Association of cardiovascular risk burden with risk of dementia and brain pathologies: A population-based cohort study

Ruixue Song1,2,3  |  Kuan-Yu Pan4  |  Hui Xu5  |  Xiuying Qi1,2,3  |  Aron S. Buchman6  |  David A. Bennett6  |  Weili Xu1,2,3,7

1 Department of Epidemiology and Biostatistics, School of Public Health, Tianjin Medical University, Tianjin, China
2 Tianjin Key Laboratory of Environment, Nutrition and Public Health, Tianjin, China
3 Center for International Collaborative Research on Environment, Nutrition and Public Health, Tianjin, China
4 Department of Psychiatry, Amsterdam Public Health Research Institute, Amsterdam University Medical Center, Vrije Universiteit, Amsterdam, the Netherlands
5 Big Data and Engineering Research Center, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China
6 Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago, Illinois, USA
7 Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

Correspondence
Weili Xu, Department of Epidemiology & Biostatistics, School of Public Health, Tianjin Medical University, 300070, Qixiangtai Road 22, Heping district, Tianjin, P.R., China.
E-mail: weili.xu@ki.se

David A. Bennett and Weili Xu contributed equally as last authors.

Funding information
Swedish Research Council, Grant/Award Number: No. 2017-00981; National Natural Science Foundation of China, Grant/Award Number: No. 81771519; Konung Gustaf V:s och Drottning Victoria:s Frimurare Foundation, Grant/Award Number: No. 2016-2020; Alzheimerfonden, Grant/Award Number: No. 2017-2019; National Institutes of Health, Grant/Award Numbers: No. R01AG17917, UH2NS100599; European Union’s Horizon 2020 Research and Innovation Programme, Grant/Award Number: No. 667375

Abstract

Introduction: The impact of cardiovascular risk burden on brain pathologies remains unclear. We aimed to examine the association of the Framingham General Cardiovascular Risk Score (FGCRS) with dementia risk, and brain pathologies.

Methods: Within the Rush Memory and Aging Project, 1588 dementia-free participants were assessed on FGCRS at baseline and followed up to 21 years. During the follow-up, 621 participants died and underwent autopsies.

Results: The multi-adjusted hazard ratios (HRs) (95% confidence intervals [CIs]) of FGCRS were 1.03 (1.00–1.07) for dementia and 1.04 (1.01–1.07) for Alzheimer’s disease (AD) dementia. Further, a higher FGCRS was associated with higher gross chronic cerebral infarctions (odds ratio [OR] 1.08, 95% CI 1.02–1.14), cerebral atherosclerosis (OR 1.10, 95% CI 1.03–1.17), and global AD pathology (OR 1.06, 95% CI 1.01–1.12).

Conclusions: A higher FGCRS is associated with an increased risk of dementia and AD dementia. Both vascular and AD pathologies in the brain may underlie this association.

KEYWORDS
Alzheimer’s disease dementia, brain pathology, cohort study, dementia, Framingham General Cardiovascular Risk Score

1 | INTRODUCTION

Due to population aging worldwide, the number of people affected by dementia is increasing, posing one of the greatest challenges for health and social care in the 21st century.1 As an effective treatment for dementia is still not available, identifying modifiable risk factors and promoting the prevention of it has been the priority of public health authorities.1,2

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. Alzheimer’s & Dementia published by Wiley Periodicals LLC on behalf of Alzheimer’s Association.
HIGHLIGHTS

- A higher cardiovascular risk burden is associated with an increased risk of dementia and Alzheimer’s disease dementia.
- In addition to vascular lesions, high cardiovascular risk burden may also lead to neurodegenerative changes in the brain.
- Interventions designed to maintain cardiovascular health may represent significant opportunities for preventing or delaying dementing disorders.

Many studies have investigated the impact of individual cardiovascular risk factors, including old age, diabetes, hypertension, smoking, and hypercholesterolemia on dementia risk, and have shown inconsistent results.\(^3\)–8 Given that these cardiovascular risk factors tend to cluster and interact in an individual, a multivariate risk prediction algorithm incorporating these risk factors is preferable to examine the overall impact of cardiovascular risk burden on dementia. The Framingham General Cardiovascular Risk Score (FGCRS) is a predictive algorithm to assess cardiovascular risk burden and the risk of developing cardiovascular disease (CVD), by incorporating demographics (i.e., age and sex) with traditional cardiovascular risk factors.\(^10\) We have recently reported that FGCRS was associated with cognitive decline.\(^11\) Several other studies have used different composite scores summarizing vascular risk factors (including FGCRS and the dementia risk score) to predict dementia risk.\(^12\)–15 However, uncertainty remains regarding the association of multiple vascular risk factors in combination (such as FGCRS) with the risk of Alzheimer’s disease (AD) dementia.

Although a cardiovascular risk burden has been recognized as an important target to prevent dementia,\(^2\) the mechanisms underlying this association are not well understood. In aging and dementia research, post mortem neuropathological evaluation generally includes a uniform and structured assessment of AD pathology, vascular pathology, Lewy body disease, and other pathologies.\(^16\) Several neuropathological studies have focused on individual cardiovascular risk factor and brain pathologies with some inconsistent findings.\(^17\)–22 Few studies have shown the association of diabetes or hypertension with AD pathology such as neuritic plaques and neurofibrillary tangles.\(^17,21\) However, other studies have shown that diabetes, hypertension, or the Framingham Stroke Risk Profile (including age, systolic blood pressure, current smoking status, antihypertensive medication use, prevalent diabetes, prevalent CVD, and prevalent atrial fibrillation) is related to cerebrovascular pathologies (including cortical infarctions and atherosclerosis stage) but not AD pathology.\(^16\)–20,22 Possible explanations for the discrepancies could be explained by the differences in age of the study populations, study settings, ascertainment of the exposure, assessment of brain pathologies, follow-up time, and major causes of death among these studies. Therefore, the association of vascular risk burden with brain pathology, especially AD pathology, needs to be further clarified in population-based cohort studies with neuropathological examinations.

In the present study, we aimed to examine the association of cardiovascular risk burden assessed by FGCRS with the risk of dementia and AD dementia, and further to explore the relationship of FGCRS with vascular and AD pathologies in the brain.

2 | METHODS

2.1 | Study population

The Rush Memory and Aging Project (MAP) is an ongoing, longitudinal cohort study consisting of older adults from continuous care retirement communities, senior and subsidized housing, church groups, and social service agencies in northeastern Illinois.\(^23\) At the time of enrollment and thereafter, all participants underwent a comprehensive
clinical assessment, neurologic examination, and extensive cognitive testing conducted by trained staff. Details regarding the MAP study design and evaluation protocol have been provided previously.22

Beginning in 1997 through 2019, 2155 participants were annually followed up for a maximum of 21 years. Among all participants, we excluded 115 participants with prevalent dementia, 311 with missing information on FGCRS at study entry, and 282 without data on clinical diagnosis of cognitive status after baseline examination. Thus, 1588 dementia-free participants were included in the current study. Among them, 727 participants died during the follow-up, of whom 621 (85.42%) underwent autopsy (Figure S1 in supporting information).

The study was approved by the Institutional Review Board of Rush University Medical Center and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent and an Anatomic Gift Act was obtained from all participants at baseline as well as a repository consent, which allowed the data to be shared.

2.2 Data collection

Data on demographic characteristics, anthropometrics, and lifestyle factors were collected at study entry.24 Education was recorded as the maximum years of formal schooling. Weight and height were measured and recorded by a trained technician; body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). Grams of alcohol consumption was measured by the average amount of alcohol (including beer, wine, and liquor) consumed per day during the past year. Physical activity was assessed by the total hours of participation per week, based on the National Health Interview Survey. Smoking was categorized as never or former, and current smoker.

Information on medical conditions was also collected based on self-report during the interview and clinical/neurologic examination at study entry.24 Blood pressure was measured twice in the sitting position with a 5-minute interval using a mercury sphygmomanometer. The mean of two values was recorded. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or the use of antihypertensive drugs. Diabetes was defined by any of the following criteria: hemoglobin A1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, random blood glucose ≥200 mg/dL, history of diabetes, or the use of diabetes medication.25 Heart disease was ascertained based on self-report. Clinical stroke diagnosis was made by clinicians through self-report and neurological examination and was dichotomized as probable versus not present. Blood samples were taken at study entry and total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol were measured with a lipid panel. In addition, apolipoprotein E (APOE) alleles genotype was assessed by Polymorphic DNA Technologies and was categorized as ε4 carriers or non-carriers. Additional details about the data collection can be found on the Rush Alzheimer’s Disease Center Resource Sharing Hub at www.radc.rush.edu.

2.3 Framingham General Cardiovascular Risk Score

FGCRS was calculated based on age, sex, smoking, SBP, medication for hypertension, TC, HDL cholesterol, and diabetes for each participant at study entry (as shown in Tables S1 and S2 in supporting information).30 Missing data on TC and HDL cholesterol at study entry (n = 340) was imputed using data within 5 years, if the participants had no dementia. The score was obtained by summing up the points from all these risk factors and was further categorized into tertiles as the lowest, middle, and the highest (risk categories: lowest risk = 4–13, middle risk = 14–16, highest risk = 17–28). A higher FGCRS indicates a greater risk of future cardiovascular events.

2.4 Assessment of mild cognitive impairment, dementia, and AD dementia

Clinical diagnoses of mild cognitive impairment (MCI) and dementia (including AD and non-AD dementia) were made by clinicians at each assessment following a standard procedure, taking into account scores of cognitive tests and clinical judgment of neuropsychologists.26,27 MCI was defined as having cognitive impairment without meeting criteria for dementia.26 Clinical diagnoses of dementia and AD dementia were based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA).27 The diagnosis of AD dementia requires evidence of a meaningful decline in cognitive function relative to a previous level of performance with impairment in memory and at least one other area of cognition.27

2.5 Assessment of brain pathologies

The procedures of post mortem neuropathological evaluation followed recommendations by the National Alzheimer’s Coordinating Center (NACC). Examiners blinded to all clinical data followed a standard protocol for tissue preservation, tissue sectioning, and quantification of pathologic findings, as previous described.28 We also generated a global AD pathology burden that was dichotomized by the median.29 Chronic infarcts, including gross infarcts and microinfarcts;16 cerebral vascular disease pathology including atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy;30 typical hippocampal sclerosis;31 and Lewy bodies16 were categorized as present or absent.

2.6 Statistical analysis

The characteristics of the study population by FGCRS tertiles were compared using one-way analysis of variance and nonparametric tests (chi-square and Wilcoxon rank-sum tests).
Multiple imputation by chained equation was used to impute data for 381 (24.0%) participants with missing values on covariates. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia and AD dementia associated with cardiovascular risk burden (i.e., continuous and categorical FGCRS). Follow-up time was calculated as the time from study entry to dementia diagnosis, death, or the last examination. To further explore the role of APOE ε4 in the association between FGCRS and dementia, an interaction term of FGCRS categories and APOE ε4 status was included in the models first, and then stratified analysis by APOE ε4 was performed. Binomial logistic regression was used to estimate odds ratios (ORs) with 95% CIs of the relationship between FGCRS at baseline and burdens of AD and other brain pathologies. The basic models were adjusted for age, sex, and education. The multi-adjusted models were further adjusted for BMI, heart disease, stroke, alcohol consumption, physical activity, and APOE ε4. Considering that persons with a lower FGCRS might live longer leading to further accrued brain pathology due to other insults to the brain, we additionally adjusted for the time from study entry until death in logistic regression.

In supplementary analysis, we excluded 385 individuals with MCI at study entry, and the association between FGCRS and dementia was checked among cognitively intact participants at study entry (n = 1203). We also repeated the analyses by excluding participants with missing values for covariates. The level of statistical significance was set at a value less than 0.05. All analyses were performed with Stata SE for windows, version 15.0 (StataCorp LP).

3 | RESULTS

3.1 | Characteristics of the study population

Among the 1588 dementia-free participants (1203 [75.76%] women and 385 [24.24%] men; mean [standard deviation (SD)] age, 79.50 [7.45] years), FGCRS ranged from 4 to 28 (mean [SD] score = 15.64 [3.74]). Of all participants, 454 (28.6%) had the lowest cardiovascular risk burden, 475 (29.9%) were in the middle tertile, and 659 (41.5%) belonged to the highest tertile. Compared to participants with the lowest FGCRS tertile, those with the highest were more likely to be older and male; to have lower education, HDL, physical activity, and Mini-Mental State Examination (MMSE); higher BMI and SBP; as well as more likely to have diabetes, heart disease, and stroke at study entry (Table 1).

Participants with incident dementia were more likely to have higher FGCRS compared to those without (Table S3 in supporting information). Compared to the survivors, participants who died were more likely to be male, older, less educated, and have higher FGCRS and more vascular disorders (Table S4 in supporting information).

3.2 | Relationship of cardiovascular risk burden to dementia and AD dementia

Over 10,030 person-years of follow-up (median = 6.00 years, range = 1–21 years), 378 participants developed dementia, including 343 with AD dementia. In both basic- (age, sex, and education) and multi-adjusted (additionally adjusted for BMI, heart disease, stroke, alcohol consumption, physical activity, and APOE ε4) Cox models, FGCRS as a continuous variable was dose-dependently related to dementia (multi-adjusted HR = 1.03, 95% CI 1.00–1.07), and AD dementia (multi-adjusted HR = 1.04, 95% CI 1.01–1.07). Compared to those in the lowest FGCRS tertile, the multi-adjusted HRs (95% CIs) of dementia and AD dementia related to the highest FGCRS were 1.31 (1.00–1.72) and 1.37 (1.03–1.83), respectively (Table 2). No interaction between FGCRS and APOE ε4 on dementia was detected (all P values > 0.05). In the stratified analysis by APOE ε4, the association between higher FGCRS and increased dementia or AD dementia risk was present only among APOE ε4 non-carriers, but not among carriers (Table 3).

3.3 | Relationship of cardiovascular risk burden to brain pathologies

Among 621 participants who underwent autopsies, multi-adjusted logistic regression showed that a higher FGCRS was associated with a higher burden of gross chronic cerebral infarctions (OR 1.08, 95% CI 1.02–1.14), cerebral atherosclerosis (OR 1.10, 95% CI 1.03–1.17), and AD pathologies (OR 1.06, 95% CI 1.01–1.12), but not with other brain pathologies (Table 4).

Compared to those in the lowest FGCRS tertile, ORs (95% CIs) of gross chronic cerebral infarctions, cerebral atherosclerosis, and AD pathology in relation to the highest FGCRS tertile were 1.43 (0.90–2.29), 2.18 (1.28–3.73), and 1.73 (1.09–2.74), respectively (Figure 1).

3.4 | Supplementary analysis

The association of FGCRS with dementia or AD dementia was not substantially altered when we repeated the following analyses: (1) by excluding participants with MCI at study entry (n = 385; Table S5 in supporting information), (2) by excluding participants with missing values (n = 380; Table S6 in supporting information), and (3) by removing age from the covariates in the Cox regression analysis (Table S7 in supporting information). Finally, we performed stratified analysis by sex, and the association between FGCRS and dementia did not differ much between men (HR 1.07, 95% CI 1.00–1.16) and women (HR 1.03, 95% 1.00–1.06).
TABLE 1  Characteristics of the study population by cardiovascular disease risk categories (n = 1588)

| Characteristic                  | Cardiovascular disease risk\(^a\) |                |                |                |  
|---------------------------------|-----------------------------------|----------------|----------------|----------------|----------------|
|                                 | Lowest risk \(n = 454\) (28.6%)   | Middle risk \(n = 475\) (29.9%) | Highest risk \(n = 659\) (41.5%) |  
| Age (years), mean (SD)          | 76.85 (±8.51)                     | 79.93 (±7.01)  | 81.02 (±6.43)  |  
| Women, n (%)                    | 415 (91.4)                        | 373 (78.5)     | 415 (63.0)     | <0.001         |  
| Education (years), mean (SD)    | 15.16 (±3.12)                     | 14.81 (±3.17)  | 14.72 (±3.29)  | 0.023          |  
| BMI, mean (SD)                  | 26.45 (±5.02)                     | 27.21 (±5.46)  | 28.13 (±5.13)  | <0.001         |  
| Alcohol consumption (g), median (IQR) | 1.08 (0.00–5.83) | 1.08 (0.00–6.96) | 0.00 (0.00–4.08) | 0.300          |  
| SBP (mmHg), mean (SD)           | 120.90 (±12.44)                   | 132.04 (±12.95) | 145.82 (±16.52) | <0.001         |  
| HDL-C (mg/dL), mean (SD)        | 66.93 (±17.39)                    | 62.78 (±17.76) | 56.20 (±19.01) | <0.001         |  
| TC (mg/dL), mean (SD)           | 188.90 (±35.22)                   | 192.52 (±38.15) | 194.03 (±46.18) | 0.181          |  
| Smoking status, n (%)           | 265 (58.4)                        | 284 (59.8)     | 377 (57.2)     | 0.064          |  
| Previous smoker                 | 184 (40.5)                        | 181 (38.1)     | 257 (39.0)     | 0.003          |  
| Current smoker                  | 5 (1.1)                           | 10 (2.1)       | 25 (3.8)       | 0.003          |  
| Physical activity, n (%)        | 2.83 (1.10–5.04)                  | 2.92 (1.00–5.00) | 2.27 (0.75–4.08) | <0.001         |  
| FGCRS, mean (SD)                | 11.15 (±1.90)                     | 15.01 (±0.82)  | 19.18 (±1.99)  | <0.001         |  
| APOE ε4 carriers, n (%)         | 94 (24.0)                         | 102 (24.1)     | 124 (20.4)     | 0.262          |  
| Diabetes, n (%)                 | 9 (2.0)                           | 32 (6.7)       | 175 (26.6)     | <0.001         |  
| Hypertension, n (%)             | 161 (35.5)                        | 309 (65.1)     | 605 (91.8)     | <0.001         |  
| Heart disease, n (%)            | 33 (7.5)                          | 58 (12.6)      | 86 (13.9)      | 0.005          |  
| Stroke, n (%)                   | 35 (8.6)                          | 28 (6.4)       | 67 (10.9)      | 0.036          |  
| MMSE, mean (SD)                 | 28.41 (±1.77)                     | 28.15 (±1.84)  | 27.89 (±2.06)  | <0.001         |  
| Incident dementia, n (%)        | 91 (20.0)                         | 119 (25.1)     | 168 (25.5)     | 0.083          |  
| Follow-up time, median (IQR)    | 5.99 (2.82–9.05)                  | 6.00 (2.84–9.06) | 5.02 (2.83–8.31) | 0.114          |  

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; HDL-C, high density lipoprotein cholesterol; IQR, interquartile range; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol.

\(^a\)Risk categories: lowest risk = 4–13, middle risk = 14–16, highest risk = 17–28.

Missing data: BMI = 23, incident stroke = 129, heart disease = 67, alcohol consumption = 1, APOE ε4 carriers = 163.

TABLE 2  Hazard ratios and 95% CIs for the association between levels of FGCRS and dementia in dementia-free participants after multiple imputation (n = 1588)

| FGCRS | No. of subjects | Dementia | AD dementia |
|-------|-----------------|----------|------------|
|       | HR (95% CI)\(^a\) | HR (95% CI)\(^b\) | n         | HR (95% CI)\(^a\) | HR (95% CI)\(^b\) |
| Continuous | 1588            | 378      | 1.03 (1.00–1.06) | 1.03 (1.00–1.07) |
| Categories |                  |          |                |                |
| Lowest risk | 454             | 91       | Reference     | Reference     |
| Moderate risk | 475             | 119      | 1.08 (0.82–1.43) | 1.12 (0.84–1.48) |
| Highest risk  | 659             | 168      | 1.29 (0.99–1.69) | 1.31 (1.00–1.72) |
|               |                  |          | 343          | 1.03 (1.00–1.06) | 1.04 (1.01–1.07) |

\(^a\)Adjusted for age, sex, and education.

\(^b\)Adjusted for age, sex, education, BMI, heart disease, stroke, alcohol consumption, physical activity, and APOE ε4.

Abbreviations: AD, Alzheimer’s disease; APOE, apolipoprotein E; CI, confidence interval; BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; HR, hazard ratio.

4 | DISCUSSION

In this community-based prospective study of older adults, we found that (1) a higher cardiovascular risk burden assessed by FGCRS was associated with an increased risk of dementia and AD dementia in a dose-dependent manner; and (2) a higher FGCRS was related to the presence of both cerebral infarctions and atherosclerosis, and AD pathologies. Our study suggests that in addition to vascular lesions, a
TABLE 3  Hazard ratios and 95% CIs for the association between levels of FGCRS and dementia or AD dementia in dementia-free participants in APOE ε4 non-carriers (n = 1221) and APOE ε4 carriers (n = 367)

| FGCRS                  | APOE ε4 non-carriers | APOE ε4 carriers |
|------------------------|----------------------|------------------|
|                       | No. of subjects      | Dementia         | AD dementia       |
|                       |                      | n  | HR (95% CI)a | HR (95% CI)b | n  | HR (95% CI)a | HR (95% CI)b |
| Continuous Categorical| 1,221                | 256 | 1.06 (1.02–1.10) | 1.05 (1.01–1.09) | 234 | 1.05 (1.01–1.09) | 1.05 (1.01–1.10) |
| Lowest risk            | 340                  | 55  | Reference    | Reference    | 50  | Reference    | Reference    |
| Moderate risk          | 358                  | 79  | 1.21 (0.85–1.71) | 1.25 (0.87–1.77) | 72  | 1.25 (0.87–1.81) | 1.32 (0.91–1.91) |
| Highest risk           | 523                  | 122 | 1.61 (1.15–2.24) | 1.59 (1.13–2.23) | 112 | 1.54 (1.08–2.18) | 1.61 (1.13–2.30) |
| Continuous Categorical| 367                  | 122 | 1.00 (0.95–1.05) | 1.00 (0.95–1.06) | 109 | 1.01 (0.95–1.06) | 1.02 (0.96–1.07) |
| Lowest risk            | 114                  | 36  | Reference    | Reference    | 32  | Reference    | Reference    |
| Moderate risk          | 117                  | 40  | 0.87 (0.54–1.40) | 0.85 (0.52–1.38) | 37  | 0.90 (0.55–1.49) | 0.90 (0.54–1.50) |
| Highest risk           | 136                  | 46  | 0.83 (0.52–1.33) | 0.89 (0.55–1.43) | 40  | 0.90 (0.54–1.50) | 0.96 (0.58–1.60) |

*Adjusted for age, sex, and education.
*Adjusted for age, sex, education, BMI, heart disease, stroke, alcohol consumption, and physical activity.

Abbreviations: AD, Alzheimer’s disease; APOE, apolipoprotein E; CI, confidence interval; BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; HR, hazard ratio.

TABLE 4  Odds ratios and 95% CIs for the association between FGCRS as continuous variable and brain pathologies using logistic regression model (n = 621)

| Pathology                  | OR (95% CI)a        | OR (95% CI)b        | OR (95% CI)c        |
|----------------------------|----------------------|----------------------|----------------------|
| Gross chronic cerebral infarctions | 1.08 (1.02–1.13)   | 1.08 (1.02–1.14)   | 1.08 (1.02–1.14)   |
| Cerebral atherosclerosis   | 1.09 (1.02–1.15)   | 1.10 (1.03–1.16)   | 1.10 (1.03–1.17)   |
| Global AD pathology burden | 1.04 (1.00–1.09)   | 1.06 (1.01–1.12)   | 1.06 (1.01–1.12)   |
| Arteriosclerosis           | 1.01 (0.96–1.06)   | 1.01 (0.96–1.07)   | 1.01 (0.96–1.07)   |
| Cerebral amyloid angiopathy | 1.00 (0.95–1.06)   | 1.01 (0.95–1.07)   | 1.00 (0.94–1.07)   |
| Chronic microinfarcts      | 0.98 (0.93–1.03)   | 0.98 (0.93–1.03)   | 0.97 (0.92–1.03)   |
| Hippocampal sclerosis      | 0.92 (0.85–1.00)   | 0.92 (0.84–1.00)   | 0.91 (0.83–1.00)   |
| Pathologic diagnosis of Lewy body disease | 0.96 (0.90–1.01)   | 0.96 (0.91–1.02)   | 0.96 (0.91–1.02)   |

*Adjusted for age, sex, education, BMI, heart disease, stroke, alcohol consumption physical activity, and APOE ε4.
*Adjusted for age, sex, education, BMI, heart disease, stroke, alcohol consumption physical activity, APOE ε4, and time from study entry till death.

Abbreviations: AD, Alzheimer’s disease; APOE, apolipoprotein E; CI, confidence interval; BMI, body mass index; FGCRS, Framingham General Cardiovascular Risk Score; OR, odds ratio.

high cardiovascular risk burden is also associated with neurodegenerative changes in the brain.

The relationship between individual cardiovascular risk factors and dementia has been well documented, yet the findings have been inconsistent. Three studies showed that older age, smoking, diabetes, hypertension, and hypercholesterolemia were individually associated with dementia.3,5,6 By contrast, one study reported that the decline in serum TC level may be a marker of preclinical dementia.4 Another study also found that TC was significantly lower in both AD dementia and vascular dementia cases.8 Moreover, pooled results from a secondary analysis of the 10/66 population-based cohort study indicated that there was no significant association between smoking and dementia of any kind.7 One longitudinal study examining the association between FGCRS and dementia showed that a higher CVD risk was associated with a greater risk of dementia.13 In the current study, we found that FGCRS was associated with an increased risk of dementia and AD dementia.

Exploring the association between FGCRS and neuropathological changes in the brain is essential to understand the pathogenesis of dementia in relation to cardiovascular risk burden. Although several neuropathological studies have examined the association between cardiovascular risk factors and AD pathologies, the underlying mechanisms have not been entirely understood. Studies showed that diabetes was associated with neuritic plaques and neurofibrillary tangles in the cerebral cortex and the hippocampus,17 and that an elevated blood pressure has also been suggested to compromise vascular integrity, leading to cerebral amyloid angiopathy and impaired amyloid beta (Aβ) clearance from the brain.21 However, the association of diabetes or hypertension with AD pathology was not found in other studies.18–20 Moreover, mid-life vascular risk burden assessed by the Framingham Stroke Risk Profile was predictive of cerebrovascular pathologies, but not AD pathology.22 In addition, another autopsy study showed the association between dementia risk score (incorporating age, sex,
education, SBP, BMI, cholesterol, physical activity, and APOE ε4 status) and cerebral infarcts. However, neuroimaging studies indicated the association of vascular risk factors (including hypertension, hypercholesterolemia, diabetes, vitamin B12 deficiency, depression, smoking, alcohol abuse, ischemic attack, stroke, obesity, and cardiovascular disorders) with AD biomarkers in cerebrospinal fluid, and the relation of dementia risk score to both neurodegeneration and vascular lesions. Accumulating evidence has suggested the impact of vascular risk factors on both vascular and degenerative brain changes.

In the current study, we found that a higher FGCRS was not only associated with higher gross chronic cerebral infarctions and cerebral atherosclerosis, but also AD pathology. These findings support our recent report that a higher FGCRS was related to smaller volumes of the hippocampus, total gray matter, and total brain volumes (i.e., neurodegenerative markers), but a greater white matter hyperintensities volume (i.e., a marker of vascular lesions).

A cerebral infarction is an area of necrotic tissue in the brain resulting from a blockage or narrowing in the arteries supplying blood and oxygen to the brain, while cerebral atherosclerosis is a type of atherosclerosis with build-up of plaque in the blood vessels of the brain that may cause infarctions leading to stroke as well as vascular dementia. It is well known that vascular risk burden is related to stroke, thus it is not surprising that we found high vascular risk burden in relation to dementia risk. However, emerging evidence suggests that brain vascular lesions (such as infarcts and atherosclerosis) caused by cardiovascular risk factors might disclose the expression of AD pathology in old age. Vascular and neurodegenerative brain damage may overlap and develop in parallel, leading to more severe cognitive disorders than either single pathological process. Mixed pathologies are very common in the aging brain. Indeed, in this study, we found a significant association between high vascular risk burden and AD pathologies, supporting the notion that both brain vascular and neurodegenerative lesions may underlie the vascular risk burden–dementia association. Therefore, it is crucial for public health researchers to identify older adults with higher vascular burden for the prevention of clinical consequences (i.e., dementia) using tools measuring vascular risk burden. FGCRS was developed to identify clinical peripheral vascular events and has been extended to identify individuals at risk for stroke. However, there is a paucity of studies that have examined to what extent FGCRS may predict brain pathologies. Our results indicate that cardiovascular risk burden may contribute to not only vascular but also AD pathologies, suggesting that FGCRS may also identify older adults at risk for accumulating AD pathologies in the brain.

The biological mechanisms contributing to the link of FGCRS to both vascular and AD pathologies may involve complex processes. Exposure to cardiovascular risk factors might accelerate cognitive decline by causing cerebral hypoperfusion, hypoxia, emboli, or infarcts. In addition, cardiovascular risk factors have divergent effects on cerebral blood flow velocity, which may contribute to dementia due to vascular brain lesions. Furthermore, epidemiological and clinicopathological studies have shown that multiple larger infarcts are more commonly present in mixed dementia (i.e., AD dementia plus vascular dementia). Meanwhile, vascular impairment accompanies or even precedes the development of AD pathology, which plays a dominant role in the pathogenesis of AD. Blood-brain barrier dysfunction and cerebral hypoperfusion play a central and pivotal role in the heterogeneous etiological profile of AD. Chronic cerebral hypoperfusion and vascular events may trigger AD pathological processes in the brain through mitochondrial damage, oxidative stress, reduced adenosine triphosphate synthesis, and impaired cellular metabolism. This process particularly occurs in the brain areas that are most susceptible to brain hypoperfusion. At the same time, further circulation defects caused by hypoxia change the peptide clearance rate, promoting brain deposition of Aβ and, consequently AD dementia occurrence. Therefore, some researchers even consider that AD dementia is mainly a cerebrovascular injury rather than a neurodegenerative disorder.

APOE ε4 is a well-established genetic risk factor for dementia. Several studies have examined the role of APOE ε4 in the association...
between vascular risk factors and dementia, and results have been mixed. Two studies reported that diabetes and smoking were associated with a higher dementia and AD dementia risk in APOE ε4 carriers.50,51 One study found that high cholesterol in late life was associated with a higher AD dementia risk in APOE ε4 carriers;52 while in another study, this association was observed in APOE ε4 non-carriers.53 In the current study, we found that the association between FGCRS and dementia/AD dementia was present among APOE ε4 non-carriers, but not among carriers. This can be explained by the following reasons. First, APOE ε4 carriers might have been excluded at study entry because they were more likely to develop dementia,54 whereas APOE ε4 non-carriers might require further physiological insults, such as cardiovascular risk burden, to bring them to the threshold for expressing dementia/AD dementia. Second, similar to a previous study assessing the interaction between APOE genotype and different vascular risk to the occurrence of dementia and AD dementia among old people,55 we also did not find a significant interaction between cardiovascular risk burden and APOE ε4 status on dementia/AD dementia. However, the smaller sample size of APOE ε4 carriers (n = 367) in our study might have led to a lack of statistical power. Thus, the role of ε4 in the FGCRS–dementia associations needs further investigation.

Notable strengths of our study involve the long-term follow-up, a relatively large sample size, and the access to brain pathological data among deceased participants. Furthermore, by generating a composite score using multiple cardiovascular risk factors, we were able to study the risk of dementia in relation to the overall cardiovascular risk burden. However, several limitations need to be pointed out. First, our participants were volunteers who were not randomly selected from the community, and about 76% of participants were women in this study. However, the association between FGCRS and dementia was similar in men and in women. Second, 13.09% of participants dropped out mainly due to poor health conditions, thus, the association of FGCRS with dementia and brain pathologies in this study might have been underestimated. Third, several medical conditions and lifestyle behaviors were self-reported retrospectively, which could be subject to measurement error. Fourth, caution is required when generalizing our findings, especially the results regarding the brain pathology, to younger populations because the mean age of our population was 79.5 years. Finally, residual confounding due to unmeasured factors could not be completely ruled out.

In conclusion, our study provides new evidence that a higher cardiovascular burden evaluated by FGCRS is associated with an increased risk of dementia and AD dementia, and both vascular lesions and neurodegeneration may underlie this association. Our findings underscore the detrimental effect of a high cardiovascular risk burden on the brain. Interventions designed to maintain cardiovascular health may represent important opportunities for the prevention of dementing disorders.

ACKNOWLEDGMENTS

The authors express their gratitude to the participants and staff involved in data collection and management in the Rush Memory and Aging Project. Weili Xu received grants from the Swedish Research Council (No. 2017-00981), the National Natural Science Foundation of China (No. 81771519), Demensfonden, the Konung Gustaf V:s och Drottning Victorias Frimurare Foundation (No. 2016-2020), and Alzheimerfonden (2017-2019). Bennett received grants from the National Institutes of Health (No. R01AG17917 and UH2NS100599). This project is part of CoSTREAM (www.costream.eu) and received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No. 667375.

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

CONFLICTS OF INTEREST

The authors report no disclosures relevant to the manuscript.

REFERENCES

1. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet. 2017;390:2673-2743.
2. Klivpeitlo M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol. 2018;14:653-666.
3. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64:277-281.
4. Stewart R, White LR, Xue QL, Launer LJ. Twenty-six-year change in total cholesterol levels and Incident dementia: the Honolulu-Asia Aging Study. Arch Neurol. 2007;64:103-107.
5. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA Neurol. 2017;74:1246-1254.
6. Knopman DS, Gottesman RF, Sharrett AR, et al. Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: the Atherosclerosis Risk in Communities Study. Alzheimers Dement. 2018;14:1406-1415.
7. Otuyama LJ, Oliveira D, Locatelli D, et al. Tobacco smoking and risk for dementia: evidence from the 10/66 population-based longitudinal study. Aging Ment Health. 2019;24(11):1796-1806. 1-11.
8. Liu H, Reynolds GP, Wei X. Uric acid and high-density lipoprotein cholesterol are differently associated with Alzheimer’s disease and vascular dementia. J Alzheimers Dis. 2020;73:1125-1131.
9. Poortinga W. The prevalence and clustering of four major lifestyle risk factors in an English adult population. Prev Med. 2007;44:124-128.
10. D’Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117:743-753.
11. Song R, Xu H, Dintica CS, Pan KY, Qi X, Buchman AS, et al. Associations between cardiovascular risk, structural brain changes, and cognitive decline. J Am Coll Cardiol. 2020;75:2525-2534.
12. Li J, Ogrodnik M, Devine S, Auerbach S, Wolf PA, Au R. Practical risk score for 5-, 10-, and 20-year prediction of dementia in elderly persons: framingham Heart Study. Alzheimers Dement. 2018:14:35-42.
13. Zeki Al Hazzouri A, Haan MN, Neuhaus JM, et al. Cardiovascular risk score, cognitive decline, and dementia in older Mexican Americans: the role of sex and education. J Am Heart Assoc. 2013;2:e004978.
14. de Oliveira F, Bertolucci PF, Chen E, Smith M. Assessment of risk factors for earlier onset of sporadic Alzheimer’s disease dementia. Neurology India. 2014;62:625.
15. LiSS, Zheng J, Mei B, Wang HY, Zheng M, Zheng K. Correlation study of Framingham risk score and vascular dementia: an observational study. Medicine (Baltimore). 2017;96:e8387.
16. Wilson RS, Boyle PA, Yu L, Barnes LL, Schneider JA, Bennett DA. Lifespan cognitive activity, neuropathologic burden, and cognitive aging. Neurology. 2013;81:314-321.
17. Beere MS, Silverman JM, Davis KL, et al. Type 2 diabetes is negatively associated with Alzheimer’s disease neuropathology. J Gerontol A Biol Sci Med Sci. 2005;60:471-475.
18. Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology. 2006;67:1960-1965.
19. Alafuzoff I, Aho L, Helisalmi S, Mannenmaa A, Soininen H. Beta-amyloid deposition in brains of subjects with diabetes. Neuropathol Appl Neurobiol. 2009;35:60-68.
20. Wang LY, Larson EB, Sonnen JA, et al. Blood pressure and brain injury in older adults: findings from a community-based autopsy study. J Am Geriatr Soc. 2009;57:1975-1981.
21. Shah NS, Vidal JS, Masaki K, et al. Midlife blood pressure, plasma beta-amyloid, and the risk for Alzheimer disease: the Honolulu Asia Aging Study. Hypertension. 2012;59:780-786.
22. Conner SC, Pase MP, Carneiro H, et al. Mid-life and late-life vascular risk factor burden and neuropathology in old age. Ann Clin Transl Neurol. 2019;6:2403-2412.
23. Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious Orders Study and Rush Memory and Aging Project. J Alzheimers Dis. 2018;64:S161-S189.
24. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the rush Memory and Aging Project. Curr Alzheimer Res. 2012;9:646-663.
25. American Diabetes A. 2. Classification and diagnosis of diabetes: standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41:S13-S27.
26. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. Neurology. 2002;59:198-205.
27. Bennett DA, Schneider JA, Aggarwal NT, et al. Decision rules guiding the clinical diagnosis of Alzheimer’s disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. Neuroepidemiology. 2006;27:169-176.
28. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006;66:1837-1844.
29. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Neuropil-billary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. Arch Neurol. 2004;61:378-384.
30. Arvanitakis Z, Capuano AW, Lamar M, et al. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. Neurology. 2018;91:e517-e525.
31. Crystal HA, Schneider JA, Bennett DA, Leurgans S, Levine SR. Associations of cerebrovascular and Alzheimer’s disease pathology with brain atrophy. Curr Alzheimer Res. 2014;11:309-316.
32. Hooshmand B, Polvikoski T, Kivipelto M, et al. CAIDE Dementia Risk Score, Alzheimer and cerebrovascular pathology: a population-based autopsy study. J Intern Med. 2018;283:597-603.
33. Bos I, Vos SJH, Schindler SE, et al. Vascular risk factors are associated with longitudinal changes in cerebrospinal fluid tau markers and cognition in preclinical Alzheimer’s disease. Alzheimers Dement. 2019;15:1149-1159.
34. Vuorinen M, Spulber G, Damangir S, et al. Midlife CAIDE dementia risk score and dementia-related brain changes up to 30 years later on magnetic resonance imaging. J Alzheimers Dis. 2015;44:93-101.
35. Stephen R, Liu Y, Ngando T, et al. Associations of CAIDE Dementia Risk Score with MRI, PIB-PET measures, and cognition. J Alzheimers Dis. 2017;59:695-705.
36. O’Brien JT, Firbank MJ, Ritchie K, et al. Association between midlife dementia risk factors and longitudinal brain atrophy: the PREVENT-Dementia study. J Neurol Neurosurg Psychiatry. 2020;91:158-161.
37. Sweeney MD, Kislir K, Montagne A, Toga AW, Zlokovic BV. The role of brain vasculature in neurodegenerative disorders. Nat Neurosci. 2018;21:1318-1331.
38. Rahimi J, Kovacs GG. Prevalence of mixed pathologies in the aging brain. Alzheimers Res Ther. 2014;6:82.
39. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nat Rev Cardiol. 2015;12:267-277.
40. Pase MP, Grima NA, Stough CK, Sloe a, Pipingas A. Cardiovascular disease risk and cerebral blood flow velocity. Stroke. 2012;43:2803-2805.
41. Jellinger KA. The enigma of mixed dementia. Alzheimers Dement. 2007;3:40-53.
42. Wardlaw JM, Doublt F, Armitage P, et al. Lacunar stroke is associated with diffuse blood-brain barrier dysfunction. Ann Neurol. 2009;65:194-202.
43. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer’s disease—lessons from pathology. BMC Med. 2014;12:206.
44. de la Torre JC. Is Alzheimer’s disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol. 2004;3:184-190.
45. de la Torre JC. Pathophysiology of neuronal energy crisis in Alzheimer’s disease. Neurodegener Dis. 2008;5:126-132.
46. Bink DI, Ritz K, Aronica E, van der Weerd L, Daemen MJ. Mouse models to study the effect of cardiovascular risk factors on brain structure and cognition. J Cereb Blood Flow Metab. 2013;33:1666-1684.
47. Dotti CG, De Strooper B. Alzheimer’s dementia by circulation disorders: when trees hide the forest. Nat Cell Biol. 2009;11:114-116.
48. Farkas E, Luiten PG. Cerebral microvascular pathology in aging and Alzheimer disease. Prog Neurobiol. 2001;64:575-611.
49. Royall DR. Alzheimer disease as a vascular disorder: nosological evidence. Stroke. 2002;33:2147-2148. author reply 47-8.
50. Rusanen M, Rovio S, Ngando T, et al. Midlife smoking, apolipoprotein E and risk of dementia and Alzheimer’s disease: a population-based cardiovascular risk factors, aging and dementia study. Dement Geriatr Cogn Disord. 2010;30:277-284.
51. Tang Y, Li YM, Zhang M, Chen YQ, Sun Q, Epsilon3/4 genotype of the apolipoprotein E is associated with higher risk of Alzheimer’s disease in patients with type 2 diabetes mellitus. Gene. 2019;703:65-70.
52. Borroni B, Grassi M, Costanzi C, Archetti S, Caimi L, Padovani A. APOE genotype and cholesterol levels in Lewy body dementia and Alzheimer disease: investigating genotype-phenotype effect on disease risk. Am J Geriatr Psychiatry. 2006;14:1022-1031.
53. Evans RM, Emsley CL, Gao S, et al. Serum cholesterol, APOE genotype, and the risk of Alzheimer’s disease: a population-based study of African Americans. Neurology. 2000;54:240-242.
54. DeMichele-Sweet MA, Sweet RA. Genetics of psychosis in Alzheimer’s disease: a review. J Alzheimers Dis. 2010;19:761-780.
55. Qiu C, Xu W, Winblad B, Fratiglioni L. Vascular risk profiles for dementia and Alzheimer’s disease in very old people: a population-based longitudinal study. J Alzheimers Dis. 2010;20:293-300.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Song R, Pan K-Yu, Xu H, et al. Association of cardiovascular risk burden with risk of dementia and brain pathologies: A population-based cohort study. *Alzheimer’s Dement*. 2021;17:1914–1922. https://doi.org/10.1002/alz.12343