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Cognition and incident coronary heart disease in late midlife: The Whitehall II study

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ABSTRACT

The purpose of this study was to investigate whether cognitive function in midlife predicts incident coronary heart disease (CHD), followed up over 6 years. Data on 5292 (28% women, mean age 55) individuals free from CHD at baseline were drawn from the British Whitehall II study. We used Cox regression to model the association between cognition and CHD in analyses adjusted for socio-demographic variables, cardiovascular risk factors and health behaviors. The results show a one standard deviation lower score on the "general" cognitive measure and measures of reasoning and vocabulary to be associated with elevated CHD risk. There was some evidence that these effects differed between high and low socioeconomic status (SES) groups with associations only seen in the low SES group. These results were not explained by threshold effects or by the different SES groups representing different parts of the cognitive test score distribution. Three other possible explanations of these results are discussed: sub clinical vascular disease drives the observed association but no effect is observed in the high SES group due to compensation provided by greater cognitive reserve, cognition is a marker of overall bodily integrity particularly in low-SES groups, and SES is a moderator of the association between cognition and CHD, because it marks a range of other risk factors.

Impaired adult cognition predicts future health outcomes like dementia (Chertkow, 2002; Morris et al., 2001) and mortality (Bassuk, Wypij, & Berkman, 2000; Dewey & Saz, 2001; Fried et al., 1998; Gale, Martyn, & Cooper, 1996), and there is some evidence to link it to health functioning at older ages (Mehta, Yaffe, & Covinsky, 2002). However, there is little research on adult cognition as a risk factor for chronic diseases at older ages. The emerging field of cognitive epidemiology posits such a role for cognitive function (Deary & Batty, 2007). The objective of this paper is to examine whether cognitive function is a risk factor for coronary heart disease (CHD). CHD is a global problem, with the risk of disease shown to increase as societies undergo urbanization (Yusuf, Reddy, Ounpuu, & Anand, 2001). In many western countries, including the United Kingdom, it remains the leading cause of death (Department of Health, UK, 2007).

Examining the status of cognition as a risk factor for CHD is complicated by the fact that vascular risk factors and indicators of vascular disease are established risk factors for both cognitive impairment (Breteler et al., 1994; Desmond, Tatemichi, Paik, & Stern, 1993; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995) and dementia (Aronson et al., 1990; Breteler, 2000; de la Torre, 2002; Shi, Perry, Smith, & Friedland, 2000). The atherosclerotic process and related hypoperfusion is seen to be responsible for this association (de la Torre, 2002). However, dementia has also been shown to be a risk factor for future heart disease (Bursi et al., 2006). Clearly, cause and effect is difficult to tease apart in very elderly populations due to high levels of co-morbidities. Even in younger populations the results that show an

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association between cognition and CHD may be driven by the effects of underlying cardiovascular risk factors. Furthermore, few studies have studied whether the association between cognition and CHD is independent of socioeconomic status (SES); SES is associated with both CHD (Yusuf et al., 2001) and cognition (Singh-Manoux, Ferrie, Lynch, & Marmot, 2005).

Data from the Whitehall II study allowed us to assess the association between cognition and incidence of CHD, with the possibility of adjusting for a range of cardiovascular risk factors. A further reason of examining the association between cognition and CHD in the Whitehall II study was the opportunity to assess whether SES modified the association. To improve outcome precision, we included a range of cognitive tests, considered them individually and then in combination using factor analysis to constitute a "general" cognitive factor.

1. 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 (6895 men and 3413 women) (Marmot & Brunner, 2005). All civil servants aged 35–55 years in 20 London based departments were invited to participate by letter, and 73% agreed. Baseline screening (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. The clinical examination included measures of blood pressure, anthropometry, biochemical measurements, neuroendocrine function, and sub clinical markers of cardiovascular disease. Subsequent phases of data collection have alternated between postal questionnaire alone (Phases 2 (1989–1990), 4 (1995–1996), 6 (2001) and 8 (2006)) and postal questionnaire accompanied by a clinical examination (Phases 3 (1991–1993), 5 (1997–1999) and 7 (2002–2004)). The University College London ethics committee approved the study.

Cognitive function was assessed at Phase 5 using a battery of five standard tasks, described below.

Short-term verbal memory was assessed with a 20-word free recall test. 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 2 min to do so.

The Alice Heim 4-I (AH4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty (Heim, 1970). It tests inductive *reasoning*, measuring the ability to identify patterns and infer principles and rules. Participants had 10 min to do this section.

Vocabulary was assessed using the *Mill Hill Vocabulary test* (Raven, 1965), used in its multiple-choice 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 (Borkowski, Benton, & Spreen, 1967). *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.

Principal component analysis of these 5 cognitive measures was used to construct a composite measure of the *general cognitive (g) factor* (Plomin, 1999). The first factor accounted for 56% of the variance and the factor loadings were 0.32 for memory, 0.50 for AH4-I, 0.46 for Mill Hill, 0.45 for phonemic fluency and 0.49 for semantic fluency.

Incident CHD events included coronary death (ICD 9 codes 410–414 or ICD 10 codes I20-25), non-fatal myocardial infarction (MI) and definite angina. MI was determined using data from questionnaires, study ECGs, hospital acute ECGs, cardiac enzymes, and physician records following MONICA criteria (Tunstall-Pedoe et al., 1994). Angina was assessed based on the participant's reports of symptoms (Rose et al., 1977), with corroboration in medical records for nitrate medication use or abnormalities on a resting electrocardiogram, an exercise electrocardiogram, or a coronary angiogram. We excluded angina cases that were based solely on self-reported data. The independent variable in our analysis is cognitive function and the dependent variable is CHD, starting the follow-up period for CHD subsequent to cognitive testing ensures that we only include "incident" events. All participants with prevalent CHD were excluded from the analysis.

Covariates used were age, sex, sociodemographic variables, cardiovascular risk factors and health behaviors, all assessed at Phase 5.

Socio-demographic variables were composed of marital status (married/cohabiting, single, widowed, and divorced/separated), education (no academic qualifications, lower secondary school, higher secondary school, university, and higher university degree) and last civil service employment grade at Phase 5, classified into high, intermediate and low grade. Employment grade in the Whitehall II study is a comprehensive marker of SES and is related to salary, social status and level of responsibility.

Cardiovascular risk factors included diabetes, based on 2-hr glucose tolerance test or fasting glucose results using WHO criteria (Alberti & Zimmet, 1998) or self-reports. Systolic and diastolic blood pressure were measured twice with the participant sitting after a 5-minute rest using the Hawksley random-zero sphygmomanometer. The average of these two readings was taken to be the measured blood pressure. Serum cholesterol was measured within 72 h in serum stored at 4 °C using enzymatic colorimetric methods. We also adjusted for cardiovascular disease medication; diuretics, beta-blockers, ACE and AII inhibitors, calcium channel blockers and other antihypertensive drugs, lipid lowering drugs, nitrates and antiplatelet drugs.

Health behaviors were assessed from questionnaire data; smoking (current, past, never), alcohol consumption (units of alcohol consumed last week), frequency of fruit and vegetable consumption (single item measure on a 8-point scale, ranging from 'seldom or never' to 'two or more times a day'), and hours of physical activity (sum of the hours of weekly moderate and vigorous physical activities in response to a 20-item questionnaire on the frequency and duration of participation in walking, cycling, sports, gardening, housework, and home maintenance).

2. Statistical analysis

We first examined the form of the cognition–CHD relationships in order to ensure that all these associations could be adequately described using a single linear term across the whole

Table 1
Sample characteristics of participants in those with and without subsequent incident CHD.

	CHD	No CHD	*p*
N (%)	181 (3.4%)	5111 (96.6%)	
% women	36 (19.9%)	1463 (28.6%)	0.01
Age *M* (SD)	59.4 (5.5)	55.2 (5.9)	<0.0001
% married	141 (77.9%)	3932 (76.9%)	0.76
% university degree or higher	58 (32.0%)	1564 (30.6%)	0.68
% high employment grade	86 (47.5%)	2234 (43.7%)	0.31
% diabetes	61 (33.7%)	777 (15.2%)	<0.0001
Total cholesterol, mmol/L *M* (SD)	6.1 (1.1)	5.9 (1.0)	0.06
Systolic blood pressure, mm Hg *M* (SD)	130.3 (19.1)	122.2 (16.4)	<0.0001
Diastolic blood pressure, mm Hg *M* (SD)	80.4 (12.2)	77.3 (10.4)	0.001
% CVD medication	48 (26.5%)	633 (12.4%)	<0.0001
% smokers	28 (15.5%)	767 (15.0%)	0.86
Units of alcohol consumed/week *M* (SD)	13.2 (16.3)	13.8 (14.8)	0.59
% frequent fruit and vegetable consumption[a]	140 (77.4%)	3784 (74.0%)	0.32
Hours of physical activity/week *M* (SD)	15.6 (14.7)	12.9 (11.9)	0.02
Memory (range 0–20) *M* (SD)	6.6 (2.6)	6.9 (2.4)	0.04
AH4-I (range 0–65) *M* (SD)	44.3 (12.9)	47.1 (10.8)	0.004
Mill Hill (range 0–33) *M* (SD)	24.5 (4.8)	25.1 (4.4)	0.05
Phonemic fluency (range 0–35) *M* (SD)	16.0 (4.4)	17.0 (4.4)	0.004
Semantic fluency (range 0–35) *M* (SD)	15.9 (4.2)	16.6 (4.2)	0.03

M: mean; SD: standard deviation.
[a] Denotes at least daily consumption of fruits and vegetables.

distribution of cognitive scores. Tests for non-linearity in the associations between cognitive measures and CHD were performed using the SAS macro rcs.mac (Heinzl & Kaider, 2007). We then examined whether the association between cognition and incident CHD was similar in men and women by fitting appropriate interaction terms. We modeled the association between each cognitive measure and CHD using Cox proportional hazards regression models after confirming that the proportionality assumption was not violated (p for interaction of cognitive scores with log(time) >0.35 for all cognitive tests). We present these results by showing the hazard ratio of CHD associated with a one standard deviation decrease in each cognitive measure. The analyses were first adjusted for age and sex (model 1). Subsequent models were further adjusted for socio-demographic measures (model 2), cardiovascular risk factors (model 3) and health behaviors (model 4). The analyses were performed using SAS statistical software, version 9.1.

3. Results

We present results for incident CHD events among those who did not have a history of CHD. At phase 5, 7830 individuals were still participating in the study. Data on all covariates included in the analysis were available for 5628 individuals. After excluding those with a previous CHD event, 5292 participants remained; 28% were women. At the start of the follow-up period individuals were on average 55.4 (Standard Deviation (SD) = 6.0) years old and the mean follow-up period was 6.4 years (SD = 1.0). One hundred and eighty-one incident CHD events were observed over the follow-up period. Table 1 presents the sample characteristics in those with and without a subsequent CHD event.

We examined the correlations between the 'general' cognitive factor and the continuously measured covariates. Higher scores were associated with age inversely ($r = -0.25$, $p<0.01$), more physical activity ($r = 0.08$, $p<0.01$), greater alcohol consumption ($r = 0.27$, $p<0.01$), more frequent fruit and vegetable consumption ($r = 0.19$, $p<0.01$), higher education ($r = 0.45$, $p<0.01$), higher grade (measured in 6 categories, r = 0.56, $p<0.01$), with both lower diastolic ($r = -0.04$, $p<0.01$) and systolic ($r = -0.10$, $p<0.01$) blood pressure but not with cholesterol ($r = -0.02$, $p = 0.13$).

For all cognitive measures, there was no evidence of non-linearity in the association with CHD (the p for non-linearity was 0.11 for the 'general' cognitive factor, 0.42 for memory, 0.06 for the AH4-I, 0.36 for Mill-Hill, 0.41 for phonemic and 0.16 for semantic fluency). The results for the interaction terms provide no evidence for sex differences in the association between cognitive measures and incident CHD (all p from 0.09 to 0.79) justifying combined analyses of men and women. However, since there was some evidence of an interaction with SES (the interaction term in model 1 was 0.05 for the 'general' cognitive factor, 0.18 for memory, 0.06 for the AH4-I, 0.52 for Mill-Hill, 0.34 for phonemic and 0.08 for semantic fluency), we will first show results on the whole sample and then show the results stratified by SES.

In the whole sample, a one standard deviation lower score on the "general" cognitive factor was associated with a 17% greater risk of incident CHD in the analysis adjusted for

Table 2
The association between cognition and incident coronary heart disease (CHD).

	Model 1	Model 2	Model 3	Model 4
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
"General" factor	1.17 (1.01–1.37)*	1.27 (1.06–1.53)*	1.22 (1.01–1.46)*	1.10 (0.95–1.27)
Memory	1.00 (0.86–1.16)	1.00 (0.86–1.17)	0.98 (0.83–1.14)	0.97 (0.83–1.13)
AH4-I (reasoning)	1.24 (1.07–1.44)*	1.36 (1.14–1.62)*	1.32 (1.11–1.57)*	1.26 (1.06–1.52)*
Mill Hill (vocabulary)	1.21 (1.05–1.39)*	1.32 (1.12–1.55)*	1.29 (1.09–1.52)*	1.24 (1.04–1.47)*
Phonemic fluency	1.10 (0.94–1.29)	1.12 (0.95–1.32)	1.09 (0.93–1.28)	1.06 (0.90–1.24)
Semantic fluency	1.04 (0.89–1.21)	1.05 (0.89–1.24)	1.02 (0.86–1.20)	0.98 (0.83–1.16)

Model 1: adjusted for age and sex.
Model 2: model 1 + employment grade, education and marital status.
Model 3: model 2 + diabetes, systolic and diastolic blood pressure, total cholesterol, medication for cardiovascular disease.
Model 4: model 3 + smoking, alcohol consumption, fruit and vegetable consumption, hours of moderate and vigorous physical activity.
* $p<0.05$.

Table 3
Cognition function measures in the total population and the high and low SES groups.

	Total population	High SES	Low SES [a]	p [b]
	N = 5292	N = 2320	N = 2972	
Memory (range 0–20) M (SD)	6.9 (2.4)	7.3 (2.3)	6.6 (2.5)	p<0.001
AH4-I (range 0–65) M (SD)	47.0 (10.9)	52.5 (7.3)	42.7 (11.3)	p<0.001
Mill Hill (range 0–33) M (SD)	25.1 (4.4)	27.2 (2.7)	23.5 (4.8)	p<0.001
Phonemic fluency (range 0–35) M (SD)	17.0 (4.4)	18.3 (4.2)	15.9 (4.3)	p<0.001
Semantic fluency (range 0–35) M (SD)	16.5 (4.2)	17.9 (3.8)	15.5 (4.2)	p<0.001

M: mean; SD: standard deviation.
[a] Includes low and intermediate employment grade.
[b] Difference between the high and low SES group.

age and sex (Hazard Ratio (HR) = 1.17; 95% confidence interval (CI) = 1.01–1.37) — Table 2. This association was much attenuated after adjustment for cardiovascular risk factors and health behaviors (HR = 1.10; 95% CI = 0.95–1.27). However, a one standard deviation lower score in the AH4-I (HR = 1.26; 95% CI = 1.06–1.52) and Mill-Hill (HR = 1.24; 95% CI = 1.04–1.47) remained associated with 24–26% excess incidence of CHD in the fully adjusted analysis (model 4).

In further analysis we examined the association between cognition and CHD in analysis stratified by SES. The stratified analyses are on two groups: the high SES and low SES group, the latter combined the intermediate and low grades due to the small number of CHD events and similarity in the association between cognition and CHD. Table 3 shows the mean and standard deviation for the 5 cognitive tests in the total population and in the two SES groups. Table 4 shows the association between cognition and incident CHD separately in the high and low SES groups; the results show no evidence of an association between cognitive scores and CHD in the high SES group. However, in the lower SES group the general "cognitive" factor (HR = 1.28; 95% CI = 1.01–1.62) and specific measures, such as AH4-I (HR = 1.35; 95% CI = 1.07–1.69) and Mill Hill (HR = 1.23; 95% CI = 1.00–1.50), were all associated with incident CHD in analysis adjusted for all covariates (model 4).

4. Discussion

This paper presents two key findings. First, some cognitive test scores are associated with incident CHD in middle-aged individuals; aged on average 55 years at the start of the follow-up. The association is evident with measures of reasoning and vocabulary but not with measures of memory and verbal fluency. Second, SES moderates the association between cognition and CHD so that in the high SES group cognitive measures show no association with incidence of coronary heart disease. Thus, the first finding reported here is evident in the lower socioeconomic groups only.

These findings need to be considered in light of the fact that vascular pathology is seen as one of the three key determinants of cognitive ageing and dementia outcomes (Holland & Rabbitt, 1991). Our own previous work has shown history of CHD to be associated with poor cognitive function, with stronger effects for long-standing CHD (Singh-Manoux et al., 2008b). The cognitive test battery was introduced at the Phase 5 of the Whitehall II study, when participants were on average 55 years old, in order to study the social, behavioral and biological determinants of cognitive ageing. Although the tests assess a range of cognitive abilities, they all tap into verbal ability, except the numerical part of the AH4-I, and are well suited to this white-collar cohort. As our primary concern is research on associations between cognition and health rather than intelligence per se, it is possible that our 'general' cognitive score might not be equivalent to other constructions of the *g* score.

Table 4
The association between cognition (decrease by one standard deviation) and incident coronary heart disease (CHD). [‡]

	Model 1	Model 2	Model 3	Model 4
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
High SES (N = 2320; No. CHD events = 86)				
"General" factor	0.93 (0.69–1.25)	0.95 (0.70–1.29)	0.92 (0.67–1.25)	0.88 (0.65–1.21)
Memory	0.86 (0.69–1.08)	0.88 (0.70–1.10)	0.85 (0.68–1.07)	0.84 (0.67–1.06)
AH4-I (reasoning)	1.05 (0.78–1.43)	1.07 (0.78–1.46)	1.07 (0.78–1.45)	1.04 (0.76–1.42)
Mill Hill (vocabulary)	1.20 (0.87–1.66)	1.22 (0.88–1.70)	1.21 (0.87–1.69)	1.17 (0.82–1.66)
Phonemic fluency	1.00 (0.79–1.26)	1.02 (0.80–1.30)	0.99 (0.78–1.26)	0.98 (0.77–1.25)
Semantic fluency	0.84 (0.66–1.06)	0.85 (0.66–1.08)	0.82 (0.65–1.05)	0.81 (0.64–1.03)
Low SES[†] (N = 2972; No. CHD events = 95)				
"General" factor	1.38 (1.13–1.68) *	1.48 (1.18–1.86) *	1.40 (1.11–1.76) *	1.28 (1.01–1.62) *
Memory	1.13 (0.91–1.39)	1.12 (0.91–1.40)	1.07 (0.86–1.33)	1.04 (0.84–1.29)
AH4-I (reasoning)	1.44 (1.18–1.76) *	1.55 (1.24–1.93) *	1.46 (1.17–1.82) *	1.35 (1.07–1.69) *
Mill Hill (vocabulary)	1.27 (1.07–1.50) *	1.35 (1.12–1.65) *	1.31 (1.08–1.60) *	1.23 (1.00–1.50) *
Phonemic fluency	1.21 (0.97–1.51)	1.20 (0.95–1.51)	1.16 (0.93–1.45)	1.10 (0.88–1.37)
Semantic fluency	1.24 (1.00–1.54) *	1.25 (0.99–1.57)	1.20 (0.96–1.52)	1.13 (0.90–1.43)

Model 1: adjusted for age and sex.
Model 2: model 1 + residual effects of employment grade (low SES group only), education and marital status.
Model 3: model 2 + diabetes, systolic and diastolic blood pressure, total cholesterol, medication for cardiovascular disease.
Model 4: model 3 + smoking, alcohol consumption, fruit and vegetable consumption, hours of moderate and vigorous physical activity.
[‡]Test for interaction of the effects in Model 1 between the high and low SES groups.
[†]Includes low and intermediate employment grade.
* $p<0.05$.

The objective of the present paper is to examine the association the other way around to assess whether poor cognition is a risk factor for CHD in individuals free of manifest disease at baseline at mean age 55. A major difference from our previous work is that the results reported here are based on late onset CHD. It is important to recognize that cognition and health outcomes have reciprocal effects with the importance of one over the other varying over the lifecourse. The mechanisms linking vascular risk factors to cognitive outcomes in the elderly are much researched and fairly well established (Breteler, 2000; Breteler et al., 1994; de la Torre, 2002; Desmond et al., 1993; Launer et al., 1995; Shi et al., 2000). In contrast, the mechanisms that would make cognition a risk factor for CHD are less well understood. One comprehensive framework suggests that intelligence influences health as it is a record of bodily insults, an indicator of system integrity, is related to healthy behaviors and is a predictor of entry into safer environments (Whalley & Deary, 2001). Our analysis adjusts for education, health behaviors and many cardiovascular risk factors to examine these different pathways. Even though our results show some attenuation on adjustment for cardiovascular risk factors and health behaviors, the cognition–CHD association is robust and dependent on employment grade, a comprehensive measure of SES in our cohort. As this is a new finding, we will devote the rest of the discussion to this issue. We propose and discuss four possible explanations.

First, one possible explanation for observing differing associations in high and low SES groups may be a consequence of threshold effects in the association between cognition and subsequent CHD. If this was the case then differing distributions of cognitive scores between the two SES groups might result in differing associations. Even though our results show differences between the two SES groups, these are not large enough to lead to the current results observed with CHD. Furthermore, associations of the cognitive scores with CHD were consistent with a linear relationship across the whole distribution of scores. Thus, the differential results by SES seem not to be due to the different SES groups representing different parts of the cognitive test score distribution.

The second explanation is drawn from work on the association between cognition and mortality that advances the view that cognition may be a marker of 'bodily integrity' and in this way be associated with health outcomes (Shipley, Der, Taylor, & Deary, 2007; Whalley & Deary, 2001). This is one of the four principal mechanisms proposed to explain the association between early life cognition and subsequent mortality (Whalley & Deary, 2001). If there is an SES difference in 'bodily integrity' then our cognitive measures do not capture it.

A third explanation of the results is that, as previously shown (Bell & Dominici, 2008; Kelly, Nazroo, McMunn, Boreham, & Marmot, 2001), socioeconomic factors can indeed act as moderating variables. 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 effect modification hypothesis would suggest that poorer cognitive status in the low SES group is also associated with other factors like underlying health status and other health behaviors not taken into account in the analysis. Thus, low cognitive scores create vulnerability in the lower socioeconomic groups because they are associated with a range of other risk factors. Considering that our covariates comprised major established major risk factors for CHD and that adjusting analyses for them had little effect on the associations, it remains unclear what specifically these other underlying factors could be.

Finally, a further explanation of the results involves cognitive reserve, seen broadly as the ability of an individual to tolerate progressive brain pathology without manifestation of clinical cognitive symptoms (Stern, 2002). It is possible that subclinical vascular disease creates an association between cognition and CHD in the lower SES group but has no impact in the high SES group due to the compensation provided by greater cognitive reserve. We have previously shown common carotid artery intima media thickness (IMT), a measure of generalized atherosclerosis, to be associated with cognitive function in the low but not the high SES group (Singh-Manoux et al., 2008a). Thus, it is possible that the results reported here reflect an effect of subclinical disease rather than cognition as a risk factor for CHD.

There are some limitations to the results reported in this paper. First, the analysis on CHD is on small numbers and includes incidence of CHD after Phase 5, when participants were on average 55 years old. Cognition was for the first time measured on the full Whitehall II population at Phase 5 and we chose to examine the association between cognition and CHD prospectively so all CHD events prior to Phase 5, constituting the majority of cases, were excluded from the analysis. However, in uix 1 we provide the analysis using all CHD events, 547 events instead of the 181 analysed for this paper, and the results are no different to those reported above. A further limitation is that the analysis is based on British white-collar civil servants and may not apply to wider populations. However, generalizability may be less limited than first imagined. The majority of the working population in post-industrial countries is now employed in white collar jobs, and Whitehall II participants cover a wide range of employment grades with annual full-time salaries in 1995 ranging from $10,006 U.S. (£4995) to $300,480 U.S. (£150,000).

In conclusion, we show an association between cognition and incident CHD to be dependent on SES and discuss four possible explanations. Our analysis does not allow us to pick one explanation over another, although there is little support for the threshold explanation in our data. Interest in the interaction between SES and cognition in predicting health outcomes is increasingly manifested in the research literature and it appears that these might have both shared and unique effects on health (Batty, Der, Macintyre, & Deary, 2006; Singh-Manoux et al., 2005). One of the challenges of cognitive epidemiology, when defined essentially as an interest in cognitive measures as risk factors for health (Deary & Batty, 2007), is to delineate the effects of cognition and socioeconomic factors on health.

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Appendix A

The association of cognition with all (prevalent and incident) events of coronary heart disease (CHD) in the Whitehall II study.

	Total sample $N=5861$ CHD = 9.3% OR (95% CI)	High SES $N=2537$ CHD = 9.1% OR (95% CI)	Low SES $N=3324$ CHD = 9.4% OR (95% CI)
"General" factor	1.24 (1.14–1.36)*	1.09 (0.89–1.33)	1.33 (1.18–1.50)*
Memory	1.10 (1.01–1.21)*	1.08 (0.92–1.25)	1.12 (0.99–1.26)
AH4-I (reasoning)	1.23 (1.13–1.35)*	1.07 (0.87–1.31)	1.32 (1.17–1.48)*
Mill Hill (vocabulary)	1.24 (1.14–1.35)*	1.23 (0.99–1.53)	1.25 (1.13–1.39)*
Phonemic fluency	1.11 (1.01–1.22)*	1.04 (0.89–1.21)	1.14 (1.00–1.29)*
Semantic fluency	1.17 (10.6–1.28)*	0.95 (0.81–1.12)	1.32 (1.16–1.50)*

*$p<0.05$; Analysis carried out using logistic regression and adjusted for age and sex.

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