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Featured Article

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

Q3 **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 Swedish National Study on Aging and Care in Kungsholmen (n = 2189, age ≥60) and the embedded magnetic resonance imaging (MRI) (n = 448) studies. Volumes of white matter hyperintensities (WMHs), total gray 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 years) but not in old-old (≥78 years). Larger volumes of cerebral WMHs and ventricles and smaller volumes of total gray matter and hippocampus were all associated with accelerated MMSE decline ($P < .01$); these associations were stronger among *APOE*-ε4 carriers than noncarriers. 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

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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 gray 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 because of 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 to June 2004) [14]. Of these, we excluded 1174 subjects because of 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 because of death). Thus, this study included 2189 persons who were free of dementia, had a baseline MMSE score ≥24, and had at least 1 follow-up MMSE assessment.

During September 2001 to October 2003, noninstitutionalized, nondisabled, and nondemented participants in SNAC-K were invited to undertake structural brain magnetic resonance imaging (MRI) scans, and 555 persons were scanned at baseline [15]. Of these, we excluded 76 subjects because of 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 because of brain disorders. Thus, the analytical SNAC-K MRI sample included 448 subjects. Supplementary Fig. 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 versus 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 hemoglobin ≥6.5% [16]. The *APOE* gene was dichotomized into any ε4 allele versus 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.