Vascular disease and cognitive function: evidence from the Whitehall II Study.

Archana Singh-Manoux, Annie R Britton, Michael Marmot

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Archana Singh-Manoux, PhD (Research Psychologist)[1]

Annie R. Britton, PhD (Lecturer in Epidemiology)[1]

Michael Marmot, PhD, MPH, MB BS, FFPHM (Professor of Epidemiology & Public-Health)[1]

Archana Singh Manoux (corresponding author) E-mail: A.Singh-Manoux@public-health.ucl.ac.uk

[1]International Centre for Health and Society

Department of Epidemiology and Public Health, University College London

1-19 Torrington Place, London WC1E 6BT, U. K.

Tel.: 44 (0)20 7679 1692, Fax: 44 (0)20 7813 0242

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Abstract

Objective: To test the hypothesis of an inverse association between indicators of vascular disease and cognitive function in the general, stroke free population.

Design: A longitudinal, British civil service based cohort study. Measures of vascular disease examined were either prevalent at baseline or traced over a median of 11 years, between Phases 1 (1985-1988) and 5 (1997-1999) of data collection. Cognitive function was assessed at Phase 5 of data collection.

Participants: 4141 men and 1681 women, aged 46 to 68 years when tested for cognitive function.

Main outcome measures: A battery of cognitive tests consisting of the following tests: memory test, AH 4, Mill-Hill, phonemic and semantic fluency.

Results: The occurrence of angina ($p<0.001$), myocardial infarction ($p=0.02$), all coronary heart disease ($p<0.001$) and intermittent claudication ($p=0.004$) was associated with poor cognitive function. These effects were independent of age and socioeconomic status. The association between indicators of vascular disease and cognitive function applied to the entire range of cognitive function measures examined in the study.

Conclusions: The findings support the view that vascular disease is predictive of poor cognitive function in the general population. The fact that presence of vascular disease was associated with diminished cognitive function even in a relatively young cohort has implications for the management of vascular disease.

Key words: vascular disease, cognitive impairment, socioeconomic position, Whitehall II

Introduction

Research into cognitive function in prospective cohort studies reveals that it is likely that there are multiple determinants of cognitive decline. Besides age, the other two factors most widely implicated in cognitive decline are pathology and socioeconomic factors.[1] Recent evidence suggests that vascular risk factors (such as hypertension, diabetes mellitus, cholesterol level, fibrinogen level) and indicators of vascular disease are associated with both cognitive impairment[2-7] and dementia.[8-10] In the research literature a distinction is made between vascular and non-vascular dementia,[11-12] based on establishing a temporal connection between vascular disease and decline in cognitive functioning in the case of vascular dementia. However, the generalized association between vascular disease and poor cognitive function suggests that the atherosclerotic process and related hypoperfusion may be causally linked to both vascular and non-vascular dementia.[9]

Our paper aims to provide further evidence for the link between vascular disease and cognitive function in a sample of middle aged individuals, undiagnosed of dementia. We wish to test whether the presence of vascular disease is predictive of poor cognitive function, even in a functioning, healthy group of individuals. By using indicators of peripheral vascular disease and coronary heart disease as measures of generalized atherosclerosis, we hypothesize that these might act as surrogate measures of cerobrovascular disease and will be related to impaired cognitive function. As there is some evidence suggesting that memory loss may not always be associated with cognitive impairment due to vascular causes,[13-14] we will examine a wide range of measures of cognitive function.

Participants and Methods

Participants

The Whitehall II study was established in 1985 as a longitudinal study to examine the socioeconomic gradient in health and disease among 10,308 non-industrial civil servants (6,895 men and 3,413 women).[15] All civil servants aged 35-55 years in 20 London based departments were invited to participate by letter. The screening at baseline (Phase 1) took place during 1985-1988, and involved a clinical examination and a self-administered questionnaire containing sections on demographic characteristics, health, lifestyle factors, work characteristics, social support and life events. Clinical examination included measures of blood pressure, anthropometry, biochemical measurements (total and HDL cholesterol, triglycerides, fasting and post load glucose and insulin, fibrinogen), neuroendocrine function (blood pressure reactivity, urinary catecholamines, heart rate variability), subclinical markers of cardiovascular disease (ECG, ischemia, left ventricular mass, ultrasound measures of arterial structure and function) and cognitive function. Subsequent phases of data collection have alternated between postal questionnaire alone and postal questionnaire accompanied by a screening examination. Since baseline screening five phases of data collection rounds have been completed, with the most recent phase of data collection (Phase 6) completed in 2001.

Socioeconomic position of participants was assessed through employment grade as all jobs in the civil service have a grade of employment. Employment grade of participants included in this study ranges from grade 1 to grade 6, with grade 1 representing the top of the socioeconomic hierarchy and grade 6 the bottom. People in different grades differ with respect to salary, social status and level of responsibility. As on January 1, 1987 salaries ranged from £62,100 for grade 1 to £3061 for a grade 6 civil servant.

In total, 73 % of those invited agreed to take part in Phase 1. Response rate at baseline varied by employment grade, being 81% among the top three employment grade categories

and 68% among the lower three categories. Sample characteristics of the Whitehall II study are shown in Table 1.

Measures of vascular disease (phases 1 - 5)

Potential cases of angina and myocardial infarction (MI) arose from positive responses to self completed questions on symptoms of chest pain,[16] doctor diagnoses of angina or MI, cardiac investigation items (exercise electrocardiography and angiography) and treatments (nitrate medications and revascularisations). 12 lead resting ECGs (Siemans Mingorec) were performed in the screening clinics (phase 1, 3 and 5). Informed participant consent and ethical approval were obtained to examine medical records in order to validate self-reported events. Participants were classified as having validated angina or MI on the basis of clinical test abnormality or physician confirmation. An inclusive measure of all coronary heart disease (CHD) included validated MI and angina, and doctor-diagnosed CHD. Cases of Intermittent claudication (IC) were obtained from recall of a doctor's diagnosis alone.

Tests of Cognitive function

The cognitive test battery consisted of five standard tasks, chosen to provide a relatively comprehensive evaluation of cognitive functioning in middle aged adults. Cognitive function reported here was assessed at Phase 5 of data collection and was composed of the following tests which took 30 minutes to complete:

The first test was a 20-word free recall test of short term memory. Participants were presented a list of 20 one or two syllable words at two-second intervals and were then asked to recall in writing as many of the words in any order and had two minutes to do so (Maximum possible score = 20, Mean = 6.86, SD = 2.45).

The AH 4[17] is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty. This is a test of inductive reasoning that measures the ability to identify patterns and infer principles and rules. Participants had 10 minutes to do this section. The

numerical (Maximum possible score = 33, Mean = 22.61, SD = 6.50) and verbal (Maximum possible score = 32, Mean = 23.87, SD = 5.25) aspects of this test have been scored separately in order to ensure that effects in one domain only are not missed by looking at the global score.

The Mill Hill Vocabulary test[18] assesses knowledge of verbal meaning and encompasses the ability to recognize and comprehend words. We used the test in its multiple format, which consists of a list of 33 stimulus words ordered by increasing difficulty, and six response choices (Maximum possible score = 33, Mean = 24.86, SD = 4.64).

We used two measures of verbal fluency: phonemic and semantic. Phonemic fluency was assessed via "S" words (Mean = 16.86, SD = 4.53) and semantic fluency via "animal" words (Mean = 16.39, SD = 4.23). Subjects were asked to recall in writing as many words beginning with “S” and as many animal names as they could. One minute was allowed for each test.

Statistical methods

As it is widely accepted that stroke has an adverse effect on cognitive function,[19-20] all participants who had a stroke by Phase 5 of data collection were excluded from our analyses. Four (one for each disease measure) X 2 (vascular disease, no vascular disease) X 2 (men, women) between-subjects MANCOVA were performed on 6 outcome measures of cognitive function. As the outcome measures (different tests of cognitive function) are correlated with each other we preferred to analyze data using MANCOVA rather than ANCOVA. Adjustment was made for two covariates: age and employment grade. Other covariates considered were cardiovascular risk factors such as hypertension, cholesterol, and cigarette smoking. However, the patterning and magnitude of the association between vascular disease and cognitive function was the same prior to and after adjustment for these cardiovascular risk factors. In light of this, we report results adjusted for age and employment grade alone. A full-

factorial model was tested for each measure of vascular disease, allowing the predictor variables to interact. The effects of the predictor variables on the outcome variables after adjustment for covariates was further investigated in univariate analysis to check for cognitive impairment in selective domains.

In order to assess the impact of a significant main effect on individual outcome variables, each measure of cognitive function was assessed using a univariate F test at $p<0.05$. For statistically significant effects, the difference between means was expressed as an effect size. The measure of effect size used here is Cohen's *d* where the difference between means is expressed as a proportion of the standard deviation for that test.[21] The advantage of expressing mean differences this way is that it allows comparison of effects across the various tests of cognitive function. The convention is to regard effect sizes of "*d*=.2" as "small", "*d*=.5" as "medium", "*d*=.8" as "large".

Results

Missing data

The Whitehall II study, established between 1985 and 1988 had a total of 10,308 civil servants at Phase 1 of data collection (see Table1). 7830 respondents answered the questionnaire at Phase 5 and 6552 attended the screening clinic where the cognitive tests were administered. The median length of follow up from Phase 1 to Phase 5 was 11 years, with 355 individuals dying during this period. 66% of the original sample, excluding deaths, were seen at the screening clinic at Phase 5. The loss to follow-up is not influenced by age ($p=0.44$) or sex ($p=0.43$), but is influenced by employment grade ($p<0.01$), with the attrition rate being significantly higher in the lower socioeconomic group. This analyses did not show an interaction between vascular disease and employment grade, indicating that the association between vascular disease and cognitive function is not modified by employment grade.

56 of the 6552 individuals who attended the phase 5 screening clinic had a record of stroke so were excluded from further analysis. Out of 6496 remaining individuals (4601 men, 1895 women), 476 did not do any cognitive function tests due to various reasons. The missing data here were not influenced by age (p=0.70) or sex (p=0.60), but were influenced by employment grade (p=0.01), with fewer of the higher socioeconomic group individuals who attended screening actually doing the cognitive tests. There was a further set of 157 individuals who did some of the cognitive tests but not the entire battery. This missing information was not influenced by age (p=0.99), sex (p=0.12), or employment grade (p=0.25). However, our analysis reveals that when compared to individuals with complete information on cognitive tests, missing information was related to poorer scores on all tests - memory (p<0.01), AH 4-numerical (p<0.01), AH 4-verbal (p<0.01), Mill-Hill (p<0.01), phonemic fluency (p<0.01), & semantic fluency (p<0.01).

Vascular disease and cognitive function

Individuals for whom there was no evidence of any of the four vascular disease measures are compared with each disease measure in turn. The disease groups are not mutually exclusive and the numbers involved along with the results of analyses are shown in Table 2. The table shows the adjusted mean scores on the cognitive function tests. The means have been adjusted for the effects of age and socioeconomic position, with statistically significant differences further expressed as an effect size.

The presence of angina between was associated with poorer cognitive function at phase 5 in both men and women ($F(6, 5680) = 5.16$, $p<.001$, Table 2). Angina was associated with poor cognitive function on all tests, although the effect sizes were small - average .21 for men and .24 for women. Non-fatal myocardial infarction (MI) was associated with poor cognitive function but univariate analysis revealed that this effect was not significant for all tests of cognitive function ($F(6, 5535) = 2.56$, $p<.02$, Table 2). There was no influence of non-

fatal MI on memory, numerical reasoning and phonemic fluency. However, there was a significant association between presence of MI and verbal reasoning, Mill Hill and semantic fluency with an average effect size of .23 for men and .22 for women.

There was a comprehensive association between all CHD (MI and angina) and cognitive function for both men and women ($F(6, 5747) = 4.80$, $p<.001$, Table 2). Individuals with heart disease had poorer scores on all cognitive tests, with the average effect sizes being .21 for men and .15 for women. Respondents reporting a diagnosis of intermittent claudication (IC) were also found to have poorer cognitive function ($F(6, 5418) = 3.23$, $p=.004$). As is evident from Table 2, there was an interaction between IC and sex for measures of memory and semantic fluency. IC was associated with memory impairment and poor semantic fluency in men but not in women. The average effect size for IC was .41 for men and .25 for women.

Sex and cognitive function

As sex had a significant main effect in the analyses examining the associations between vascular disease and cognitive function a separate MANCOVA was run to examine the main effect of sex. As is evident from Table 3 there was a significant effect of sex on cognitive function. The effect was due to men doing better at the numerical component of the AH 4 ($p<0.001$) and at Mill Hill ($p<0.02$). Women scored better on the memory test ($p<0.001$) and the verbal fluency tests - both phonemic ($p<0.001$) and semantic fluency ($p<0.001$). Research shows that the link between vascular pathology and cognitive impairment is particularly acute in women amongst the very old.[22] However, our results do not show this to be the case in a relatively young sample.

Discussion

We investigated the association between indicators of vascular disease and cognitive function in a large, stroke free, UK cohort. Three key results from this study need to be

emphasized. First, this association was evident in a relatively young sample, the average age of respondents being only 56 years when tested for cognitive function, indicating early neurological consequences of vascular disease. Due to the established links between stroke and cognitive impairment we have excluded individuals with known stroke from the analyses in order not to bias the association between vascular disease and cognitive function. The focus in this paper is an examination of the association between vascular disease, prevalent at baseline or incident during the follow up period, and impaired cognitive function. The size of the difference in cognitive performance between those with and without indicators of vascular disease was of similar magnitude to that in the Caerphilly cohort.[23]

This study adds to the growing body of evidence linking vascular disease and cognitive impairment. The mechanisms underlying this association remain to be explicated. Shi and colleagues[10] reviewed recent research and concluded that vascular pathology may be part of the spectrum of changes underlying both Alzheimer's disease and cerebrovascular dementia. Not only is vascular disease linked to cognitive decline,[2] but individuals with cognitive decline have been shown to have abnormalities consistent with cerebrovascular disease.[24] It is plausible that progressive occlusion of arteries resulting in vascular disease is likely to include occlusion of the cerebral arteries resulting in cerebral tissue loss and cognitive decline .

Second, there was little specificity in this association as all areas of cognitive function examined were found to be affected by indicators of vascular pathology. There has been some evidence to suggest that memory is not always affected by vascular disease,[13-14, 20, 25] but we found that in this healthy, relatively young sample that is not the case. MI was the only condition where memory was not affected, but then the effect of MI was more selective (see Table 2) than the other indicators of vascular disease. Other studies have also found the link between MI and poor cognitive performance to be tenuous.[26] We found larger effects for

intermittent claudication, arguably the more accurate marker of chronic vascular disease. Weaker effects were found for myocardial infarction and all coronary heart disease which are likely to include processes other than generalized vascular impairment.

The debate on specificity of cognitive impairment is linked to the relationship between cognitive impairment and dementia.[20] Defective memory and orientation are the hallmarks of dementia.[27] The results from this study suggest that vascular pathology is linked to global cognitive impairment, including domains that are key to the diagnosis of dementia. At the population level cognitive impairment is frequently examined using the Mini-Mental State Examination (MMSE). However, as the MMSE has ceiling effects among younger non-demented populations[28] it would not have been suitable for this population. The battery of tests that we used allowed an examination of different aspects of cognitive function rather than dementia per se.

Finally, there were no significant interactions between age and vascular disease, nor between employment grade and vascular disease. This implies that the negative effects of vascular disease did not vary by age or by employment grade. In a slightly older, African-Caribbean population, some vascular risk factors were found to be associated with poorer cognitive function only in those with lower levels of education.[29]

Public health implications

Cognitive impairment has been shown to be a predictor of functional decline,[20] dependent living,[20] and mortality.[3] The significance of the results reported here is that vascular pathology is predictive of poor cognitive function relatively early, and the ensuing functional decline and dementia dictate that efforts be made to alter the sequence of events. There is some evidence to suggest that antithrombotic medication may protect cognitive function in men with cardiovascular disease.[30] Consequently, the public health implications are in the domain of more aggressive management of vascular risk factors and vascular

disease even in stroke free populations. There may be additional benefits from treatment if it also slows down the process of cognitive decline and therefore should become more widespread.

Limitations of study

Some limitations of the current study should be noted. Firstly, the indicators of vascular disease used in this study are only proxy markers of cerebral circulation and cerebro-vascular disease. Stronger associations may be found if better measures of vascular disease were used. Secondly, the findings reported here are based on a single measure of cognitive function. With repeated measures of the cognitive tests it will be possible to explore changes in function in relation to vascular disease. Finally, it is likely that the strength of association between vascular disease and cognitive impairment has been underestimated in this study due to missing data. Apart from the reported biases relating to low socioeconomic position and poor cognitive function, it is likely that loss to follow-up is also influenced by poor health.

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Table 1 Sample characteristics of the Whitehall II study

		Phase 1 N=10308	Phase 2 N=8133	Phase 3 N=8637	Phase 4 N=8629	Phase 5 N=7830
Age (Mean)		44.45	47.41	49.76	52.72	55.96
Sex	Men	66.9%	68.0%	69.0%	69.3%	69.2%
	Women	33.1%	32.0%	31.0%	30.7%	30.6%
Grade†	1	11.0%	15.0%	17.2%	18.0%	21.7%
	2	18.4%	20.0%	21.0%	21.3%	20.1%
	3	13.8%	14.6%	14.1%	13.6%	13.6%
	4	19.2%	17.7%	16.9%	16.7%	15.5%
	5	14.9%	14.5%	14.1%	13.8%	14.2%
	6	22.7%	18.2%	16.8%	16.6%	14.9%

† Grade 1 represents high status and grade 6 represents low status.

Table 2 Association between vascular disease and cognitive function

Cognitive function	**MEN**			**WOMEN**		
	Mean*	Mean*	Effect size†	Mean*	Mean*	Effect size†
	No disease (N=3861)	Angina (N=205)		No disease (N=1591)	Angina (N=73)	
Memory test	6.76	6.36	.17	7.27	6.68	.22
AH 4-num	23.17	21.94	.22	21.91	20.07	.26
AH 4-verbal	24.06	22.91	.24	23.91	22.35	.27
Mill Hill	25.08	24.15	.24	24.80	23.60	.21
Phonemic fluency	16.61	15.98	.15	17.72	16.85	.18
Semantic fluency	16.27	15.33	.23	17.06	15.73	.28
	No disease (N=3861)	MI (N=110)		No disease (N=1591)	MI (N=24)	
Memory test	6.76	6.18	ns	7.28	6.87	ns
AH 4-numerical	23.21	22.75	ns	21.89	21.24	ns
AH 4-verbal	24.09	22.61	.32	23.90	23.26	.11
Mill Hill	25.10	24.52	.15	24.80	22.90	.34
Phonemic fluency	16.63	16.14	ns	17.73	18.50	ns
Semantic fluency	16.29	15.38	.23	17.06	16.10	.21
	No disease (N=3822)	CHD (N=305)		No disease (N=1564)	CHD (N=105)	
Memory test	6.77	6.30	.20	7.26	6.85	.15
AH 4-numerical	23.20	21.89	.23	22.93	20.61	.18
AH 4-verbal	24.08	22.82	.27	23.92	23.21	.12
Mill Hill	25.08	24.44	.17	24.82	23.87	.17
Phonemic fluency	16.63	16.01	.14	17.74	17.40	.07
Semantic fluency	16.29	15.37	.23	17.07	16.19	.19
	No disease	IC		No disease	IC	

	(N=3822)	(N=50)		(N=1564)	(N=32)	
Memory test	6.76	6.02	.32	7.28	7.65	-.14
AH 4-numerical	23.23	20.53	.48	22.91	19.78	.30
AH 4-verbal	24.10	22.08	.43	23.91	22.48	.25
Mill Hill	25.10	24.47	.17	24.82	23.01	.33
Phonemic fluency	16.64	14.97	.38	17.74	17.21	.11
Semantic fluency	16.31	13.74	.65	17.06	16.92	ns

*Analysis/means adjusted for effects of age and employment grade.

†Effect size (shown if statistically significant) is the difference between means expressed as a proportion of the standard deviation for that test.

Table 3 Association between sex and cognitive function

Cognitive function	MEN (N=4141) Mean*	WOMEN (N=1681) Mean*	Effect size†
Memory test	6.72	7.24	-.21
AH 4-numerical	23.06	21.83	.19
AH 4-verbal	23.95	23.86	ns
Mill Hill	25.02	24.74	.06
Phonemic fluency	16.56	17.70	-.25
Semantic fluency	16.19	17.01	-.19

*Analysis/means adjusted for effects of age and employment grade, $F(6, 5813) = 52.42$, $p<.001$

†Effect size (shown if statistically significant) is the difference between means expressed as a proportion of the standard deviation for that test.