History of coronary heart disease and cognitive performance in midlife: the Whitehall II study.

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Abstract

Aims: Some studies show coronary heart disease (CHD) to be a risk factor for cognitive function while others report no association between the two. We examine the effect of CHD history and duration on cognition in a middle-aged population.

Methods: Data come from the Whitehall II study of 10308 participants (33% women), aged 35–55 years at baseline (phase 1; 1985-1988). CHD events were assessed up to Phase 7 **(**2002-2004) when 5837 participants (28.4% women) undertook 6 cognitive tests: reasoning, vocabulary, phonemic and semantic fluency, memory and the Mini-Mental-State-Examination (MMSE); standardized to T-scores (mean=50, standard deviation=10). Analysis of covariance was used first to model the association between CHD history and cognition and then to examine the effect of time since ***first*** CHD event (in the last 5 years, 5-10 years ago, over 10 years ago).

Results: Among men, in analyses adjusted for age, education, marital status and medication for cardiovascular disease, CHD history was associated with lower T-scores on reasoning (-1.16; 95% Confidence Interval (CI)=-2.07,-0.25), vocabulary (-2.11; 95% CI=-3.01,-1.21), and the MMSE (-1.45; 95% CI=-2.42,-0.49). In women, these effects were also evident for phonemic and semantic fluency. Among men, the trend within CHD cases suggested progressively lower scores on reasoning, vocabulary and semantic fluency among those with longer duration of CHD.

Conclusion: Our findings go some way towards suggesting an association between CHD history and cognitive performance in middle-aged adults.

Age, vascular pathology and socioeconomic factors are seen to be the three key determinants of cognitive ageing.[1] Impaired adult cognition is an important health outcome because it predicts dementia[2,3] and mortality.[4-7] Vascular risk factors and indicators of vascular disease are associated with both cognitive impairment[8-10] and dementia.[11-13] The atherosclerotic process and related hypoperfusion is seen to be responsible for this association.[12] Coronary heart disease is a global problem, with the risk of disease shown to increase as societies undergo urbanization.[14] In many western countries, the United Kingdom for instance, it remains the leading cause of death.[15]

The objective of this paper is to examine the association between coronary heart disease (CHD) and cognitive performance in middle-aged adults. The evidence for this association in the elderly is inconsistent, some studies suggest an association[16-21] while others don't.[22-24] Research interest on the link between cardiovascular disease and dementia has focused more on cerebrovascular disease than on CHD.[25] Furthermore, when heart disease has been the focus, research has mostly been on the influence of coronary artery bypass graft (CABG) surgery on cognitive status.[26-28] Thus, few large scale studies have examined the association between CHD, a disease that is highly prevalent, and poor cognitive status. We use data from a large prospective cohort study to examine this association, using a range of cognitive tests. A further objective is to examine whether the strength of this association is dependent on the duration of disease, seen here as the time since the *first* coronary event.

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).[29] 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 subclinical 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.

CHD events were assessed up to Phase 7 and included 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.[30] Angina was assessed based on the participant's reports of symptoms,[31] 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. In our analysis we consider only the ***first*** CHD event, taken as an indicator that the participant has heart disease. The date of the cognitive testing is used to further classify the ***first*** CHD event as having occurred in the last 5 years, 5-10 years or over 10 years ago. CHD events (N=21) prior to inclusion in the study are self-reported and were set as having occurred at the start of the study.

Cognitive function was assessed at Phase 7 using a battery of six standard tasks, described below.

The Alice Heim 4-I (AH4-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.

Vocabulary was assessed using the *Mill Hill Vocabulary test*,[33] used 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.

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 two minutes to do so.

Finally, the 30-item Mini-Mental-State-Examination (MMSE) was used to assess global cognitive status.[35]

Covariates used were age, sex, highest qualification on leaving full-time education (no academic qualifications, lower secondary school, higher secondary school, university, and higher university degree), marital status (married/cohabiting, single, widowed, and divorced/separated) and medication for cardiovascular disease consisting of diuretics, beta-

blockers, ACE and AII inhibitors, calcium channel blockers and other antihypertensive drugs, lipid lowering drugs, nitrates and antiplatelet drugs. All covariates used in the analyses were concurrent with the measures of cognition.

Statistical analysis

The cognitive test scores, separately in men and women, were standardized by conversion to T-scores (mean 50; standard deviation 10) in order to allow comparison of effect size between the tests. We first examined the association between CHD and cognitive function using the broad categorization of those with and without a history of CHD at Phase 7. Any event occurring up to Phase 7 led the individual to be classified as having a history of CHD. Analysis of covariance (ANCOVA) was used to calculate mean differences in standardized cognitive scores between those with and without a history of CHD. We then examined the effect of the duration of CHD on cognition by categorizing the ***first*** CHD as having occurred in the last 5 years, 5-10 years or over 10 years ago. For these analyses the reference category was again those without a CHD event. All analyses were first adjusted for age and then for education, marital status and use of medication for cardiovascular disease. We tested for a trend in the mean difference in T-scores with duration of CHD by fitting a single linear term for the CHD duration groups. In addition, by fitting a term using the exact duration of CHD we estimated the mean difference in each cognitive test associated with each 5-year-duration of CHD. All p-values (≤ 0.05) are based on a two-tailed test. The analyses were performed using SAS statistical software, version 9.1.

Results

The Whitehall II study had 10,308 participants at Phase 1 (1985–1988); subsequent phases had the following numbers: 8133 (Phase 2), 8637 (Phase 3), 8629 (Phase 4), 7830 (Phase 5), 7344 (Phase 6) and 6967 (Phase 7). 605 participants had died by Phase 7, 175 of these were of cardiovascular origin. Data on all measures included in our analysis were available for 5837 individuals. Compared to those not included in the analysis, this group was younger when tested for cognition (61.0 years compared to 62.7 years), composed of fewer women (28.4% compared to 33.1%) and contained more individuals with a university degree or higher (30.4% compared to 27.5%), all $p < 0.001$. Characteristics of the study participants by CHD status are shown in Table 1. Participants with a history of CHD were older, less well educated, and had lower scores on all cognitive measures. All analyses were carried out separately in men and women as the interaction term between CHD and sex (for the 6 tests

p=0.002-0.90) suggested gender differences in the association between CHD and some of the cognitive tests. Of the 460 events in men 163 were MI cases and the rest were 'definite' angina. Among women, there were 65 cases of MI and 95 of 'definite' angina.

Table 2 presents the association between CHD history (a CHD event prior to cognitive testing) and cognitive performance, separately in men and women. The association between history of CHD and cognition was evident for three of the six cognitive tests in men. Among women, CHD history was associated with lower scores on reasoning (-3.40; 95% Confidence Interval (CI)=-4.79,-2.01), vocabulary(-3.01; 95% CI=-4.46,-1.57), phonemic fluency (-2.85; 95% CI=-4.36,-1.34), semantic fluency (-1.75; 95% CI=-3.20,-0.29) and the MMSE (-1.93; 95% CI=-3.53,-0.32).

The association between the duration since first event of CHD and cognition in men is shown in Table 3. The date of cognitive testing at Phase 7 was used to categorise the ***first*** CHD event, going backwards, as having occurred in the last 5 years, 5-10 years ago or over 10 years ago. The reference category was composed of individuals who had never had CHD. Results in Table 3 show that men whose ***first*** CHD event occurred over 10 years ago had lower scores on reasoning (-2.94; 95% CI=-4.35,-1.52), vocabulary (-3.58; 95% CI=-5.00,-2.16), semantic fluency (-2.10; 95% CI=-3.54,-0.64), and the MMSE (-1.84; 95% CI=-3.35,-0.32).The test for trend and an examination of the effect per 5 years among those with CHD suggests a trend for lower cognitive scores with increase in the time since first CHD event for the AH4-I, Mill Hill and semantic fluency. The association between time since first event and cognitive performance among women is shown in Table 4. Although the analysis is on small numbers, this reveals a trend of lower scores for semantic fluency with longer duration of CHD.

Discussion

The purpose of this study was to examine the association between CHD and cognitive performance in middle-aged men and women. Data from a large British occupational cohort show clear associations between CHD and cognition using a range of cognitive tests and the MMSE, a test of global cognitive status. Long standing CHD, particularly in men, was associated with poorer cognitive performance.

Cardiovascular disease remains a major health problem in the developed world and it is heart disease, not cerebrovascular disease that makes up the bulk of the cases. The effect of cerebrovascular disease, stroke and TIA, on cognitive outcomes like deficit and dementia is well established.[21,36] However, little is known about the association between heart disease and

cognition. Typically, heart disease manifests itself in midlife. Dementia occurs late in life but it is increasingly recognized that there is a long preclinical phase characterized by progressive neuropathological changes that then become clinically detectable as cognitive deficit or dementia. Furthermore, the "life-long" view of dementia stresses the importance of risk factors in midlife.[37] The salient finding of the present study was to show, not only an association between CHD history and lower cognitive scores in men and women, but also increasingly poorer cognitive scores with increase in the duration of CHD. The tests for trend were calculated within the CHD cases. In men, where there were enough cases to examine this issue, those who had a ***first*** CHD event that was over 10 years ago were more likely to have poor cognition. Thus, our results go some way towards suggesting an association between CHD history and cognition.

We did not explore the pathophysiological pathway involved in the observed effect of CHD on cognitive function. As both coronary heart disease and cognition are influenced by socioeconomic factors we adjusted for the effect of education. Even though education was strongly associated with CHD, it was not differentially associated with CHD history. In men 46% of all events and 50% of the oldest events (over 10 years old) were in the low education group (less than higher secondary school). Among women the corresponding numbers were 62% and 59%. Analyses (not shown but available from authors) using other, later life measures of socioeconomic position did not change the results much from those presented here. It is possible that shared risk factors, vascular risk factors have been widely linked to cognition,[9-13] drive this association. It is also possible that heart disease influences cognition through cerebral embolism or decreased cerebral perfusion.[18,22,38] There is certainly evidence of lowered cognitive performance among those with congestive heart failure in the elderly.[38,39] Our results suggest that even among middle-aged individuals CHD is associated with poor cognitive performance with some evidence to suggest a stronger effect among those with longest standing ***first*** CHD event. However, these results do not allow judgements to be made on the causal direction of the association between CHD and cognition. Impaired cognition or incipient dementia, through poor health self-care rule is also likely to lead to CHD.

Comparison with other studies

There are few large scale studies that have examined the association between CHD and cognition. Much of the work on cognition was until recently carried out in the elderly and the evidence from these studies on the role of CHD in cognition is mixed. Some studies failed to find an association between CHD and dementia[16,17,22,36]. Other, relatively small scale, on

non-elderly samples have also not shown an association.[23,24] However, there is increasing evidence from non-elderly adults showing CHD to be a risk factor for cognition.[17,19] One of the problems with many studies in this domain is that they are based on cross-sectional analysis,[17-19,23,40] that do not allow a judgment to be made on whether CHD preceded or was a consequence of poor cognitive status.

We found only one study that had examined the association between time since myocardial infarction and cognition.[36] This study was on individuals aged 71 to 93 years and showed no effect of time since coronary event on cognitive deficit. It is likely that CHD is not comparable across age groups in terms of severity of disease. Furthermore, there is some evidence to suggest that the preclinical phase of dementia itself might modify the risk factors for heart disease.[41] Thus, examining of the association between CHD and cognition in midlife or early old age offers some advantage over examining it in the elderly.

Study strengths and limitations

This study has a number of strengths including the prospective nature of the analyses which, in comparison to others studies, utilises objective measures of CHD, followed up actively over the course of the study as opposed to self-reported data. We were able to examine a wide range of cognitive measures. We analysed all six cognitive tests together using multiple analysis of covariance (MANCOVA) to ensure that multiple cognitive tests did not induce Type I error. These results reveal that history of CHD is associated with cognition in both men and women ($p<0.001$). Furthermore, as cognitive deficit is linked to dementia[2,3] we repeated the analysis using cognitive scores in the worst quintile to define deficit. The results (not shown but available on request) remain unchanged.

The present study also has some limitations. One, the population is drawn from the British Civil Service and is not representative of the general population as all participants had stable white-collar jobs on entry to the study. Two, despite the size of the study the analyses are clearly underpowered, particularly in women and do not allow firm conclusions to be drawn on gender differences in the association between CHD and cognition. It is possible that the lack of trend for duration of CHD on cognition in women is a consequence of low numbers leading to a Type II error. Larger numbers are also required in order to examine possible explanations for the associations reported here. Three, it is possible that measures of disease that combine duration and severity will allow a better assessment of the association between CHD and cognition. Four, missing data due to non-response and CHD-mortality prior to collection of cognitive data are likely to bias the results, perhaps by leading to an underestimation of the association between CHD and cognition. Finally, we do not have

baseline cognitive data so causal inferences on the direction of the association cannot be made in the present study.

In conclusion, we show CHD history to be a risk factor for cognitive function in middle-aged men and women. CHD is a leading cause of morbidity and mortality. The prevalence of dementia rises with age, doubling every 4-5 years after the age of 60 so that over a third of those over 80 are likely to have dementia.[42] It is important to elucidate the link between these two diseases. Major risk factors for CHD, cigarette smoking, diabetes, hyperlipidemia, and hypertension, are seen to be modifiable,[43,44] with smoking, diet and physical exercise seen to be particular targets for prevention.[45] Our results on the link between CHD and cognition show the importance for preventive strategies in highlighting the importance of these risk factors not only for CHD but also cognitive outcomes.

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Tables 1. Sample characteristics of those with and without CHD in men and women at Phase 7 (2002-2004).

	Men			**Women**		
	CHD	no CHD	p	CHD	no CHD	p
N (%)	460 (11.0 %)	3720 (89.0%)		160 (10.0%)	1497 (90.0%)	
Age (M (SD))	63.6 (5.8)	60.6 (5.9)	<0.0001	64.4 (5.7)	60.8 (5.9)	<0.0001
% married	382 (83.0 %)	3094 (83.2 %)	0.60	102 (63.8 %)	894 (59.7 %)	0.30
% university degree or higher	132 (28.7 %)	1273 (34.2 %)	0.08	27 (16.9 %)	342 (22.9 %)	0.02
% CVD medication	113 (24.6%)	893 (24.0%)	0.42	39 (24.4%)	382 (25.5%)	0.42
Cognitive function						
AH4-I (M (SD))	43.7 (11.1)	46.1 (9.6)	<0.0001	32.9 (12.5)	39.9 (12.0)	<0.0001
Mill Hill (Mean (SD)	24.9 (4.3)	25.8 (3.6)	<0.0001	21.2 (6.0)	23.6 (5.2)	<0.0001
Phonemic fluency (M (SD))	15.4 (4.0)	15.9 (4.0)	0.01	13.6 (4.5)	15.6 (4.3)	<0.0001
Semantic fluency (M (SD))	15.4 (3.8)	15.9 (3.6)	0.002	13.6 (4.1)	15.3 (4.3)	<0.0001
Memory (M (SD))	6.3 (2.3)	6.8 (2.3)	<0.0001	6.1 (2.9)	7.0 (2.6)	<0.0001
MMSE (M (SD))	28.5 (1.3)	28.8 (1.2)	<0.0001	28.3 (1.6)	28.7 (1.3)	0.0009

M: Mean; SD: Standard Deviation; CVD: cardiovascular disease

Table 2. The association between history of Coronary Heart Disease (CHD) and cognitive function.[†]

	MEN		WOMEN	
	No CHD	CHD	No CHD	CHD
	N=3720	N=460	N=1497	N=160
		Difference (95% CI)[‡]		**Difference (95% CI)[‡]**
AH4-I (reasoning)				
adjusted for age	ref	-1.51 (-2.50, -0.54)	ref	-3.90 (-5.00, -1.93)
+ marital status, education & CVD medication	ref	-1.16 (-2.07, -0.25)	ref	-3.40 (-4.79, -2.01)
Mill Hill (vocabulary)				
adjusted for age	ref	-2.53 (-3.51, -1.55)	ref	-3.22 (-4.84, -1.60)
+ marital status, education & CVD medication	ref	-2.11 (-3.01, -1.21)	ref	-3.01 (-4.46, -1.57)
Phonemic fluency				
adjusted for age	ref	-0.33 (-1.30, 0.63)	ref	-2.90 (-4.43, -1.30)
+ marital status, education & CVD medication	ref	-0.09 (-1.04, 0.85)	ref	-2.85 (-4.36, -1.34)
Semantic fluency				
adjusted for age	ref	-0.43 (-1.40, 0.52)	ref	-1.80 (-3.40, -0.23)
+ marital status, education & CVD medication	ref	-0.16 (-1.09, 0.77)	ref	-1.75 (-3.20, -0.29)
Memory				
adjusted for age	ref	-1.08 (-2.03, -0.13)	ref	-1.60 (-3.15, 0.01)
+ marital status, education & CVD medication	ref	-0.90 (-1.84, 0.05)	ref	-1.57 (-3.12, -0.02)
MMSE				
adjusted for age	ref	-1.57 (-2.54, -0.60)	ref	-2.00 (-3.60, -0.40)
+ marital status, education & CVD medication	ref	-1.45 (-2.42, -0.49)	ref	-1.93 (-3.53, -0.32)

[†] Using T scores, Mean =50 and Standard Deviation = 10.
[‡] Difference in cognitive score from reference group.
CVD: cardiovascular disease.

Table 3: The association between duration of CHD and cognitive function in men.[†]

		Time since first incidence of CHD			Among those with CHD	
	No CHD	≤ 5 years	5.1-10 years	> 10 years	P for trend*	Difference in cognitive score per 5 years (p)
	N=3720	N=141	N=145	N=174		
		Difference (95% CI)[‡]	Difference (95% CI)[‡]	Difference (95% CI)[‡]		
AH4-I (reasoning)						
adjusted for age	ref	0.13 (-1.51, 1.80)	-0.60 (-2.25, -1.00)	-3.61 (-5.11, -2.10)	0.002	-1.44 (0.008)*
+ marital status, education & CVD medication	ref	0.11 (-1.44, 1.67)	-0.31 (-1.84, 1.23)	-2.94 (-4.35, -1.52)	0.01	-1.21 (0.02)*
Mill Hill (vocabulary)						
adjusted for age	ref	-0.94 (-2.62, 0.73)	-2.04 (-3.70, -0.40)	-4.25 (-5.80, -2.72)	0.008	-1.28 (0.02)*
+ marital status, education & CVD medication	ref	-1.08 (-2.62, 0.47)	-1.38 (-2.91, 0.14)	-3.58 (-5.00, -2.16)	0.04	-1.04 (0.05)
Phonemic fluency						
adjusted for age	ref	0.45 (-1.20, 2.11)	0.41 (-1.22, 2.05)	-1.61 (-3.12, -0.10)	0.06	-0.79 (0.10)
+ marital status, education & CVD medication	ref	0.50 (-1.13, 2.10)	0.60 (-1.00, 2.18)	-1.15 (-2.62, 0.33)	0.17	-0.62 (0.18)
Semantic fluency						
adjusted for age	ref	1.80 (0.15, 3.44)	0.00 (-1.62, 1.62)	-2.64 (-4.14, -1.14)	0.0001	-1.79 (0.0003)*
+ marital status, education & CVD medication	ref	1.77 (0.18, 3.36)	0.25 (-1.32, 1.82)	-2.10 (-3.54, -0.64)	0.001	-1.49 (0.002)*
Memory						
adjusted for age	ref	-0.08 (-1.26, 3.01)	-1.06 (-2.67, 0.55)	-1.93 (-3.42, -0.45)	0.08	-0.62 (0.19)
+ marital status, education & CVD medication	ref	-0.07 (-1.68, 1.55)	-0.86 (-2.45, 0.73)	-1.61 (-3.09, 0.14)	0.24	-0.43 (0.35)
MMSE						
adjusted for age	ref	-1.13 (-2.80, 0.53)	-1.42 (-3.10, 0.22)	-2.10 (-3.60,-0.60)	0.41	-0.81 (0.12)
+ marital status, education & CVD medication	ref	-1.15 (-2.81, 0.51)	-1.28 (-2.92, 0.35)	-1.84 (-3.35, -0.32)	0.57	-0.76 (0.15)

[†] Using T scores, Mean =50 and Standard Deviation = 10.

[‡] Difference in cognitive score from reference group. *Test for trend on those with CHD.

CVD: cardiovascular disease.

Table 4: The association between duration of CHD and cognitive function in women.

		Time since first incidence of CHD			Among those with CHD	
	No CHD	≤ 5 years	5.1-10 years	> 10 years	**P for trend***	Difference in cognitive score per 5 years **(p)**
	N=1497	**N=45**	**N=57**	**N=58**		
		Difference (95% CI)‡	**Difference (95% CI)‡**	**Difference (95% CI)‡**		
AH4-I (reasoning)						
adjusted for age	ref	-2.31 (-5.10, -0.44)	-4.70 (-7.15, -2.22)	-3.15 (-5.60, -0.70)	0.71	0.10 (0.91)
+ marital status, education & CVD medication	ref	-2.24 (-4.74, 0.27)	-4.30 (-6.53, -2.07)	-3.41 (-5.63, -1.19)	0.50	-0.33 (0.72)
Mill Hill (vocabulary)						
adjusted for age	ref	-0.94 (-2.62, 0.73)	-2.04 (-3.70, -0.40)	-4.25 (-5.80, -2.72)	0.94	0.71 (0.48)
+ marital status, education & CVD medication	ref	-2.31 (-4.91, 0.29)	-4.05 (-6.37, -1.74)	-2.53 (-4.84, -0.23)	0.75	1.00 (0.93)
Phonemic fluency						
adjusted for age	ref	-1.65 (-4.50, 1.20)	-2.60 (-5.11, -0.04)	-4.10 (-6.60, -1.55)	0.21	-0.72 (0.40)
+ marital status, education & CVD medication	ref	-1.57 (-4.28, 1.15)	-2.33 (-4.75, 0.08)	-4.37 (-6.78, -1.96)	0.09	-1.28 (0.16)
Semantic fluency						
adjusted for age	ref	0.26 (-2.54, 3.10)	-2.21 (-4.70, 0.30)	-3.00 (-5.50, -0.50)	0.08	-0.77 (0.35)
+ marital status, education & CVD medication	ref	0.21 (-2.43, 2.84)	-1.88 (-4.22, 0.46)	-3.16 (-5.49, -0.83)	0.05	-1.12 (0.18)
Memory						
adjusted for age	ref	-0.30 (-3.12, 2.60)	-1.35 (-3.90, 1.20)	-2.80 (-5.31, -0.26)	0.23	-0.55 (0.55)
+ marital status, education & CVD medication	ref	-0.64 (-3.43, 2.16)	-1.01 (-3.49, 1.48)	-2.85 (-5.32, -0.38)	0.23	-0.74 (0.45)
MMSE						
adjusted for age	ref	-2.51 (-5.42, 0.40)	-1.20 (-3.80, 1.40)	-2.32 (-4.90, 0.25)	0.97	0.07 (0.94)
+ marital status, education & CVD medication	ref	-2.40 (-5.30, 0.50)	-1.07 (-3.65, 1.50)	-2.41 (-5.00, 0.15)	0.99	-0.07 (0.95)

† Using T scores, Mean =50 and Standard Deviation = 10.

‡ Difference in cognitive score from reference group. *Test for trend on those with CHD.

CVD: cardiovascular disease.