
Received 15 January 2012; accepted in revised form 16 November 2012

Smoking, hypercholesterolaemia and hypertension as risk factors for cognitive impairment in older adults

O LAOLUWA OKUSAGA1, MARLENE C. W. STEWART2, ISABELLA BUTCHER2, IAN DEARY3,4, F. GERRY R. FOWKES2,5, JACKIE F. PRICE2,4

1Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, TX, USA
2Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK
3Department of Psychology, University of Edinburgh, Edinburgh, UK
4Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
5Wolfson Unit for the Prevention of Peripheral Vascular Diseases, Department of Public Health Sciences, The University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK

Address correspondence to: O. Okusaga. Tel: (+1) 7137413952; Fax: (+1) 7137416909. Email: Olaoluwa.O.Okusaga@uth.tmc.edu

Abstract

Background: the prevalence of all types of cognitive impairment, including dementia, is increasing but knowledge of aetiological factors is still evolving.
Objective: this study aimed to evaluate the association between cardiovascular risk factors and cognitive function in older persons.
Design, setting and subjects: a population-based cohort design involving 2,312 men and women (aged 50–75) enrolled in the University of Edinburgh Aspirin for Asymptomatic Atherosclerosis trial.
Methods: cognitive tests included the Mill Hill Vocabulary Scale, auditory verbal learning test (AVLT), digit symbol test, verbal fluency test (VFT), Raven’s Progressive Matrices and the trail making test. A ‘g’ score (measure of general intelligence) was computed for each subject. Regression analysis was used to evaluate the association between relevant variables.
Results: higher diastolic BP was negatively associated with AVLT ($\beta = -0.153$, $P < 0.01$), and with an estimated decline on AVLT ($\beta = -0.125$, $P < 0.01$). Smoking was negatively associated with all the cognitive variables except VFT. The total cholesterol level was not associated with cognitive function or estimated decline.
Conclusions: smoking and elevated blood pressure may be risk factors for cognitive decline, and thus potential targets for preventive and therapeutic interventions.

Keywords: hypertension, smoking, cholesterol, cognition, older people
Introduction

The increasing proportion of older adults in the general population means that the number of people with all types of cognitive impairment, including dementia, is increasing. In the UK for example, it is projected that 1.7 million individuals will be diagnosed with dementia by 2051 [1], an increase of 154% from the current estimate of 700,000. An additional fifth of the population is affected by age-related cognitive impairment, which falls short of frank dementia [2]. The cost of caring for those with significant cognitive impairment, in terms of the burden on caregivers and financial expense is immense [3] and this underlines the need for a better understanding of factors contributing to the pathogenesis of cognitive impairment in older adults to inform the development of preventive and therapeutic measures.

Links between vascular disease and cognitive impairment in older age are increasingly recognised. Vascular disease predisposes to cerebrovascular accidents (strokes) which in turn impact negatively on cognitive abilities and may lead to vascular dementia. Atherogenic levels of vascular risk factors, including cigarette smoking, hypercholesterolaemia and hypertension, may contribute to the development of both cardiovascular disease and cognitive impairment. If this is the case, then treatment of such risk factors may help reduce rates of cognitive decline in older age. To date, few clinical trials have been performed to address this possibility and these have produced inconclusive results [4, 5]. Furthermore, previous studies have demonstrated an association between worse cognitive ability and increased smoking [6], hypercholesterolaemia [7] and hypertension [6], but these findings notwithstanding, the National Institute of Health State-of-the-Science Conference Statement on Preventing Alzheimer Disease and Cognitive Decline concluded that ‘currently, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer disease’ [8] and additional studies have been advocated for.

To expand the current understanding of the connection between cardiovascular risk factors and cognitive function as well as to overcome the limitations of small sample size and less comprehensive cognitive testing in a number of previous studies [9, 10], we examined the association of smoking status, raised blood pressure/anti-hypertensive medication use and raised plasma total cholesterol/cholesterol-lowering medication with both cognitive ability and estimated cognitive decline. We carried out a large, prospective study of individuals free of symptomatic cardiovascular disease at baseline. We used a battery of individual cognitive tests applied 5 years after entry into the study and estimated pre-morbid cognitive ability at baseline to enable an estimation of decline in cognitive ability since early adult life.

Methods

Study population

Data were derived from the Aspirin for Asymptomatic Atherosclerosis (AAA) trial. The AAA trial is a randomised controlled trial of low-dose aspirin in the prevention of cardiovascular events and deaths in asymptomatic subjects at high risk of cardiovascular events (i.e. those with ankle brachial pressure index ≤0.95). Details of how subjects were recruited into this trial and the characteristics of the subjects have been described elsewhere [5]. In brief, 3,350 individuals aged 50–75 years were recruited from general practices in central Scotland. Subjects were excluded if they had a history of cardiovascular disease, aspirin or other anticoagulant use and any contraindication to aspirin. Of the total 3,350 individuals, 2,312 initially recruited into the AAA trial underwent detailed cognitive testing at the 5-year follow-up. The remaining 1,038 did not undergo cognitive testing for the following reasons: 160 died, 157 withdrew, 668 refused cognitive testing, 40 could not be contacted and testing was incomplete in 13.

Clinical and cognitive examination

Details of physical and cognitive assessments have been described previously [5]. Ankle brachial index (ABI) and brachial blood pressure were measured at baseline. ABI was calculated as the ratio of the lowest systolic blood pressure in either ankle (measured with a Doppler probe) to the higher of either arm systolic pressure (measured with a standard sphygmomanometer). Plasma total cholesterol levels and smoking status (current, previous and never, where previous smokers were those who had stopped smoking at least 6 months prior to examination) were measured at baseline. The Mill Hill Vocabulary Scale (MHVS) (junior and senior synonyms combined) [11], also administered at baseline, was used to estimate peak prior (pre-morbid) cognitive functioning, on the basis that vocabulary scores have been shown to change very little during ageing [12].

At the 5-year follow-up a cognitive test battery was administered by trained researchers, including: the Mini-Mental State Examination (screening test for dementia) [13], the verbal fluency test (VFT) (a test of executive function) [14], Raven’s Progressive Matrices (assesses non-verbal reasoning) [11], auditory verbal learning test (AVLT) (assesses verbal learning, immediate and delayed memory) [14], trail making test (TMT) (visual search, scanning, speed of processing, mental flexibility and executive functions) [14] and the digit symbol test (assesses processing speed) [15]. Principal components analysis [16] was used to generate a general cognitive ability score (designated ‘g’) using information from the test battery (excluding Mini-Mental State Examination). With the aid of a scree plot, one component was identified and extracted as the first unrotated principal component. The principal component (‘g’) accounted for 56.9% of the variance in the cognitive test battery data. All five cognitive tests loaded strongly on ‘g’.
O. Okusaga et al.

Serum total cholesterol levels were measured on a venous blood sample at the Biochemistry Department, Gartnavel General Hospital, Glasgow on a Beckman CX4 analyser using the cholesterol oxidase method.

**Data analysis**

Statistical analysis was carried out using SPSS version 14 (SPSS, Inc., Chicago IL, USA) and all significance levels reported are two-sided with \( P < 0.01 \) considered statistically significant (the alpha level was lowered to maintain adequate control over type I error rate). The TMT was skewed to the right and natural log of this variable was, therefore, computed and used for all analyses. Age- and sex-adjusted Pearson correlation coefficients were calculated for the cognitive function variables with total cholesterol, systolic and diastolic blood pressure. Multiple linear regression was used to model the relationship of cognitive variables with risk factor variables, where the covariates age, systolic blood pressure, diastolic blood pressure, cholesterol, smoking, gender, cholesterol medication, anti-hypertensive medication and deprivation were fitted together. The deprivation variable was the Scottish Index of Multiple Deprivation (SIMD), an index used to classify the degree of deprivation in a geographical region based on 38 different indicators including education [17]. The smoking status was fitted as a binary variable (current versus previous/never smoker). Models adjusting for prior cognitive ability (MHVS) were used to analyse the association of the cardiovascular risk factor variables with estimated decline in cognitive function. The use of a regression-based methodology (adjusting for vocabulary scores) in estimating cognitive change has been validated previously [18]. Furthermore, adjusting for estimated prior cognitive ability circumvents confounding by regression-to-the-mean and practice effect. In the regression models, cognitive function variables were the dependent variables and the cardiovascular risk factors were predictor variables.

**Results**

**Description of cohort**

Table 1 shows baseline characteristics of the AAA trial participants who were cognitively tested compared with those not tested. Those not tested were slightly older, more likely to be men, more socially deprived and more likely to be current smokers, but overall differences were not large. 804 of the 2,312 subjects cognitively tested were 65 years and above, while 319 were 70 years or older. For the 1,038 not tested, 428 were 65 years and above while 207 were 70 years or older.

**Association of cardiovascular risk factors with cognitive function**

After adjustment for age and sex, the total cholesterol level was not correlated with any of the cognitive function variables (Table 2). There were small but statistically significant correlations of diastolic and systolic blood pressure with estimated pre-morbid cognitive ability (MHVS), ‘g’, and all of the individual age-sensitive cognitive ability tests. In all cases, the direction of the correlation indicated worse cognitive ability associated with raised blood pressure. Table SA1, Supplementary data available in *Age and Ageing* online, shows the result of fitting regression models in which all of the covariates were included simultaneously (but without MHVS). Being a current smoker was significantly associated with worse performance on all the cognitive function tests except VFT. Higher diastolic blood pressure was significantly associated with worse performance on AVLT \((\beta = -0.153, P < 0.01)\).

**Association of cardiovascular risk factors with estimated cognitive decline**

After adjusting for MHVS diastolic BP was significantly associated with worse performance on AVLT \((\beta = -0.125, P < 0.01)\) (Table 3). As in the model unadjusted for MHVS, the ‘current smoker’ status was negatively associated with scores on all the cognitive function variables except VFT.

**Discussion**

We evaluated the effects of blood cholesterol, cholesterol-lowering medication, systolic and diastolic blood pressure, anti-hypertensive medication and smoking on a broad range of cognitive domains in men and women aged over 50 years from the general population. We found no
evidence of an association of blood cholesterol or cholesterol-lowering medication with cognitive ability after the 5-year follow-up. There was evidence of an association between raised blood pressure and poorer cognition, in that both higher diastolic and systolic blood pressures were correlated with poorer general cognitive ability and with each of the individual cognitive tests, after controlling for the effects of age and sex. After adjusting for all other co-variates, including deprivation, and estimated prior cognitive ability, statistically significant negative association was retained for elevated diastolic blood pressure and AVLT only. However, the most consistent association was found between cognition and smoking status, which persisted across all measures of cognitive ability (except VFT) and after multivariate adjustment including estimated prior cognitive ability, suggesting that smoking may be associated with both cognitive impairment and with age-related cognitive decline.

The lack of evidence of an association between cholesterol and cognition observed in this study is consistent with findings from a number of previous studies [19]. A systematic review and meta-analysis by Anstey et al. [20] indicated that there is stronger evidence of an association between cholesterol (particularly in mid-life) and an increased risk of dementia than there is between cholesterol and cognitive impairment which falls short of frank dementia. Animal models suggest that cholesterol may increase the production of amyloid precursor protein (APP) and subsequent beta cleavage of APP to beta amyloid [21]. Overall, there is currently no consensus on the relationship between serum cholesterol and age-related cognitive decline. In our study, cognition was not related to the use of cholesterol-lowering medication, although the number of individuals taking these medications was relatively small. A number of randomised controlled trials have also not observed any significant effect of cholesterol-lowering medication (statins) on cognitive function in individuals without dementia [22]. A Cochrane review [23] did not show any beneficial effect of statins in the prevention of dementia and concluded that ‘statins should not be prescribed to prevent dementia by health care professionals practicing evidence based medicine’. Furthermore, a randomised double blind placebo controlled trial of low-dose aspirin in the AAA trial sample revealed that aspirin did not affect cognition [5].

Our findings add to the growing body of evidence suggesting that elevated blood pressure in mid-life impacts negatively on cognition and may predispose to the development of dementia [24]. High blood pressure is a recognised risk factor for white matter (subcortical) damage which results in impaired cognition, in particular reduced psychomotor speed, attention, working memory and executive function [25]. However, knowledge of the precise
mechanism by which elevated blood pressure may contribute to cognitive change over time is still evolving. Available evidence indicates that hypertension can cause direct damage to cerebral vascular endothelium, and alter cerebral autoregulatory mechanisms [26] ultimately resulting in cerebral hypoperfusion—an important common pathway by which vascular pathology is felt to impact negatively on cognitive function [27].

The negative effect of smoking on cognition observed in the current study is consistent with the results of a systematic review [28], suggesting that smoking may result in poorer cognitive ability in middle to late age. However, it is also worth considering whether poor cognitive ability in early to mid-life could lead to a disadvantageous cardiovascular risk factor profile in individuals later in life, i.e. the association between cognitive ability and altered risk factor levels may be bidirectional. For example, individuals with lower cognitive ability have been shown to have clustering of cardiovascular disease risk factors and low IQ has been associated with a raised mortality rate from cardiovascular disease in middle-aged men and women [29]. Detailed data on the cognitive function of the AAA trial population prior to inclusion in the trial were not available and it was therefore not possible to fully control for the possibility that smoking initiation in their earlier years may have been mediated by cognitive ability. However, we were able to adjust for estimated prior cognitive ability, following which the association between smoking and cognitive ability persisted. Cigarette smoking, apart from acting synergistically with systolic blood pressure to cause vascular endothelial damage, has also been found to reduce neurogenesis and increase death of brain cells [30].

Strengths of this study include the large number of participants and the selection of participants from the community who were therefore representative of individuals seen routinely by health-care professionals. Also informative was the use of a comprehensive battery of cognitive assessment tools, and our ability to adjust for estimated prior cognitive ability. The use of a detailed cognitive assessment ensured that several cognitive domains were considered when studying associations with risk factors. This is in contrast to a number of studies that have employed very basic cognitive assessment tools such as the Mini-Mental State Examination alone.

The study is limited in that cholesterol, blood pressure and smoking status were measured only once, at baseline, and smoking status and number of cigarettes smoked were self-reported. Another limitation is the fact that the cognitive test battery was administered only at the 5-year follow-up and we estimated baseline (pre-morbid) cognitive function with the use of the MHVS. We also did not control for apolipoprotein-E alleles/genotypes. In addition, participants were recruited from general practice surgeries in the Lanarkshire, Glasgow and Edinburgh districts of Scotland and may therefore not be generalisable to other areas and/or countries with different demographic characteristics. Ideally the potential causal association between cognitive decline and the vascular risk factors studied here should be tested in randomised controlled trials, as has started to be done for hypercholesterolaemia and hypertension. However, such trials are resource intensive and observational studies such as the one described here are useful to indicate which risk factors should be targeted for retention of cognitive function in specific domains.

In conclusion, we have demonstrated that both elevated diastolic blood pressure and smoking are associated with poorer cognitive function in individuals older than 50 years and may also be associated with an age-related cognitive decline. The outcome of this study supports the recommendation of good control of blood pressure and smoking cessation to prevent an accelerated cognitive decline in middle-aged individuals.

**Key points**

- Smoking and elevated blood pressure are associated with poorer cognitive function.
- Cholesterol was not associated with cognitive function.
- Good control of blood pressure and smoking cessation may prevent accelerated cognitive decline.

**Conflicts of interest**

None declared.

**Funding**

Funding for the Aspirin for Asymptomatic Atherosclerosis (AAA) trial, including cognitive testing, was provided by the Wellcome Trust, the British Heart Foundation and the Chief Scientist Office, Scotland.

**Supplementary data**

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

**References**