activity and physical fitness. Some studies show that a high level of physical activity is associated with lower dementia risk.\textsuperscript{34,35} However, the correlation between RHR and physical activity was weak in our cohort, and the adjustment for physical activity had little impact on the effect estimates. Our data capture physical activity at just a single time point, and life-long physical activity might be more important to determine RHR. In addition, the high prevalence of the use of beta blockers might be associated with a weak correlation. Finally, an elevated RHR may be just a marker of various poor health outcomes, instead of a risk factor. For example, research has shown the association between RHR and non-CVD such as cancer.\textsuperscript{36}

This study showed associations of elevated RHR with accelerated cognitive decline and an increased hazard of dementia in older adults beyond cardiovascular risk factors and CVDs. RHR is simple and easily obtained, so it might help identify potentially high-risk populations for cognitive decline in a wide variety of settings. RHR is also manageable via exercise and medications. A meta-analysis showed that regular exercise, especially yoga and endurance training, could reduce RHR,\textsuperscript{37} while medications such as beta blockers and ivabradine reduce RHR. Thus, RHR might be considered a potential target for intervention. Some randomized controlled trials showed that the intervention to reduce RHR using ivabradine brought some benefits to patients with HF and IHD, suggesting that RHR can be considered a modifiable risk factor for these conditions.\textsuperscript{38–40} Therefore, a reduction in RHR through exercise or medical treatment may be explored as an intervention target to delay cognitive decline. Further intervention studies are needed to prove the potential beneficial effects of RHR reduction on cognitive outcomes.

The major strengths of our study refer to the long follow-up period of a relatively large and well-characterized cohort of older adults. Furthermore, we assessed cognitive function and determined dementia status at multiple follow-up time points. In addition, we assessed RHR based on sinus rhythm using standard 12-lead ECG, to provide a reliable and uniform assessment. However, our study does have several limitations. First, although we could adjust for a range of potential confounders, residual confounding might still play a role due to imperfect measurements of confounders. Second, because a substantial proportion of participants died during the follow-up period, and a high RHR is associated with high mortality, the observed association between RHR and cognitive decline may be affected by selective survival bias, which usually leads to an underestimation of its true associations.\textsuperscript{41} However, this concern is partially resolved by our attempt to identify dementia cases from the patient register, clinical chart, and medical records of deceased participants. Third, the use of the MMSE to assess global cognitive function was another major limitation because the MMSE, as a widely used screening tool for dementia, has disadvantages, such as the ceiling effect, practice effect in repeated assessments, and being insensitive to subtle cognitive changes.\textsuperscript{42} However, this analysis might provide support to the main results concerning dementia as the focus of our study. More sensitive tests of global and domain-specific cognitive function would help us better understand the subtle cognitive changes associated with RHR. Fourth, there was no restriction on food intake, coffee, and smoking before ECG examination, all of which might affect RHR. Finally, participants in central Stockholm had a higher socioeconomic status than the national average. Therefore, caution might be needed when generalizing our study findings to apply to other populations.

6 | CONCLUSIONS

We found that a high RHR is associated with an increased risk for incident dementia and accelerated global cognitive decline in older adults independent of major cardiovascular risk factors and CVDs. Further research is needed to confirm our results and to explore the mechanisms at play in this association. Eventually, such evidence would lead to novel preventive strategies in the field of cognitive aging.

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AUTHOR CONTRIBUTIONS
Yume Imahori, Davide L. Vetrano, Laura Fratiglioni, and Chengxuan Qiu conceived the study design. Laura Fratiglioni and Giulia Grande contributed to initial data acquisition and assessments. Yume Imahori performed the statistical analysis and drafted the manuscript. All authors contributed to the interpretation of the results, critically revised the manuscript, and approved the final draft of this report.

CONFLICTS OF INTEREST
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REFERENCES
1. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer’s disease and other dementias 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):88–106.
2. Prince MJA. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. London: Alzheimer’s Disease International, 2015.
3. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–446.
4. Abete P, Della-Morte D, Gargiulo G, et al. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. Ageing Res Rev. 2014;18:41–52.
5. van Buchem MA, Biessels GJ, Brunner la Rocca HP, et al. The heart-brain connection: a multidisciplinary approach targeting a missing link in the pathophysiology of vascular cognitive impairment. J Alzheimers Dis. 2014;42:5443–5451. Suppl. 4.
6. Cortes-Canteli M, Iadecola C. Alzheimer’s disease and vascular aging: JACC Focus Seminar. J Am Coll Cardiol. 2020;75(8):942–951.
7. Aune D, ØH B, 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(6):526–534.
8. Tadic M, Cuspidi C, Grassi G. Heart rate as a predictor of cardiovascular risk. Eur J Clin Invest. 2018;48(3):e12892.
9. Wang S, Fashanu OE, Zhao D, 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(2):334–340.
10. Böhm M, Cotton D, Foster L, et al. Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. Eur Heart J. 2012;33(22):2804–2812.
11. Kwok C, Loke Y, Hale R, Potter J, Myint P. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. Neurology. 2011;76(10):914–922.
12. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nat Rev Cardiol. 2015;12(5):267–277.
13. Lagergren M, Fratiglioni L, Hallberg IR, et al. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). Aging Clin Exp Res. 2004;16(2):158–168.
14. Calderón-Larrañaga A, Vetrano DL, Onder G, et al. Assessing and measuring chronic multimorbidity in the older population: a proposal for its operationalization. J Gerontol A Biol Sci Med Sci. 2017;72(10):1417–1423.
15. Böhm M, Schumacher H, Teo KK, et al. Resting heart rate and cardiovascular outcomes in diabetic and non-diabetic individuals at high cardiovascular risk analysis from the ONTARGET/TRANSCEND trials. Eur Heart J. 2020;41(2):231–238.
16. Ding M, Fratiglioni L, Johnell K, et al. Atrial fibrillation, antithrombotic treatment, and cognitive aging: a population-based study. Neurology. 2018;91(19):e1732–e1740.
17. Grande G, Marengoni A, Vetrano DL, et al. Multimorbidity burden and dementia risk in older adults: the role of inflammation and genetics. Alzheimers Dement. 2021;17(5):768–776.
18. Haring B, Liu J, Rapp SR, et al. Heart rate, brain imaging biomarkers and cognitive impairment in older (≥63 years) women. Am J Cardiol. 2020;129:102–108.
19. Aune D, Sen A, 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 Metabol Cardiovasc Dis. 2017;27(6):504–517.
20.ampadu J, Morley JE. Heart failure and cognitive dysfunction. Int J Cardiol. 2015;178:12–23.
21. Cannon JA, Moffitt P, Perez-Moreno AC, et al. Cognitive impairment and heart failure: systematic review and meta-analysis. J Cardiac Fail. 2017;23(6):464–475.
22. Wolters FJ, Seguaf RA, Darweesh SKL, et al. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. Alzheimers Dement. 2018;14(11):1493–1504.
23. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. J Am Coll Cardiol. 2019;73(5):612–619.
24. Shen L, Wang Y, Jiang X, Ren Y, Han C, Yang Y. 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.
25. Shigetoh Y, Adachi H, Yamagishi S-i, 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(2):151–155.
26. 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(3):E53–E63.
27. Whelton SP, Blankstein R, Al-Mallah MH, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. Hypertension. 2013;62(3):477–484.

28. Chen S, Li W, Jin C, et al. Resting heart rate trajectory pattern predicts arterial stiffness in a community-based Chinese cohort. Arterioscler Thromb Vasc Biol. 2017;37(2):359–364.

29. Pase MP, Herbert A, Grima NA, Pipingas A, O’Rourke MF. Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. Intern Med J. 2012;42(7):808–815.

30. van Sloten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stehouwer CD. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2015;53:121–130.

31. Alvarez-Bueno C, Cunha PG, Martinez-Vizcaino V, et al. Arterial stiffness and cognition among adults: a systematic review and meta-analysis of observational and longitudinal studies. J Am Heart Assoc. 2020;9(5):e014621.

32. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. J Am Coll Cardiol. 2008;51(18):1725–1733.

33. Mahinrad S, Jukema JW, van Heemst D, et al. 10-Second heart rate variability and cognitive function in old age. Neurology. 2016;86(12):1120–1127.

34. Ravaglia G, Forti P, Lucchesare A, et al. Physical activity and dementia risk in the elderly: findings from a prospective Italian study. Neurology. 2008;70(19):1786–1794. Pt 2.

35. de Bruijn RF, Schrijvers EM, de Groot KA, et al. The association between physical activity and dementia in an elderly population: the Rotterdam Study. Eur J Epidemiol. 2013;28(3):277–283.

36. Pozuelo-Carrascosa DP, Cavero-Redondo I, Lee I, Alvarez-Bueno C, Reina-Gutierrez S, Martinez-Vizcaino V. Resting heart rate as a predictor of cancer mortality: a systematic review and meta-analysis. J Clin Med. 2021;10(7):1354.

37. Reimers AK, Knapp G, Reimers CD. Effects of exercise on the resting heart rate: a systematic review and meta-analysis of interventional studies. J Clin Med. 2018;7(12):503.

38. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875–885.

39. Tardif JC, Ponikowski P, Kahan T. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. Eur Heart J. 2009;30(5):540–548.

40. Borer JS, Fox K, Jailon P, Lerebours G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. Circulation. 2003;107(6):817–823.

41. Weuve J, Tchetgen EJT, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. Epidemiology. 2012;23(1):119.

42. R Nieuwenhuis-Mark RE. The death knoll for the MMSE: has it outlived its purpose? J Geriatr Psychiatry Neurol. 2010;23(3):151–157.

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