Socioeconomic status moderates the association between carotid intima-media thickness and cognition in midlife: evidence from the Whitehall II study.

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Abstract

Background: Common carotid artery intima media thickness (IMT) is a measure of generalized atherosclerosis and has been shown to be associated with cognitive function. We examine two questions: does socioeconomic status (SES) moderate this association and is IMT more strongly associated with specific aspects of cognitive function?

Methods: Data are drawn from the Phase 7 (2003-2004) of the Whitehall II study (N=3896). In cross-sectional analyses the association between IMT and six measures of cognition (short term verbal memory, inductive reasoning, vocabulary, semantic and phonemic fluency and a measure of global cognitive status) was examined in analyses adjusted for previous history of coronary heart disease, health behaviours and other vascular risk measures such as blood pressure, cholesterol and body mass index.

Results: The overall association between IMT and the 6 measures of cognition was restricted to the low SES group (p=0.02). Within this group, IMT was significantly associated with inductive reasoning (p=0.001), vocabulary (p=0.002), phonemic (p=0.006) and semantic fluency (p=0.02). The covariates examined explained about a quarter of the association between IMT and cognition in the low SES group. The associations with the measure of inductive reasoning (p=0.02), vocabulary (p=0.02) and phonemic fluency (p=0.04) remained after adjustment for all covariates.

Conclusions: SES is an important modifier of the association between IMT and cognition, an inverse association between the two was observed only in the low SES group. It is possible that high cognitive reserve among the high SES individuals prevents the functional manifestations of atherosclerosis. Verbal memory was not one of the cognitive domains associated with IMT.

Introduction

Cerebrovascular disease is increasingly investigated as causally linked to cognitive impairment and dementia.[1] The association between vascular factors and cognitive impairment [2-4] and dementia [5-7] in older subjects is well established. This association has also been explored in middle aged subjects as research suggests that the sub-clinical phase of reduced cognitive function precedes the appearance of diagnosed dementia.[8-11] Common carotid artery intima media thickness (IMT) is one of the more recently identified vascular risk factors.[2,12] It is a marker of structural and functional vessel wall properties and is seen as an early indicator of generalized atherosclerosis,[13] or the extent of sub-clinical atherosclerosis.[14] Consequently, it has a robust association with cardiovascular disease and risk factors.[15-22] An association between IMT and cognitive impairment has been reported,[2,12,23] and has been shown to extend to stroke free persons.[24]

The objective of this study is examine whether socioeconomic status (SES) moderates, or is an effect modifier of, the association between IMT and cognition. Socioeconomic advantage has been shown to buffer adverse effects of certain exposures, low birth weight is a much explored example.[25-27] However, whether this holds true for adult exposures remains little explored. SES is known to be associated with cognitive function[28] and with IMT and its progression over time.[29,30] Thus, we examine whether the association between IMT and cognition is similar in different SES groups. A further objective is to examine whether specific aspects of cognition are more at risk from atherosclerosis. Early studies assessing the association between IMT and cognition used the Mini Mental State Examination (MMSE),[2,12] a measure of global cognitive status; but multiple measures of cognition are increasingly being examined in order to identify associations with specific aspects of cognition. Finally, we wish to explore the role played by various risk factors and covariates in explaining the IMT-cognition association.

Besides smoking[2,12] and education,[3,12,23] very few covariates have been included in the examination of the IMT cognition association. We aim to examine the extent to which the association between IMT and cognition can be explained by previous history of coronary heart disease (CHD), health behaviours and other vascular risk measures like blood pressure, cholesterol and body mass index.

Methods

Data are drawn from the Whitehall II study, established in 1985 as a longitudinal study to examine the socioeconomic gradient in health and disease among 10,308 civil servants (6,895 men and 3,413 women).[31] All civil servants aged 35-55 years in 20 London based departments were invited to participate by letter, and 73% agreed. Baseline examination (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, neuroendocrine function, and subclinical markers of cardiovascular disease. Subsequent phases of data collection have alternated between postal questionnaire alone and postal questionnaire accompanied by a clinical examination. Since baseline seven phases of data collection have been completed. Data used in the analyses come from the most recent phase of clinical examination (Phase 7, 2003-2004) completed when respondents were 50-74 years old. The University College London ethics committee approved the study.

Carotid IMT

99.9% of the 5743 individuals who came to the medical examination at Phase 7 were invited to the vascular clinic; the invitation was blinded to their cognitive and socioeconomic status. 4112 (72% of those invited) participants attended the vascular clinic. Ultrasound vascular measures were performed at the Vascular Physiology Unit, Institute of Child Health, London UK. Measurements were taken in a temperature controlled (22-26 degrees centigrade), quiet room using a non-invasive, high- resolution ultrasound system, the Aloka 5500 with a 7.5 MHz transducer.

Participants were examined in a supine position, with the head turned to a 45 degree angle away from the side to be scanned. Intima-media thickness (IMT) was measured in the right and left common carotid arteries. Longitudinal images of the common carotid artery, triggered on the R-wave of the ECG, were magnified and recorded in DICOM format as a cine loop, on the hard drive of the ultrasound machine for later analysis. The common carotid IMT was measured at its thickest part 1 cm proximal to the bifurcation. A measurement was taken between the leading edge of the intima and the media adventitia on 3 separate images on each side using electronic callipers and the mean of the 6 measures was used for analysis.

Cognitive function

Cognitive function was assessed with a battery of six standard tasks, chosen to provide a comprehensive evaluation of cognitive functioning in middle aged adults.

The first test was a 20-word free recall test of **short term verbal 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.

The **AH4-I** (Alice Heim 4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty.[32] It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. Participants had 10 minutes to do this section.

The **Mill Hill** Vocabulary test is a test of verbal meaning and encompasses the ability to recognize and comprehend words.[33] We used the test in its multiple format, consisting of a list of 33 stimulus words ordered by increasing difficulty and six response choices.

We used two measures of **verbal fluency**: phonemic and semantic.[34] Phonemic fluency was assessed via "S" words and semantic fluency via "animal" words. 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.

Finally, the 30-item MMSE was used to assess global cognitive status.[35]

Socioeconomic status

Socioeconomic status (SES) was assessed by British civil service grade of employment at baseline. This is a three level variable representing high (administrative grades), intermediate (professional or executive grades) and low (clerical or support grades) SES. People in the three SES groups differ with respect to salary, social status and level of responsibility. Although mostly white collar, respondents covered a wide range of SES, with annual salaries in 1995 ranging from £4,995 to £150,000. We used the baseline measure of SES rather than current SES in order to rule out reverse causation, in the sense that poor health might lead to lowered SES.

Covariates

Covariates included prevalent CHD, vascular risk factors and health behaviours.

CHD prevalence up to Phase 7 was based on clinically verified events and included fatal and non-fatal myocardial infarction (MI) and definite angina. MI was defined as a coronary death (ICD 9 codes 410–414 or ICD 10 codes I20-25) or non-fatal MI verified in clinical records. Based on all available data (from questionnaires, study ECGs, hospital acute ECGs, cardiac enzymes, physician records), non-fatal MI was defined following MONICA criteria.[36] Classification of MI and angina was carried out blind to other study data, independently by two trained coders, with adjudication by a third in the (rare) event of disagreement. Angina included participants who reported symptoms of angina,[37] with corroboration in clinical records or abnormalities on a resting ECG, exercise ECG, or coronary angiogram.

Vascular risk measures were comprised of systolic blood pressure (SBP), diastolic blood pressure (DBP), serum cholesterol and body mass index (BMI). Blood pressure was measured twice in the sitting position after 5 minutes rest with an automated Omron 907 devise. The average of two measures was taken to be the measured blood pressure. Serum cholesterol was measured within 72 hours in serum stored at 4°C using enzymatic colorimetric methods. BMI was calculated as weight in kilograms divided by height in meters squared. Weight was measured using a bio impedance scale (Tanita) to read weight to the nearest 0.1 kg. Height was measured to the nearest mm using a stadiometer with the participant standing completely erect with the head in the Frankfurt plane.

Health behaviours were assessed using alcohol consumption and smoking. Alcohol consumption was assessed via questions on the number of alcoholic drinks ("measures" of spirits, "glasses" of wine, and "pints" of beer) consumed in the last seven days. This was converted to number of units of alcohol consumed in the last week. Current smoking was assessed by the question 'Do you smoke cigarettes now? Participants were categorised as a current smoker if they replied 'yes'.

Statistical analysis

As it is widely accepted that stroke has an adverse effect on cognitive function,[38] all participants who reported an 'ever' doctor diagnosis of stroke at Phase 7 were excluded from the analyses (N=88). Descriptive analyses as a function of SES were carried out and tested using chi-square analysis for trend for categorical variables and by fitting a linear trend using ANOVA for continuous variables. The distribution for units of alcohol consumed was skewed and therefore its logged value (after the addition of one to all values to remove the zeros) was used in all analyses.

The measure of carotid IMT exhibited a slight deviation from normal. We conducted the analyses with and without transforming IMT but observed no important differences, leading us to retain the non transformed continuous measure. We used multiple analysis of covariance (MANCOVA), to account for the interrelation between the six measures of cognitive function per individual, in order to examine two questions. First, we fitted an interaction term between SES and IMT in order to assess whether IMT was associated with cognitive function in a similar manner in all SES groups. To ensure that the interaction term was not evident only at the high end of the IMT distribution we repeated the analysis by removing the top 10% and 20% of the IMT measures from the analysis. Second, we examined whether IMT had an overall association with cognitive function, as checking for each measure of cognitive function separately increases the chance of Type 1 error. Subsequently, multiple linear regression was used to assess the association between IMT and individual measures of cognitive function in analysis adjusted for age and sex. For these analyses, we used standardized IMT and cognitive data (z scores, mean=0, standard deviation=1) in order to allow the different cognitive measures to be compared. The role of covariates in explaining the IMT-cognition association was examined by adding the covariate to the model containing age, sex, IMT and cognitive function. The contribution of the covariate in explaining the IMT-cognition association was expressed as percentage reduction in the regression coefficient for IMT using the formula $(\text{beta}_{\text{IMT, controlling for age}} - \text{beta}_{\text{IMT, controlling for age and covariate}})/(\text{beta}_{\text{IMT, controlling for age}})\times 100$.

Results

Data on IMT and all covariates were available for 3896 individuals (2808 men and 1088 women). Compared to all 6550 (only 5743 of these came to the screening clinic) stroke free participants at Phase 7, this cohort included more men (72.1% against 70.6%), fewer low SES individuals (14.2% against 15.8%) and the average age of participants was lower (60.9 years against 61.07 years).

Characteristics of the study participants by SES are shown in Table 1. A significantly higher ($p < 0.0001$) proportion of women belonged to the low SES group; 38.0% women against 5.0% men. The test for trend shows that SES was associated with IMT only among women but was associated with all measures of cognitive function in men and in women. SES was associated with CHD prevalence only in women ($p=0.02$). Among the vascular risk factors in men, SES was associated only with systolic blood pressure ($p=0.03$) and cholesterol ($p=0.005$), but the association was such that higher SES men had worse risk profiles. Among women, SES was associated with systolic blood pressure ($p=0.01$) and BMI ($p<0.0001$), where low SES women had worse risk profiles. The association with alcohol was such that both higher SES men and women consumed more alcohol. Finally, low SES was associated with higher smoking prevalence in men ($p<0.0001$). The two sexes were combined for further analyses as the interaction term between sex and IMT ($p=0.20$) did not suggest gender differences in the association between IMT and cognition.

In order to examine whether the IMT-cognition association was different in the three SES groups we fitted an interaction term between IMT and SES in a MANCOVA model which took into account the interrelationship between the 6 measures of cognition used. This interaction term ($p=0.02$) suggested that the association between IMT-cognition was dissimilar in the three SES groups. We repeated this analysis in data where the top 10% and then 20% of the IMT measures had been excluded from the analysis; the results for the interaction term were no different (p=0.02 and p=0.004, respectively). Further analyses, adjusted for age and sex, were carried out separately in the three SES groups. In the high and intermediate SES groups, MANCOVA analysis revealed no association between IMT and cognition (p=0.82 and 0.37, respectively). In the low SES group, IMT was significantly associated with cognition overall (p=0.02).

Table 2 presents results from regression analysis carried out separately in the three SES groups for each measure of cognitive function. These results are presented using standardized data, in order to allow comparability of regression coefficients across measures of cognitive function. For instance, the age and sex adjusted association between IMT and AH4-I, in the low SES group was -0.144, implying that one standard deviation increase in IMT in this group was associated with 0.144 of a standard deviation decrease in the AH4-I score. Table 2 shows that IMT was not associated with any of the measures of cognitive function in the high and intermediate SES groups. On the other hand, in the low SES group it was associated with AH4-I (p=0.001), Mill Hill (p=0.002), phonemic (p=0.006) and semantic fluency (p=0.02). However, even in the low SES group IMT was not associated with memory (p=0.56) and MMSE (p=0.19).

Subsequent analyses, undertaken to assess the importance of explanatory variables to the association between IMT and cognition were carried out only in the "low SES" group and only for the measures of AH4-I, Mill Hill and the two measures of verbal fluency. These results are shown in Table 3. For instance, previous history of CHD explains 6.3% of the association between IMT and AH4-I, 11.1% with Mill Hill, 5.8% with phonemic and 1.0% with semantic fluency. Overall, the covariates explain 25.7% of the association between IMT and AH4-I, 27.8% of that with Mill Hill, 20.7% of that with phonemic fluency and 33.0% with semantic fluency. The association between IMT and cognition remains significant after adjustment for all covariates for AH4-I, Mill Hill and phonemic fluency.

Discussion

This paper presents two key findings. First, carotid artery intima media thickness in stroke-free middle-aged individuals (average age 60.9) is associated with cognition only among those with the most socioeconomic disadvantage. This result is unlikely to be due to poor health leading to socioeconomic disadvantage as the measure of SES used in the analyses predates the other measures by an average of 17 years. Second, IMT in this middle aged group is not associated with either short term verbal memory or the measure of global cognitive status (MMSE). After adjustment for prevalent CHD, vascular and behavioural risk factors, IMT is significantly associated with the measure of inductive reasoning (AH4-I), vocabulary (Mill Hill) and the measure of phonemic fluency.

This is the first study to examine explicitly the association between IMT and cognition as a function of the SES of the participants. We repeated the analysis in individuals with lower IMT by removing the top 10% and then 20% of the IMT measures in order to rule out the possibility that the results were an artefact of associations at the extremes of the IMT distribution. We obtained similar results for the entire distribution of the IMT score, confirming the reliability of our results. Thus, it appears that SES, here measured by employment grade, is an important moderator of the association between IMT and cognition. A moderator (or an effect modifier) is a variable where the degree of association between an exposure and an outcome variable changes according to its value.

The view that SES may act as a moderating variable has been shown with other health outcomes,[39-41] and is also represented in the notion of cognitive reserve.[42-44] Cognitive reserve can broadly be seen as the ability of an individual to tolerate progressive brain pathology without manifestation of clinical cognitive symptoms. High SES or education is often used as a proxy for cognitive reserve and seen to buffer the effects of neuropathology in such a way that the greater the reserve, the more severe the pathology must be to cause functional impairment. The concept of cognitive reserve can be seen to be composed of two elements.[44] The first, the passive model, sees reserve as being linked to brain capacity. Thus, a decline of capacity to a certain threshold needs to be reached for specific functional or clinical cognitive deficits to emerge. The active model of reserve sees efficiency of neural networks and active compensation by alternative or more extensive networks after disease or insult to the central nervous system to provide protection against the functional consequences of neuropathology in terms of delaying or preventing the detection of the disease, rather than protecting against disease acquisition itself. Low SES, as a proxy of smaller cognitive reserve, is likely to be increasingly seen to be a risk factor for dementia. In fact, a recent attempt to predict dementia among middle aged individuals over 20 years of follow-up risk found education along with age, gender, blood pressure, body mass index, cholesterol, physical activity and APOE e4 status to reliably predict dementia and was used to elaborate a dementia risk score.[45] Education is one of the multiple indicators of SES.

We examined six different measures of cognition: short term verbal memory, inductive reasoning (AH4-I), vocabulary (Mill-Hill), 2 measures of verbal fluency and a measure of cognitive status (MMSE). Most studies that have examined the association between IMT and cognition have used measures of global cognitive status such as the MMSE,[2,12,46,47] which does not assess specific aspects of cognition. Our results show IMT not to be significantly associated with the MMSE and memory. The results relating to memory are unsurprising as the expectation is that vascular risk factors are not necessarily related to memory.[3] Our results on the MMSE could be explained by the fact that there is little variation in the MMSE scores in our sample, most individuals at this age (average age 60.9) score highly on the MMSE. The associations (Spearman correlation) between SES and memory (r=0.19) or the MMSE (r=0.19) were weaker when compared to the other measures of cognition used here: AH4-I (r=0.49), Mill Hill (r=0.52), phonemic (r=0.30), and semantic fluency (r=0.35). At this stage, it is unclear whether some specific measures of cognition are particularly vulnerable to atherosclerosis or if it is just their greater association with SES that is being picked up in the associations with IMT.

The associations between IMT and cognition we report are small but comparable to those reported by other studies on stroke-free middle-aged individuals.[12,23] While the mechanisms underlying this association remain to be explicated, it is plausible that progressive occlusion of arteries in vascular disease is likely to include occlusion of the cerebral arteries resulting in cerebral tissue loss and cognitive decline. Evidence of the link between impaired cognitive function in middle age and subsequent dementia,[8,10,11] leads us to believe that the results reported here are clinically relevant. Thus, attempts to use vascular risk profiles to predict late-life dementia in people of middle age[45] ought to consider the fact that a certain risk profile might have a different meaning in different SES groups.

The results reported here need to be interpreted with a few issues in mind. First, Whitehall II is a study on individuals who had stable white-collar jobs at baseline and thus do not represent the general population. As a result these individuals do not represent the lowest end of the socioeconomic spectrum, the unemployed or those in insecure jobs. Nevertheless, the salary range of the participants clearly indicates that the study includes a wide socioeconomic spectrum. Second, data here are drawn from the 19th year of a study, implying both survival and selection effects. This is evident in the results on covariates presented in Table 1; the participants in this study are a fairly healthy group. Therefore, it is possible that the association between IMT and cognition is underestimated in our sample. Finally, our cross-sectional results need to be replicated in longitudinal data.

In conclusion, our results show carotid artery intima-media thickness, a simple surrogate measure of atherosclerosis, to be associated with some measures of cognition in middle aged individuals in the "low" SES group. We interpret these results to imply that it is high cognitive reserve among the high SES individuals that is preventing functional manifestations of atherosclerosis. The associations with cognition are domain specific and the results suggest no association with short term verbal memory.

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Table 1: Characteristics of the sample as a function of Socioeconomic Status (SES)†

			High SES	Intermediate SES	Low SES	**p value for trend**
N	M	N (%)	1190 (42.4%)	1477 (52.6%)	141 (5.0%)	p < 0.0001
	F		185 (17.0%)	490 (45.0%)	413 (38.0%)	
Age	M	M (SD)	62.32 (5.61)	60.04 (5.77)	60.84 (6.51)	p < 0.0001
	F		59.80 (5.49)	60.07 (5.93)	62.04 (5.73)	p < 0.0001
IMT (mm)	M	M (SD)	0.80 (0.16)	0.79 (0.16)	0.82 (0.18)	p =0.33
	F		0.76 (0.13)	0.77 (0.13)	0.79 (0.14)	p = 0.02
Memory	M	M (SD)	7.18 (2.28)	6.65 (2.24)	5.67 (2.49)	p < 0.0001
	F		8.32 (2.27)	7.31 (2.41)	6.09 (2.43)	p < 0.0001
AH4-I	M	M (SD)	49.90 (7.97)	44.46 (9.44)	30.71 (11.19)	p < 0.0001
	F		50.34 (7.02)	43.11 (9.39)	31.14 (9.76)	p < 0.0001
Mill Hill	M	M (SD)	27.39 (2.72)	24.93 (3.45)	20.25 (6.02)	p < 0.0001
	F		27.96 (2.32)	25.24 (3.57)	19.34 (5.06)	p < 0.0001
Phonemic fluency	M	M (SD)	17.14 (3.88)	15.50 (3.83)	12.24 (4.28)	p < 0.0001
	F		18.81 (3.98)	16.36 (3.80)	13.71 (3.72)	p < 0.0001
Semantic fluency	M	M (SD)	17.05 (3.43)	15.58 (3.41)	11.93 (3.48)	p < 0.0001
	F		18.65 (3.876)	16.20 (3.83)	12.86 (3.50)	p < 0.0001
MMSE	M	M (SD)	28.91 (1.19)	28.71 (1.31)	27.86 (1.70)	p < 0.0001
	F		29.16 (1.01)	28.88 (1.24)	28.18 (1.55)	p < 0.0001
Coronary heart disease	M	N (%)	118 (9.9%)	116 (7.9%)	20 (14.2%)	p = 0.72
	F		8 (4.3%)	33 (6.7%)	40 (9.7%)	p =0.02
Systolic Blood Pressure (mmHg)	M	M (SD)	127.90 (15.50)	127.18 (15.22)	124.54 (14.65)	p =0.03
	F		122.84 (17.65)	124.70 (16.86)	126.50 (17.33)	p =0.01
Diastolic Blood Pressure(mmHg)	M	M (SD)	74.15 (10.32)	74.33 (10.05)	72.16 (10.06)	p =0.05
	F		71.87 (10.32)	72.57 (10.42)	72.55 (10.56)	p =0.36
Cholesterol (mmol/l)	M	M (SD)	5.68 (0.97)	5.62 (0.99)	5.41 (1.03)	p =0.005
	F		5.99 (1.02)	5.94 (1.00)	5.89 (1.03)	p =0.25
Body Mass index (kg/m^2)	M	M (SD)	26.20 (3.65)	26.50 (3.77)	26.49 (4.23)	p =0.06
	F		25.55 (5.06)	26.42 (5.30)	27.56 (4.89)	p < 0.0001
Alcohol units in a week	M	GM (SDL)	11.49 (2.61)	9.13 (3.08)	5.34 (3.55)	p < 0.0001
	F		8.23 (2.58)	5.15 (2.86)	2.62 (2.69)	p < 0.0001
Current smoker	M	N (%)	90 (7.6%)	187 (12.7%)	35 (24.8%)	p < 0.0001
	F		13 (7.0%)	45 (9.2%)	39 (9.4%)	p =0.40

† Analysis restricted to those with complete data.

† GM: Geometric mean; SDL: Standard deviation of logged values (see statistical analysis).

Table 2: Age and sex adjusted association between IMT and cognitive function, as a function of SES.[†]

Cognitive function	High SES N = 1375	Intermediate SES N = 1967	Low SES N = 554
	beta[‡] (p)	beta[‡] (p)	beta[‡] (p)
Memory	-.006 (p = 0.83)	.023 (p = 0.31)	-.026 (p = 0.56)
AH4-I	.021 (p = 0.44)	-.026 (p = 0.25)	-.144 (p = 0.001)
Mill Hill	.001 (p = 0.98)	-.00 (p = 1.00)	-.144 (p = 0.002)
Phonemic fluency	-.02 (p = 0.47)	-.02 (p = 0.40)	-.121 (p = 0.006)
Semantic fluency	-.028 (p = 0.30)	-.005 (p = 0.83)	-.106 (p = 0.02)
MMSE	.03 (p = 0.28)	.008 (p = 0.73)	-.058 (p = 0.19)

[†] Analysis restricted to those with complete data.
[‡] Standardized regression coefficient

Table 3: The role of explanatory factors in explaining the link between IMT and cognition in the low SES group.[†]

	beta[‡]	(95% CI)	p	%Δ[#]
AH4-I				
IMT (adjusted for age & sex)	-.144	(-.232, -.057)	0.001	
+ CHD	-.135	(-.223, -.048)	0.003	6.3%
+ SBP, DBP, Cholesterol, BMI	-.125	(-.215, -.035)	0.006	13.2%
+ alcohol, smoking	-.133	(-.219, -.047)	0.003	7.6%
+ all above	-.107	(-.196, -.018)	0.02	25.7%
Mill Hill				
IMT (adjusted for age & sex)	-.144	(-.232, -.055)	0.002	
+ CHD	-.128	(-.217, -.040)	0.005	11.1%
+ SBP, DBP, Cholesterol, BMI	-.136	(-.226, -.045)	0.003	5.6%
+ alcohol, smoking	-.123	(-.210, -.037)	0.005	14.6%
+ all above	-.104	(-.193, -.015)	0.02	27.8%
Phonemic fluency				
IMT (adjusted for age & sex)	-.121	(-.208, -.034)	0.006	
+ CHD	-.114	(-.201, -.027)	0.01	5.8%
+ SBP, DBP, Cholesterol, BMI	-.113	(-.203, -.024)	0.01	6.6%
+ alcohol, smoking	-.110	(-.196, -.023)	0.01	2.5%
+ all above	-.096	(-.186, -.006)	0.04	20.7%
Semantic fluency				
IMT (adjusted for age & sex)	-.106	(-.193, -.020)	0.02	
+ CHD	-.105	(-.192, -.018)	0.02	1.0%
+ SBP, DBP, Cholesterol, BMI	-.082	(-.171, .006)	0.07	22.6%
+ alcohol, smoking	-.095	(-.180, -.010)	0.03	10.4%
+ all above	-.071	(-.159, .016)	0.11	33.0%

[†] Analysis restricted to those with complete data and the "low" SES group.
[‡] Standardized regression coefficient
[#] Percentage reduction in the regression coefficient = $(\text{beta}_{\text{IMT, controlling for age}} - \text{beta}_{\text{IMT, controlling for age and covariate}})/(\text{beta}_{\text{IMT, controlling for age}})\times 100$.

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