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Mixed brain lesions mediate the association between cardiovascular risk burden and cognitive decline in old age: a population-based study

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ABSTRACT

INTRODUCTION The underlying pathological mechanisms linking cardiovascular burden to cognitive decline remain unclear.

METHODS We investigated the associations of the Framingham General Cardiovascular Risk Score (FGCRS), *APOE*-ε4, and brain structure with the Mini-Mental State Examination (MMSE) decline using the 9-year follow-up data from SNAC-K (n=2189,age≥60) and the embedded MRI (n=448) studies. Volumes of white-matter hyperintensities (WMHs), total grey matter, ventricles, and hippocampus were assessed in the MRI sample.

RESULTS A higher FGCRS was associated with faster MMSE decline in young-old people (60-72) but not in old-old (≥78). Larger volumes of cerebral WMHs and ventricles, and smaller volumes of total grey matter and hippocampus were all associated with accelerated MMSE decline (P<0.01); these associations were stronger among *APOE*-ε4 carriers than non-carriers. Simultaneously entering multiple brain lesion markers as mediators in the model substantially attenuated the association between FGCRS and MMSE decline.

DISCUSSION The effect of cardiovascular risk burden on cognitive deterioration in old age is largely mediated by mixed brain lesions.

KEYWORDS Framingham General Cardiovascular Risk Score; Magnetic Resonance Imaging; Cerebral small-vessel disease; Cognitive decline; Aging; Population study.

1 INTRODUCTION

Cardiovascular risk burden, assessed by the Framingham general cardiovascular risk score (FGCRS) [1], has been associated with cognitive decline in middle-aged adults [2,3], but whether this association remains in old age, especially among very old people, requires further investigation. Likewise, the underlying mechanisms linking cardiovascular risk burden with cognitive decline are not fully understood.

Cardiovascular risk factors cause brain lesions such as white-matter hyperintensities (WMHs), and global and regional brain atrophy [4,5]. The extent of WMHs and brain atrophy has been associated with cognitive decline and dementia in middle-aged and older people [6,7]. Therefore, it is conceivable that the link of cardiovascular risk burden with cognitive decline in aging is likely to be mediated by structural brain properties. A mediating effect of markers of brain lesions (e.g., WMHs and brain atrophy) on the associations between diabetes and poor cognitive performance was indeed documented in cross-sectional studies [8,9]. Yet, population-based longitudinal data exploring the role of structural brain characteristics in the association between cardiovascular risk burden and cognitive decline are sparse.

In addition, WMHs may contribute to cognitive decline through cortical thinning and disruption of cortical networks [10]. The effects of cardiovascular risk factors on brain structure may begin with white-matter lesions of presumed vascular origin, and then proceed to morphological changes of neurodegeneration [11]. Nevertheless, it remains unknown whether the effects of cardiovascular risk burden on neurodegeneration, as indicated by imaging markers of global and regional brain atrophy, are secondary to cerebral microvascular lesions (e.g., WMHs). Furthermore, previous studies have suggested interactive effects of individual cardiovascular risk factors with the *APOE*-ε4 allele on brain degenerative pathologies and cognitive decline [12,13], but the potential role of the ε4 allele in modifying

the associations of cardiovascular risk burden and markers of brain structure with cognitive decline has not yet been explored.

In this population-based longitudinal study of older adults, we seek to first verify the associations of FGCRS and structural brain properties (i.e., the volume of WMHs, total grey matter, ventricles, and hippocampus) with cognitive decline. Then, we explore to what extent the association between FGCRS and cognitive decline is mediated by markers of cerebral microvascular and atrophic lesions. Finally, we investigate whether the *APOE*-ε4 allele modifies the associations of FGCRS, structural brain properties, and cognitive decline.

2 METHODS

2.1 Study participants

Participants were from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), a multidisciplinary longitudinal study of aging and health, in an area of central Stockholm, Sweden [14]. The SNAC-K sample consisted of 11 age groups ranging from 60 to 99+ years. The follow-up interval was 6 years for younger age groups (age 60, 66, and 72 years), and 3 years for the older age groups (age 78+ years). This sampling and follow-up procedure was used due to more rapid health changes and higher attrition rates in the older than younger cohorts. By February 2013, one follow-up assessment for younger age groups and three follow-up examinations for older age groups had been completed.

Of all 4590 persons who were eligible to participate in SNAC-K, 3363 (73.3%) were examined at baseline (March 2001-June 2004) [14]. Of these, we excluded 1174 subjects due to prevalent dementia (n=311), the Mini-Mental State Examination (MMSE) score <24 (n=68), missing FGCRS (n=126), and having no follow-up MMSE scores (n=669, of these, 338 were due to death). Thus, this study included 2189 persons who were free of dementia, had a baseline MMSE score ≥24, and had at least one follow-up MMSE assessment.

During September 2001-October 2003, non-institutionalized, non-disabled, and non-demented participants in SNAC-K were invited to undertake structural brain MRI scans, and 555 persons were scanned at baseline [15]. Of these, we excluded 76 subjects due to dementia or MMSE score <24 (n=6), missing FGCRS (n=8) or lack of follow-up MMSE data (n=62). We further excluded 31 subjects for whom we were not able to reliably assess brain structure due to brain disorders. Thus, the analytical SNAC-K MRI sample included 448 subjects. Supplemental Figure S1 shows a flowchart of the study population.

2.2 Standard protocol approvals, registrations, and patient consents

All parts of the SNAC-K project were approved by the Regional Ethical Review Board in Stockholm. We obtained written informed consent from participants or from informants for cognitively impaired persons.

2.3 Data collection at baseline

At baseline, data on demographics, lifestyles, medical history, and current use of medications were collected through interviews and clinical examinations [14]. Information on health history for all participants was also obtained from the Stockholm inpatient register that covers all hospitalizations in Stockholm since 1969 [14,15]. Smoking was categorized as never or former smoking vs. current smoking. Diabetes was defined as having a self-reported history of diabetes, records of diabetes in the inpatient register, use of antidiabetic drugs, or glycated haemoglobin ≥6.5% [16]. The *APOE* gene was dichotomized into any ε4 allele vs. no ε4 allele. We classified alcohol consumption into no or occasional, light-to-moderate, or heavy drinking. Physical activity was defined as participating in physical exercise several times per week or every day [15].

2.4 Assessment of cardiovascular risk burden

We assessed cardiovascular risk burden with the sex-specific FGCRS that includes age, systolic blood pressure, antihypertensive treatment, high-density lipoprotein cholesterol, total cholesterol, smoking, and diabetes, in which a weighted sex-specific point is given to each factor [1]. Total FGCRS is obtained by summing up the points from all these risk factors. A higher FGCRS indicates a greater risk for future cardiovascular events. Because data on high-density lipoprotein cholesterol were available only in individuals with total cholesterol ≥6.5 mmol/l in our study, this variable was not included in the algorithm.

2.5 MRI acquisition and measurements

MRI acquisition and reading protocol

Participants were scanned on a 1.5T MR scanner (Philips Intera, The Netherlands) [15]. The protocol included an axial 3D T1-weighted fast field echo (FFE) [repetition time (TR) 15 ms, echo time (TE) 7 ms, flip angle (FA) 15°, field of view (FOV) 240, 128 slices with slice thickness 1.5 mm and in-plane resolution 0.94×0.94 mm, no gap, matrix 256×256], and an axial turbo fluid-attenuated inversion recovery (FLAIR) (TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, ETL 21, FOV 230, 22 slices with slice thickness 5mm and in-plane resolution 0.90×0.90 mm, gap 1 mm, matrix 256×256) sequences.

MRI markers of structural brain characteristics

Global WMH volume was measured using the Lesion Segmentation Toolbox in SPM 8 on the fluid-attenuated inversion recovery images [15]. All WMH maps were visually scrutinized and manually corrected for greater volumetric precision in MRIcroN. The volumes of ventricles and hippocampus were manually assessed on T1-weighted images following a standardized protocol [15]. Briefly, hippocampal volume was manually delineated in both hemispheres using the ROI tool in HERMES MultiModality. The volumes of the lateral and

third ventricles were estimated by the semiautomatic tool of Region Growing in HERMES MultiModality [15]. The T1 brain images were segmented into grey matter, white matter, and cerebrospinal fluid using SPM12b in MATLAB R2012b (MathWorks Inc., MA, USA). All segments were visually inspected by a specialist in the neuroimaging analysis (G.K.). WMH volume was log-transformed owing to skewed distribution. All MRI measurements were adjusted by total intracranial volume [17].

2.6 Assessment of global cognitive function and dementia

Global cognitive functioning was assessed with MMSE at baseline for all participants, at 3-, 6-, and 9-year follow-ups for participants aged ≥78 years, and at 6-year follow-up for those aged 60-72 years. Dementia was diagnosed by the examining physicians according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [18,19].

2.7 Statistical analysis

Baseline characteristics of study participants by whether or not they underwent MRI scan were compared using t-test for continuous variables with normal distribution, Wilcoxon-Mann-Whitney test for continuous variables not normally distributed, or chi-square test for categorical variables.

Linear mixed-effects models were used to analyze the association of FGCRS and MRI markers to MMSE scores. Each model included a predictor (FGCRS or MRI markers) at baseline, follow-up time, and an interaction term between the predictor and follow-up time. The estimated effect for the predictor reflects the cross-sectional impact of this factor on MMSE score at baseline, the effect of follow-up time reflects annual MMSE change, and the estimated effect for the interaction term reflects the additional impact of the predictor on annual change in MMSE score. Because we focused on the impact of FGCRS and brain MRI

markers on MMSE change, we only reported parameters for the interaction of FGCRS or MRI markers with follow-up time from two linear mixed-effects models. Model 1 was adjusted for demographics, and model 2 was adjusted for additional cardiovascular factors not included in the FGCRS, and cerebrovascular diseases developed over the follow-up period. Multiplicative interactions were tested by simultaneously including two predictive variables (e.g., FGCRS and *APOE*-ε4 status), follow-up time, and their cross-product term in the same model.

Structural equation modelling was used to quantify the mediating effect of brain structures on the association between FGCRS and MMSE decline, and to identify the pathways linking FGCRS to MMSE decline. Specifically, the model involved two components. First, two latent factors (latent intercept and latent slope) were extracted from the measurement component using MMSE measurements at baseline, 3-, 6-, and 9-year follow-ups: the latent intercept represented an individual's baseline MMSE score, while the latent slope represented the MMSE score changes over time. Second, the structural component reflected relationships among FGCRS, MRI markers, and change of MMSE score. In the structural component, we quantified the degree to which the brain MRI markers mediated the association between FGCRS and MMSE change. We first estimated the association between FGCRS and MMSE change over the follow-up periods by linking FGCRS to the latent slope, and further tested the mediating role of the structural brain MRI markers in their associations. Stata 13.0 (Stata Corp., College Station, Texas, USA) and SAS 9.3 (SAS Institute, Cary, NC, USA) for Windows were used for all analyses.

3 RESULTS

3.1 Characteristics of participants at baseline

Overall, the mean age of the 2189 participants was 71.7 years (SD, 9.9), 63.5% were women, and 38.0% obtained a university degree. FGCRS ranged from 6 to 31. Compared with persons

who did not undergo the MRI scan (n=1741), the MRI participants (n=448) were younger and more likely to have higher education, high total cholesterol, physical activity, lower diastolic blood pressure, a higher MMSE score, and to consume light-to-moderate alcohol, but the two groups did not differ significantly in sex, FGCRS, current smoking, systolic blood pressure, diabetes, body mass index, use of antihypertensive drugs, or *APOE*-ε4 status (all $P>0.05$) (**Table 1**).

(Insert Table 1 here)

3.2 FGCRS, *APOE*-ε4 allele, and MMSE change in the SNAC-K total sample

In the SNAC-K total sample (n=2189), after adjusting for demographics, the MMSE score declined by an average annual rate of 0.37 points (95% confidence interval [CI] -0.40, -0.34) during the follow-up period; the average annual decline rate was 0.17 point (95% CI -0.20, -0.15) in young-old (age 60-72 years) and 0.70 point (95% CI -0.81, -0.65) in old-old (≥78 years) groups.

Overall, per 1-point increment in FGCRS was significantly associated with a 0.03 point faster annual decline in MMSE score (β-coefficient -0.03; 95% CI -0.04, -0.02). There was a significant interaction between age strata (60-72 vs. ≥78 years) and FGCRS on MMSE decline ($P_{interaction}<0.01$). Further analysis stratifying by age strata suggested that in young-old group, the FGCRS was significantly associated with an annual faster MMSE decline (β-coefficient, -0.012; 95% CI, -0.018, -0.006), whereas in old-old group, the FGCRS was associated with a slower average annual decline in MMSE (β-coefficient, 0.030; 95% CI, 0.003, 0.057). When FGCRS was analysed as quartiles, the pattern of association between FGCRS and average annual changes in MMSE score was similar to that of FGCRS being analyzed as a continuous variable in the total sample, young-old group, and old-old group, respectively (**Figure 1A-C**). The results were virtually unchanged when further controlling for cardiovascular factors that were not included in FGCRS and cerebrovascular diseases

developed during the follow-up periods. Carrying an *APOE*-ε4 allele was significantly associated with a faster annual MMSE decline, even in the fully-adjusted model (β-coefficient -0.09; 95% CI -0.16, -0.02). No statistical interaction between age strata and *APOE*-ε4 on MMSE decline was detected.

(Insert Figure 1 here)

3.3 Brain MRI markers, *APOE*-ε4 allele, and MMSE change in the MRI sample

In the SNAC-K MRI sample (n=448), after adjusting for demographics, the MMSE score declined by an average of 0.28 points per year during the follow-up period (95% confidence interval [CI] -0.33, -0.23). Larger volumes of WMHs and ventricles, and smaller volumes of total grey matter and hippocampus at baseline were associated with a greater annual MMSE decline (**Table 2, Model 1**). These associations remained unchanged after further adjusting for other potential confounders (**Table 2, Model 2**). There was no significant association of *APOE*-ε4 with any of the brain MRI markers at baseline.

After controlling for demographics, there were significant interactive effects of *APOE*-ε4 with WMH volume ($P_{interaction}<0.01$) and ventricular volume ($P_{interaction}<0.01$) for annual MMSE decline, but the interaction was not significant for total grey-matter ($P_{interaction}=0.08$) or hippocampal volumes ($P_{interaction}=0.11$). Stratified analysis by *APOE* status showed stronger associations of brain MRI markers with annual MMSE decline among the ε4 allele carriers than non-carriers, although the associations were statistically evident in both carriers and non-carriers (**Table 2**).

(Insert Table 2 here)

3.4 Mediating effects of brain MRI markers on the associations between FGCRS and MMSE change in the MRI sample

A higher baseline FGCRS was associated with a faster annual MMSE decline (β-coefficient -0.019; 95% CI -0.030, -0.008). When volumes of WMHs, total grey matter, ventricles, and

hippocampus were entered into the model separately, the direct association between FGCRS and annual MMSE decline was attenuated (**Table 3**). Stratifying the analysis by *APOE*-ε4 status suggested that the association between FGCRS and annual MMSE decline was stronger among the ε4 allele carriers than non-carriers (**Table 3**).

(Insert Table 3 here)

When entering WMH volume into the model together with either total grey-matter volume or ventricular volume, the direct association of FGCRS with an annual rate of MMSE decline virtually disappeared (**Figure 2**). FGCRS showed a stronger association with WMH volume (standardized β-coefficient, 0.39) than with either total grey-matter (-0.29) or ventricular (0.20) volume. The extent of associations of WMH, total grey-matter, and ventricular volumes with annual rate of MMSE decline was comparable. In addition, the association of FGCRS with markers of brain atrophy (total grey-matter or ventricular volume) remained statistically significant even after taking the mediating effect of WMH volume into account.

(Insert Figure 2 here)

3.5 Additional analyses

Similar results were obtained when 675 persons with a history of cardiovascular diseases (i.e., coronary heart diseases, heart failure, atrial fibrillation, and cerebral vascular diseases) were excluded from the analytical samples (because FGCRS was initially developed for predicting cardiovascular events among individuals who were free of cardiovascular diseases), when 37 people with silent cerebral infarct were excluded, when 134 persons who developed incident dementia during the follow-up periods (20 patients occurred in the MRI sample) were excluded, when 60 persons with a baseline MMSE score <26 were excluded (8 in the MRI sample), when a robust estimation method was used in the linear mixed-effects models, or when the analyses were performed in a subgroup of people with data available on high-

density lipoprotein cholesterol, in which this cholesterol component could be included in FGCRS (data not shown).

4 DISCUSSION

The main findings from this long-term community-based longitudinal study of older Swedish adults can be summarized as follows: (1) a higher FGCRS was associated with accelerated decline in global cognitive function in young-old adults (age 60-72 years) independent of development of clinical stroke, but not in old-old people (≥78 years); (2) larger volumes of WMHs and ventricles, and smaller volumes of total grey-matter and hippocampus were associated with a faster global cognitive decline, and these associations were stronger among *APOE*-ε4 carriers than for non-carriers; and (3) the association of FGCRS with global cognitive decline was largely accounted for by WMH volume, together with either total grey-matter volume or ventricular volume.

The relation of cardiovascular risk factors to cognitive impairment and dementia has been well established [20]. There is increasing interest in the association between clustering of cardiovascular risk factors and cognitive deterioration in aging. A systematic review showed that an increasing cardiovascular risk score was associated with an increased risk of cognitive decline or dementia [21]. Previous studies have shown that FGCRS is associated with cognitive decline in middle-aged adults [2,3,21]. Our data extend previous observations by showing that the association also existed in young-old people independent of development of clinical cerebrovascular disease and silent infarcts. This indicates that clinical stroke and silent infarcts on MRI cannot explain the effect of cardiovascular risk burden on cognitive decline. Of note, we observed that among old-old adults (≥78 years), a higher FGCRS tended to be associated with a slower decline in global cognitive function, suggesting that FGCRS is not predictive of cognitive decline in very old individuals (e.g., age ≥75 years). This is likely

due to the facts that FGCRS was initially designed for predicting cardiovascular events in people aged 30-74 years [1], and that among very old people certain components in FGCRS (e.g., elevated systolic blood pressure and total cholesterol) have been indeed inversely associated with the risk of cognitive decline and dementia [20,22,23].

The association between structural brain measures and cognitive decline has been well established [6,7]. In addition, the *APOE*-ε4 allele was associated with accelerated cognitive decline [24]. More importantly, we revealed interactions of *APOE*-ε4 with volumes of WMHs and ventricles on cognitive decline such that carrying the ε4 allele magnified the effects of WMHs and enlarged ventricles on cognitive decline, although such interactions were not previously detected in the Rotterdam Scan Study [25]. The *APOE*-ε4 allele strongly affects deposition of cerebral β-amyloid protein [26,27], which may contribute to the interactive effect of the ε4 allele and brain MRI markers on cognitive decline.

Markers of structural brain features have often been regarded as a confounder, rather than a mediator, in relating cardiovascular risk factors to cognitive decline in earlier studies. For example, the Framingham Heart Study showed that cardiovascular risk factors were associated with faster cognitive decline, even after additionally adjusting for WMHs [5]. We sought to test the mediating effects of structural brain MRI markers by using structural equation models. Our findings suggest that the association between cardiovascular risk burden and cognitive decline is largely mediated by a load of WMHs together with either global or regional brain atrophy. Moreover, a greater cardiovascular risk burden was associated with a smaller total grey-matter volume and a larger ventricular volume, independent of markers of cerebral small-vessel disease (i.e., WMHs). In line with our findings, the SMART-MR study showed that, among people with symptomatic atherosclerotic diseases, the combination of brain atrophy and WMHs accelerated cognitive decline [28]. In addition, the Mayo Clinic Study of Aging has shown additive effects of mixed brain pathologies (i.e., cerebrovascular

disease and Alzheimer's disease) on cognitive decline [29]. The AGES-Reykjavik Study of older adults also found that the cross-sectional association between diabetes and poor cognitive performance was largely mediated by MRI markers of cerebral mixed microvascular and degenerative pathologies [8]. Taken together, these studies support the view that cardiovascular risk factors cause cognitive decline through mixed pathologies of small-vessel disease and neurodegeneration in the brain.

Several pathophysiological pathways may underlie the longitudinal relations of cardiovascular risk burden and structural brain features to cognitive decline in aging. Firstly, cardiovascular risk factors (e.g., smoking, high cholesterol, and diabetes) cause cerebral arteriosclerosis and atherosclerosis, which may predispose for microinfarcts and cerebral hypoperfusion, and subsequently lead to vascular and degenerative brain lesions that, in turn, affect cognitive functioning [30,31]. Secondly, certain cardiovascular risk factors (e.g., hypertension and diabetes) could result in structural brain changes and cognitive decline by increasing blood-brain barrier permeability and β-amyloid deposition [12, 18]. Amyloid deposition is related to synaptic and neuronal loss, which may affect grey- and white-matter tissue [32]. Thirdly, cerebrovascular and neurodegenerative lesions represent independent pathological processes in aging that may converge to cause cognitive decline [33]. Finally, white-matter lesions may impair anatomic connections, thus leading to structural brain degeneration [10]. Conversely, Wallerian degeneration, which is secondary to axonal impairment and demyelination induced by neurodegeneration, may lead to white-matter lesions [34].

Strengths of this study include a large sample of community-dwelling older adults with comprehensive data on cardiovascular risk factors, and long-term longitudinal assessment of cognitive function. Furthermore, we were able to explore mechanisms linking cardiovascular risk burden to cognitive decline in the MRI sample, where markers of brain structure and

pathologies are integrated with epidemiological, clinical, and cognitive data. A possible limitation of the study is that selective dropout might have occurred during the follow-up periods, which may lead to an underestimation of the strength of the true associations [35]. Lack of high-density lipoprotein data could be a potential limitation in defining FGCRS, but the additional analyses suggested that this appeared to have no significant impact on the main results. MMSE may be not as sensitive as measures of domain-specific cognitive function (e.g., memory and executive function), but it has been widely used as a brief screening test for cognitive impairment and dementia. Finally, although multiple markers of brain lesions were explored in this study, additional imaging markers such as β-amyloid deposition, microbleeds, and microinfarcts, which are known to contribute to cognitive decline [8,36,37] but are not available in our study, might play a part in the association between FGCRS and cognitive decline. This deserves further investigation.

This population-based longitudinal study indicates that increased cardiovascular risk burden contributes to mixed brain pathologies, which in turn may speed up cognitive decline in aging; carrying an *APOE*-ε4 allele may accelerate the deleterious effect of cardiovascular risk burden and mixed brain pathologies on cognitive function. Our findings highlight the importance of assessing structural brain abnormalities and cognitive function among young-old people who possess multiple cardiovascular risk factors and carry the *APOE*-ε4 allele. Moreover, this study supports the notion that intervention strategies to reduce cardiovascular risk burden may delay the processes of pathological brain aging and cognitive deterioration.

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6 AUTHORS' CONTRIBUTIONS

Study concept and design: R. Wang, L. Fratiglioni, and C. Qiu. Funding: L. Fratiglioni, L. Bäckman, and C. Qiu. Data acquisition: L. Fratiglioni, G. Kalpouzos, M. Lövdén, E.J. Laukka, L. Bronge, and L-O Wahlund. Data analysis: R. Wang. Interpretation of data: all the authors. Drafting of the manuscript: R. Wang and C. Qiu. Critical revision of the manuscript: all the authors. R. Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Fig. 1. Average annual changes in MMSE score over 9 years according to quartiles of FGCRS in the SNAC-K total sample (**A**) and by age strata (**B** and **C**). Model was adjusted for age, sex, and education.

Abbreviations: FGCRS, Framingham general cardiovascular risk score; MMSE: Mini-Mental State Examination.

Fig. 2. Mediating effects of brain MRI markers in the associations of FGCRS with annual MMSE change. Data are standardized coefficients (95% confidence intervals) derived from structural equation models. We present the structural components in the models. Figure 2**A** shows the total mediating effect of both WMH and total grey matter in the association between FGCRS and MMSE decline, as well as the direct effect of FGCRS on total grey matter independent of WMHs; Figure 2**B** shows the total mediating effect of both WMHs and ventricles in the association between FGCRS and MMSE decline, as well as the direct effect of FGCRS on ventricular volume independent of WMHs. $^{*}P<0.01$.

Abbreviations: FGCRS, Framingham general cardiovascular risk score; MMSE, Mini-Mental State Examination; WMHs, white-matter hyperintensities.

Table 1

Characteristics of the study participants at baseline

Characteristics	Participants (n=2189)	MRI scan		
		No (n=1741)	Yes (n=448)	*P*-value
Age (years), mean (SD)	71.7 (9.9)	72.1 (10.1)	70.3 (9.2)	<0.01
Sex (female), n (%)	1391 (63.5)	1120 (64.3)	271 (60.5)	0.13
Education, n (%)*				
Elementary or middle school	283 (12.9)	232 (13.3)	51 (11.4)	
High school	1074 (49.1)	869 (50.0)	205 (45.8)	
University	830 (38.0)	638 (36.7)	192 (42.9)	0.05
FGCRS, mean (SD)	17.9 (3.6)	18.0 (3.6)	17.7 (3.8)	0.13
Current smoking, n (%)	275 (12.3)	220 (12.6)	53 (11.6)	0.56
Systolic pressure (mmHg), mean (SD)	144.1 (19.5)	144.5 (19.6)	142.9 (19.4)	0.06
Diastolic pressure (mmHg), mean (SD)	82.1 (10.4)	81.8 (10.3)	83.1 (10.8)	0.02
Total cholesterol (mmol/l), mean (SD)	6.1 (1.1)	6.0 (1.1)	6.2 (1.1)	<0.01
Diabetes, n (%)	178 (8.1)	146 (8.4)	32 (7.1)	0.39
Body mass index (kg/m^2), mean (SD)*	25.8 (3.9)	25.7 (3.9)	26.1 (4.1)	0.08
Alcohol consumption, n (%)*				
No or occasional	643 (29.5)	533 (30.8)	110 (24.6)	
Light-to-moderate	1155 (53.0)	895 (51.5)	260 (58.0)	
Heavy drinking	383 (17.6)	305 (17.7)	78 (17.4)	0.03
Physical inactivity, n (%)	522 (23.9)	437 (25.1)	85 (19.0)	<0.01
APOE-ε4 allele, n (%)*	610 (27.9)	491 (28.2)	119 (26.6)	0.08
Use of antihypertensive drugs, n (%)	815 (37.2)	654 (37.6)	161 (35.9)	0.53
MMSE, median (IQR)†	29 (28-30)	29 (28-30)	29 (29-30)	<0.01

Abbreviations: SD, standard deviation; MRI, magnetic resonance imaging; MMSE, Mini-Mental State Examination; FGCRS, Framingham general cardiovascular risk score; IQR, Interquartile range; WMHs, white-matter hyperintensities.

*Number of subjects with missing value in SNAC-K was 2 for education, 45 for body mass index (1 in MRI group), 8 for alcohol consumption, 125 for *APOE*-ε4 status (19 in MRI sample). All subjects with missing information on *APOE* were assigned a dummy variable in further analyses that involve the SNAC-K sample.

†MMSE score was compared using Wilcoxon-Mann-Whitney test.

Table 2

Estimates of effects of brain MRI markers on annual change in the Mini-Mental State Examination score in the total SNAC-K MRI sample and by the *APOE*-ε4 allele status

Structural MRI markers	β-coefficient (95% confidence interval)	
	Model 1[†]	Model 2[†]
Total sample (n=448)[*]		
WMH volume	-0.112 (-0.149, -0.074)[‡]	-0.112 (-0.149, -0.074)[‡]
Total grey-matter volume	0.003 (0.002, 0.003)[‡]	0.003 (0.002, 0.003)[‡]
Ventricular volume	-0.009 (-0.012, -0.006)[‡]	-0.009 (-0.012, -0.006)[‡]
Hippocampal volume	0.174 (0.107, 0.241)[‡]	0.174 (0.107, 0.240)[‡]
APOE-ε4 non-carriers (n=325)		
WMH volume	-0.077 (-0.119, -0.035)[‡]	-0.077 (-0.119, -0.035)[‡]
Total grey-matter volume	0.002 (0.001, 0.003)[‡]	0.002 (0.001, 0.003)[‡]
Ventricular volume	-0.006 (-0.009, -0.003)[‡]	-0.006 (-0.009, -0.003)[‡]
Hippocampal volume	0.142 (0.064, 0.219)[‡]	0.141 (0.064, 0.218)[‡]
APOE-ε4 carriers (n=119)		
WMH volume	-0.201 (-0.281, -0.122)[‡]	-0.199 (-0.276, -0.122)[‡]
Total grey-matter volume	0.004 (0.002, 0.006)[‡]	0.004 (0.002, 0.006)[‡]
Ventricular volume	-0.017 (-0.024, -0.011)[‡]	-0.017 (-0.024, -0.011)[‡]
Hippocampal volume	0.245 (0.113, 0.377)[‡]	0.245 (0.117, 0.373)[‡]

Abbreviations: MRI, magnetic resonance imaging; WMH, white-matter hyperintensity.

[*]The total MRI sample included 4 subjects with missing value for the *APOE*-ε4 allele status.

[†]β-coefficient (95% confidence interval) was derived from linear mixed-effects models. Model 1 was adjusted for age, sex, and education; Model 2 was additionally adjusted for body mass index, diastolic blood pressure, alcohol consumption, physical inactivity, and cerebrovascular disease. [‡]$P<0.01$.

Table 3

Mediating effects of individual MRI markers of various brain lesions on the associations between FGCRS and annual MMSE change in the SNAC-K MRI total sample (n=448) and by the *APOE*-ε4 allele status

	Average annual change in MMSE score, β-coefficient (95% confidence interval)[*]		
Mediators	Total MRI sample	*APOE*-ε4 non-carriers	*APOE*-ε4 carriers
Total effect of FGCRS	-0.019 (-0.030, -0.008)[†]	-0.013 (-0.024, -0.002)[‡]	-0.037 (-0.063, -0.010)[†]
Mediator, *WMH volume*			
Direct effect of FGCRS	-0.008 (-0.019, 0.004)	-0.006 (-0.018, 0.005)	-0.008 (-0.038, 0.022)
Mediating effect of WMH volume	-0.012 (-0.017, -0.006)[†]	-0.007 (-0.012, -0.003)[†]	-0.029 (-0.048, -0.011)[†]
Percent mediation	60.0%	53.8%	78.4%
Mediator, *total grey-matter volume*			
Direct effect of FGCRS	-0.010 (-0.021, 0.001)	-0.006 (-0.018, 0.005)	-0.021 (-0.049, 0.007)
Mediating effect of volume	-0.009 (-0.014, -0.004)[†]	-0.007 (-0.012, -0.002)[†]	-0.015 (-0.028, -0.003)[‡]
Percent mediation	47.4%	53.8%	41.7%
Mediator, *ventricular volume*			
Direct effect of FGCRS	-0.010 (-0.021, 0.001)	-0.007 (-0.019, 0.004)	-0.015 (-0.042, 0.012)
Mediating effect of ventricular volume	-0.009 (-0.014, -0.005)[†]	-0.006 (-0.010, -0.002)[†]	-0.022 (-0.036, -0.007)[†]
Percent mediation	47.4%	46.2%	59.5%
Mediator, *Hippocampal volume*			
Direct effect of FGCRS	-0.012 (-0.024, -0.001)[‡]	-0.008 (-0.020, 0.004)	-0.028 (-0.055, -0.001)[†]
Mediating effect of hippocampal volume	-0.007 (-0.011, -0.003)[†]	-0.005 (-0.010, -0.001)[‡]	-0.009 (-0.018, -0.001)
Percent mediation	36.8%	38.5%	24.3%

Abbreviations: FGCRS, Framingham general cardiovascular risk score; MMSE, Mini-Mental State Examination; WMH, White-matter hyperintensity.

[*]β-coefficients (95% confidence intervals) were derived from the structural equation model.

[†]$P<0.01$; [‡]$0.01<P<0.05$.

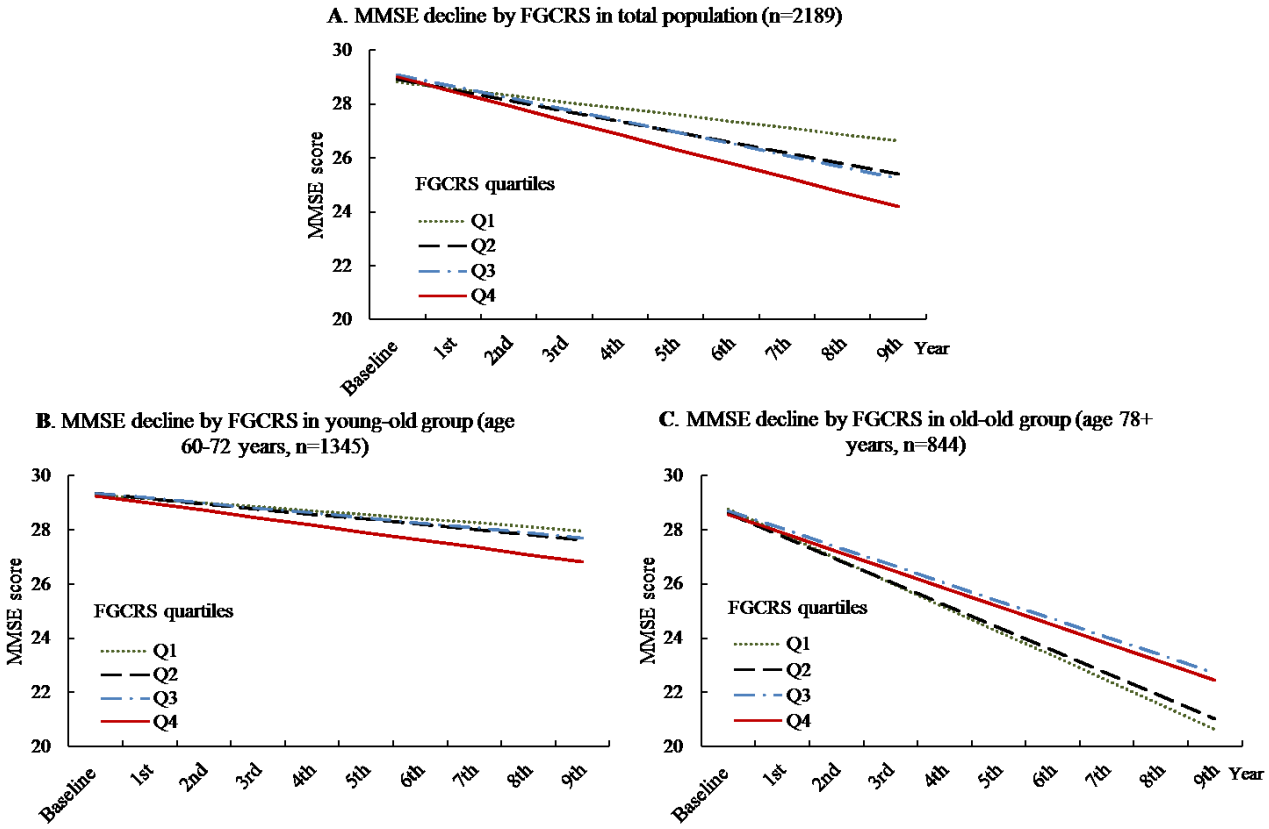
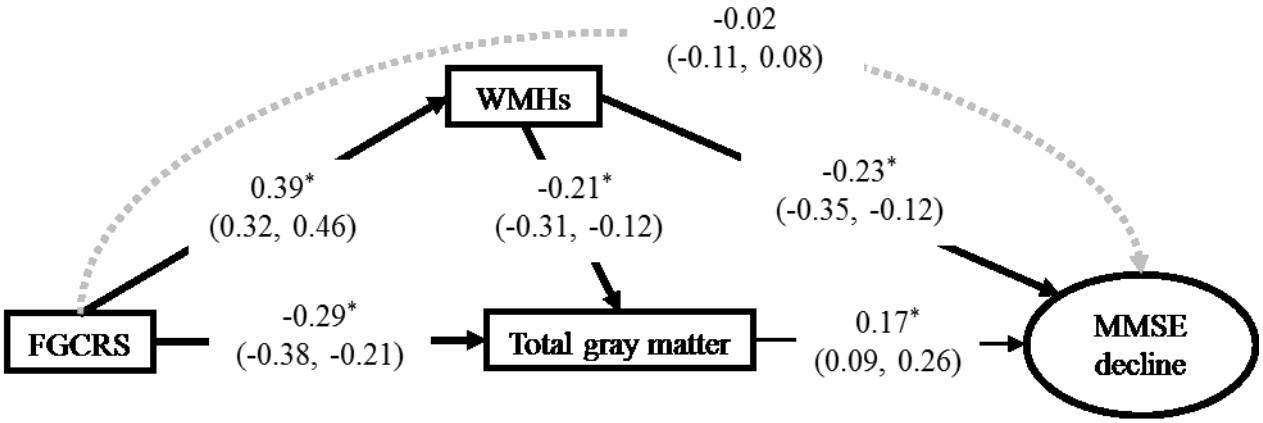

A. MMSE decline by FGCRS in total population (n=2189)
MMSE score
30
28
26
24
22
20
FGCRS quartiles
Q1
Q2
Q3
Q4
Baseline
1st
2nd
3rd
4th
5th
6th
7th
8th
9th
Year
B. MMSE decline by FGCRS in young-old group (age 60-72 years, n=1345)
C. MMSE decline by FGCRS in old-old group (age 78+ years, n=844)

Figure 1.

A. Mediating effect of WMH and total gray matter



B. Mediating effect of WMH and ventricles

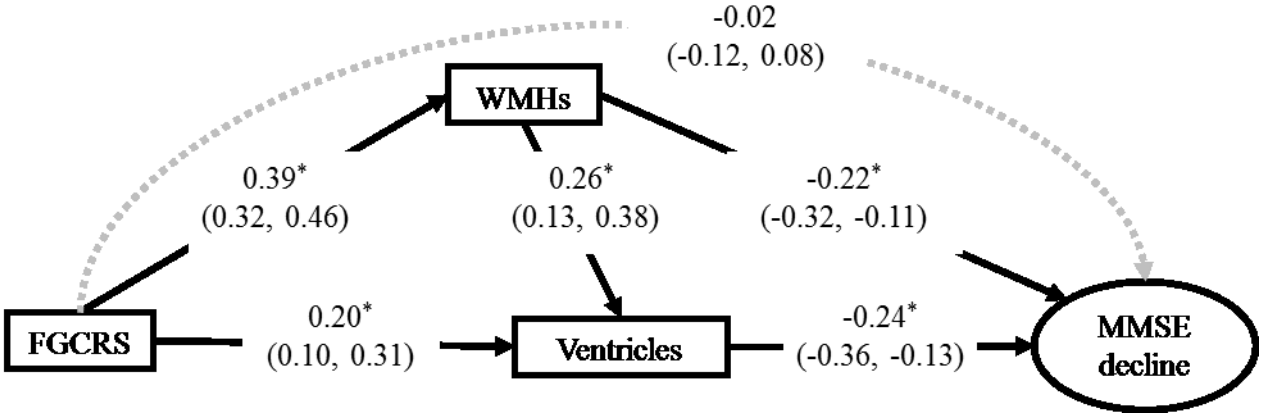


Figure 2.

SUPPLEMENTARY MATERIAL

S1. Flowchart of study participants in the SNAC-K and SNAC-K MRI studies, 2001-2004 to 2010-2013

*Note: According to the SNAC-K follow-up procedure, 1011 of the 1345 subjects aged 60 and 66 years at baseline in the SNAC-K, including 237 subjects in the SNAC-K MRI study, would not receive the second follow-up assessment until 2016.