Cognitive changes in prevalent and incident cardiovascular disease

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CLINICAL RESEARCH
Prevention and epidemiology

Cognitive changes in prevalent and incident cardiovascular disease: a 12-year follow-up in the Maastricht Aging Study (MAAS)

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Aims Cardiovascular disease (CVD) has been suggested to accelerate cognitive decline and to be a risk factor for dementia, but still little is known about the cognitive course after a first cardiovascular event. Therefore, the present study aims to investigate the cognitive trajectories in both prevalent and incident CVD over a 12-year time period in the general population.

Methods and results Cognitively healthy participants (age 24–82 years, $n = 1823$) of a prospective cohort study were serially assessed at baseline, 6 and 12 years. Verbal memory, executive function, and information processing speed were analysed in adults with prevalent, incident, and no CVD. Random effects models were used to test the association between CVD and change in cognitive function over time. At baseline, participants with prevalent CVD showed more decline in memory and information processing speed than healthy controls. Participants with incident CVD also showed more decline in these cognitive domains, but this was only significant in the follow-up period from 6 to 12 years. Associations were more pronounced in participants aged younger than 65 years at baseline, and in sub-analyses with angina pectoris or myocardial infarction as the most prevalent CVD conditions.

Conclusion Prevalent and incident CVD predict cognitive decline in middle-aged individuals. Findings for incident CVD suggest that the onset of decline is linked in time with the vascular event itself. Timely CVD management may delay the onset of decline.

Keywords Cardiovascular disease • Cognition • Dementia • Risk factors • Epidemiology • Neuropsychology

Introduction

Cardiovascular disease (CVD) predisposes individuals to cerebrovascular damage and its incidence rises with age.[1] CVD may lead to cognitive and functional impairment and increases dementia risk.[2] Ischemic brain lesions involved in the pathology of late-onset Alzheimer's disease and vascular dementia have been found in CVD.[3] However, current guidelines on CVD prevention of the European Society of Cardiology do not comment on the association between CVD and cognitive decline.[4]

While associations between prevalent CVD and cognition or dementia have been reported in cross-sectional[5–9] and prospective studies,[7,10–12] non-significant associations exist, too.[13–16] Inconsistencies may stem from differences in definition and severity of CVD, cognitive assessment, follow-up duration, and sample size.

Given the pathological cascade leading from CVD to brain lesions to cognition takes time to evolve, effects on cognition probably vary by CVD exposure duration, so that cognitive changes are still modest in incident cases. Next, associations between CVD and cognitive decline might be more pronounced in younger individuals, as has

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Table 1 Baseline characteristics of the cardiovascular disease groups[a]

Characteristic	Prevalent CVD				Incident CVD			
	No, $n = 1628$	Yes, $n = 195$	*F*-statistic	df	No, $n = 1138$	Yes, $n = 204$	*F*-statistic	df
Age	50.5 ± 17.7	69.5 ± 9.8	394.20***	1,1822	46.8 ± 16.2	58.8 ± 13.6	101.99***	1,1341
Female	854 (55.4)	56 (33.7)	26.27***	1,1822	585 (54.0)	95 (51.2)	0.49	1,1341
Education								
Low	569 (37.8)	96 (51.4)	6.05**	2,3633	340 (32.0)	106 (54.7)	18.09***	2,2680
Middle	678 (39.4)	68 (32.8)			507 (42.6)	67 (30.7)		
High	380 (22.9)	30 (15.8)			291 (25.4)	31 (14.6)		
Smokers	999 (64.1)	145 (73.5)	5.14*	1,1701	694 (63.0)	127 (68.3)	1.64	1,1252
Alcohol abuse	47 (3.1)	4 (1.4)	2.24	1,1822	29 (2.4)	5 (3.0)	0.16	1,1341
Hypertension	504 (32.2)	156 (80.4)	145.68***	1,1822	287 (25.1)	99 (49.1)	42.44***	1,1341
Body mass index	26.5 ± 4.4	27.9 ± 3.7	21.30***	1,1819	26.2 ± 4.3	27.7 ± 4.3	16.25***	1,1339
Diabetes mellitus	49 (3.4)	19 (10.4)	15.83***	1,1822	17 (1.5)	14 (7.3)	21.70***	1,1341
Depressive symptoms	20.8 ± 6.5	21.7 ± 6.4	2.96	1,1781	20.5 ± 6.0	21.3 ± 6.7	2.11	1,1326
Cardiovascular diseases[b]								
Myocardial infarct		67 (33.0)	N/A			47 (21.1)	N/A	
Angina pectoris		92 (49.3)	N/A			68 (34.2)	N/A	
Peripheral artery disease		41 (21.7)	N/A			73 (37.4)	N/A	
Heart insufficiency		26 (13.5)	N/A			15 (8.4)	N/A	
Bypass surgery		28 (13.4)	N/A			57 (26.2)	N/A	
Heart valve disease		17 (8.8)	N/A			29 (12.8)	N/A	
Open-heart surgery		6 (3.2)	N/A			11 (5.4)	N/A	
Neuropsychological tests								
Verbal learning test (raw)	9.7 ± 3.1	7.5 ± 2.9	71.78***	1,1815	10.2 ± 2.9	9.0 ± 2.7	28.40***	1,1335
Verbal learning test (transformed)	103.8 ± 57.5	66.0 ± 44.7	91.36***	1,1815	111.8 ± 56.3	88.0 ± 48.7	34.71***	1,1335
Concept shifting test (raw)	12.1 ± 12.0	17.2 ± 12.9	17.70***	1,1794	10.5 ± 9.5	14.7 ± 13.0	15.94***	1,1324
Concept shifting test (transformed)	2.2 ± 0.9	2.6 ± 0.8	22.63***	1,1733	2.1 ± 0.9	2.4 ± 0.9	19.89***	1,1276
Letter digit substitution test (raw)	48.5 ± 12.2	39.2 ± 9.6	116.78***	1,1818	50.7 ± 11.5	44.7 ± 10.4	46.26***	1,1339

Means, SDs, percentages, *F*-statistic, and df's are design-based estimates that are back-weighted to the sampling frame ($n = 10658$) from which participants were drawn. Percentages may not sum up to 100 because of rounding.
CVD, cardiovascular disease; df, degrees of freedom; SD, standard deviation.
[a]Data are presented as either mean ± SD or *n* (%).
[b]Participants could have multiple conditions.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

been shown for hypertension[17] and diabetes.[18] Insight into the onset and course of cognitive functions after incident CVD could show whether there is a margin in time for prevention.

Therefore, we studied the cognitive trajectories of individuals with prevalent and incident CVD over 12 years. It was hypothesized that (i) prevalent CVD shows large cognitive decline and (ii) incident CVD shows a more modest though more decline than those without CVD. Since sex and age differences exist in CVD and rate of cognitive decline, their possible effect modification was studied, too.

Methods

Participants

The Maastricht Aging Study (MAAS) is a prospective cohort study on determinants of cognitive aging.[19] In total, 10 801 people were invited from the Registration Network Family Practices (RNH), a patient register of collaborating general practitioners, representative of the Dutch population. Exclusion criteria were major cerebrovascular pathology, nervous system tumour or congenital malformation, multiple sclerosis, parkinsonism, epilepsy, dementia, organic psychosis, schizophrenia, affective psychosis, and intellectual disability. From those remaining, a sample of 1823 individuals was drawn using optimal stratified sampling design with strata for age, sex, and occupational achievement (low/high). Participants underwent repeated assessments of blood pressure, medical history, lifestyle, anthropomorphic and neurocognitive measures, at six [mean 6.2, standard deviation (SD) 0.2] and 12 years (mean 12.5, SD 0.3) after baseline. The study complies with the Declaration of Helsinki. The local ethics committee of Maastricht University Medical Centre approved the research protocol (MEC05-107). All participants gave informed consent.

Measures

Cardiovascular disease

People were classified with CVD if they had been diagnosed with one of the following conditions: peripheral artery disease, angina pectoris (AP),

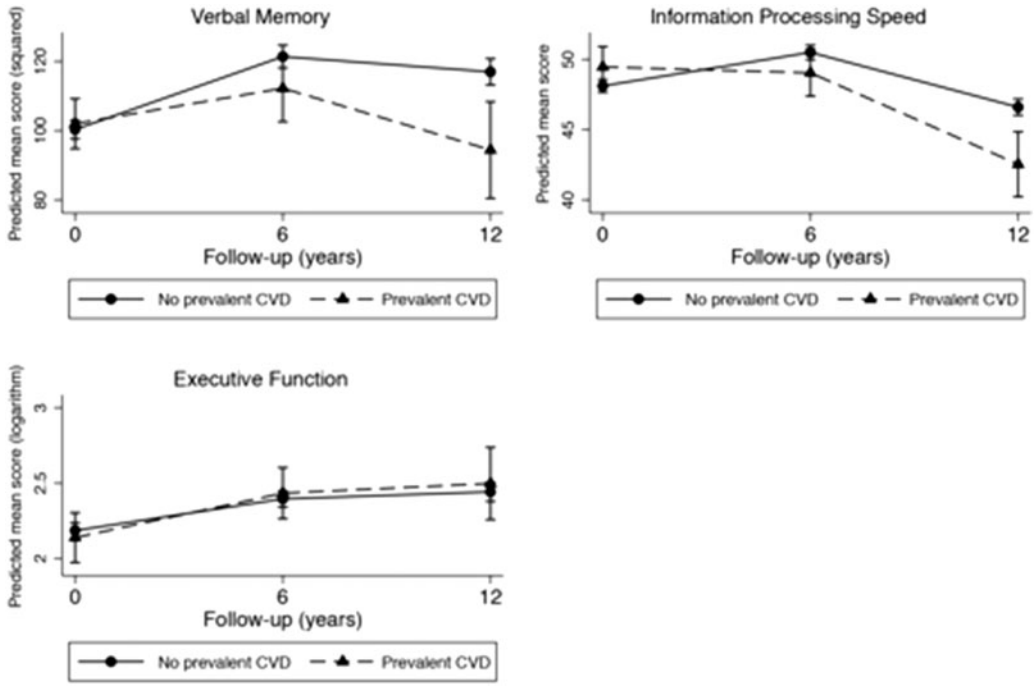

Figure 1 Cognitive trajectories of individuals with prevalent CVD ($n = 195$) and those without ($n = 1628$). CVD, cardiovascular disease. For the domains verbal memory and information processing speed, a higher score means a better performance. However, for executive function, a higher score means a worse performance.

myocardial infarction (MI), heart insufficiency, heart valve disease, bypass surgery, or open-heart surgery. Individuals who reported one of these at baseline were classified as prevalent CVD. Individuals who reported one of these at 6- or 12-year follow-up were classified as incident CVD.

Neuropsychological assessment

Psychologists or trained test assistants administered a neuropsychological battery at each wave. In the present study, the delayed recall of the visual Verbal Learning Test (VLT) was used to assess verbal memory,[20] the shifting score of the Concept Shifting Test (CST) to assess executive function,[21] and the Letter Digit Substitution Test (LDST) to assess information processing speed.[22]

Covariates

Potential confounders were demographic variables: age, sex, educational level (low, middle, high), and health-related conditions: present or past smoking (yes/no), alcohol abuse (yes/no), type 2 diabetes (yes/no, self-report based on physician's diagnosis and current anti-diabetic medication use), hypertension (yes/no, mean systolic blood pressure ≥140 mmHg and mean diastolic blood pressure ≥90 mmHg measured three times at 5-minute intervals by an automatic recording device—Critikon Dinamap 8100; Critikon, Tampa, FL—or current use of antihypertensive medication), body mass index (BMI, weight in kg/height in m^2), and depressive symptoms by using the total score of the 16 items of the depression subscale (range 16–80) of the revised 90-item Symptom Checklist.[23] Hypertension, diabetes, BMI, and depression were assessed at each wave.

Statistical analyses

Baseline differences between participants with and without CVD were analysed using independent samples *t*-tests and χ^2 tests. In addition, all analyses were back-weighted to the RNH source population from which the sample was drawn, and we therefore report the design-based *F*-statistic (see *Table 1*). The delayed recall score of the VLT and shifting score of the CST needed square and logarithmic transformation respectively, which led to a better (approximately normal) distribution. Random effects models tested the association between CVD (prevalent and incident) and change in cognition over time. As suggested by likelihood-ratio testing, the model included a random intercept and slope with an unstructured correlation matrix. In order to allow for nonlinear effects, a CVD-by-time interaction term with time entered as dummy variable for each of the two follow-ups was included in the model. Also, two inverse probability weights were added: an attrition weight that takes into account the likelihood of being lost to follow-up, and a sampling weight to generalize estimates to the total RNH population structure. All analyses were first adjusted for age, age^2, sex, education, followed by fully adjusted that included hypertension, alcohol abuse, smoking, type 2 diabetes, BMI, and depressive symptoms. Only fully adjusted models are presented. Additional analyses were stratified by sex and age (<65 and ≥65 years). All analyses were two-sided with an 0.05 α and performed in Stata 13.1 (StataCorp, TX, USA).

Table 2 Mean differences (and 95% confidence intervals) in baseline cognition and in rate of cognitive decline (slopes) from baseline between those with prevalent cardiovascular disease ($n = 195$) and those without ($n = 1628$)

	Time						
	Baseline difference		Change baseline to 6-year FU		Change baseline to 12-year FU		
Parameter	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	CVDxTime[a]
Verbal memory							
Total	1.68	-6.01 to 9.37	-10.82*	-20.09 to - 1.56	-24.23**	-38.76 to - 9.70	13.28**
Women	0.02	-14.77 to 14.81	-4.58	-22.56 to 13.39	-15.02	-42.01 to 11.97	1.35
Men	2.53	-6.26 to 11.32	-13.70*	-24.34 to - 3.07	-26.99**	-42.45 to - 11.53	13.66**
Aged <65 years	5.33	-7.27 to 17.93	-11.75	-26.91 to 3.41	-23.47**	-41.16 to - 5.78	7.54*
Aged ≥65 years	-5.43	-15.21 to 4.36	-2.71	-15.09 to 9.67	-5.05	-32.27 to 22.17	0.24
Executive function							
Total	-0.05	-0.22 to 0.13	0.08	-0.12 to 0.29	0.10	-0.19 to 0.39	0.77
Women	-0.08	-0.36 to 0.21	0.31*	0.01 to 0.61	-0.22	-0.65 to 0.21	10.93**
Men	-0.02	-0.24 to 0.20	-0.04	-0.30 to 0.22	0.31	-0.04 to 0.67	5.45
Aged <65 years	-0.08	-0.37 to 0.20	0.06	-0.27 to 0.39	0.19	-0.20 to 0.58	0.99
Aged ≥65 years	-0.02	-0.24 to 0.21	0.12	-0.17 to 0.42	-0.54	-1.14 to 0.06	5.88
Information processing speed							
Total	1.35	-0.18 to 2.88	-2.81***	-4.10 to - 1.52	-5.42***	-7.47 to - 3.37	31.04***
Women	0.97	-2.03 to 3.98	-2.81**	-4.91 to - 0.72	-4.99**	-8.10 to - 1.88	13.75**
Men	1.27	-0.42 to 2.95	-2.84***	-4.43 to - 1.25	-5.50***	-8.00 to - 3.00	20.04***
Aged <65 years	0.88	-1.52 to 3.29	-2.16**	-3.69 to - 0.64	-3.91***	-5.54 to - 2.28	22.63***
Aged ≥65 years	0.94	-1.12 to 2.99	-1.33	-3.43 to 0.77	-1.24	-6.18 to 3.70	1.56

Estimates from different cognitive domains are on different scales and cannot be directly compared. Model: CVD, time, CVDxTime, sex, age, age^2, education, baseline smoking, baseline alcohol abuse, body mass index, diabetes, depressive symptoms.
CI, confidence interval; CVD, cardiovascular disease; FU, follow-up.
[a]χ^2 test (2 degrees of freedom) of interaction between CVD (yes, no) and time (baseline, 6-year, 12-year FU); omnibus test of the null hypothesis of no difference in rate of change over time between CVD groups.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

Results

Baseline differences

Of the 1823 participants, 195 (10.7%) were classified with prevalent CVD. They were on average older, more often smokers, hypertensive, overweight, diabetic, experiencing depressive symptoms, and had a lower educational level (*Table 1*). At follow-up, 204 (15.2%) individuals had incident CVD. They were on average older, less educated, overweight, hypertensive, diabetic, and reported more depressive symptoms.

Prevalent cardiovascular disease and cognitive decline

At baseline, the prevalent CVD group did not have significantly lower cognitive scores, but a significant group-by-time interaction suggested more decline over time in verbal memory and information processing speed than the group without CVD (*Table 2*). As seen in *Figure 1*, both groups' scores increased from baseline to first follow-up in verbal memory and information processing speed, but this was less pronounced for the CVD group, suggesting a deviation from age-normal levels. No differences were found for executive functioning (*Figure 1*).

Effect modification by sex and age

Sex-stratified analyses suggest that men dictated the overall effect of CVD on verbal memory, while both sexes declined more in information processing speed if CVD was prevalent. In younger individuals, CVD predicted faster decline in memory and information processing speed, whereas in older individuals no significant decline in any domain was predicted (*Table 2*).

Incident cardiovascular disease and cognitive decline

Regarding incident CVD, the interaction with time suggested a significant decline in verbal memory and information processing speed relative to those without CVD (*Table 3*, *Figure 2*). Time-stratified analyses showed that decline was apparent from 6- to 12-years follow-up only (verbal memory: $\chi^2 = 3.90$, df = 1, $P = 0.048$; information processing speed: $\chi^2 = 21.81$, df = 1, $P < 0.001$). The interaction between incident CVD and time for executive function was not significant ($\chi^2 = 5.56$, df = 2, $P = 0.062$), but a similar time-lagged drop was observed in the 6- to 12- years follow-up period ($\chi^2 = 5.05$, df = 1, $P = 0.025$).

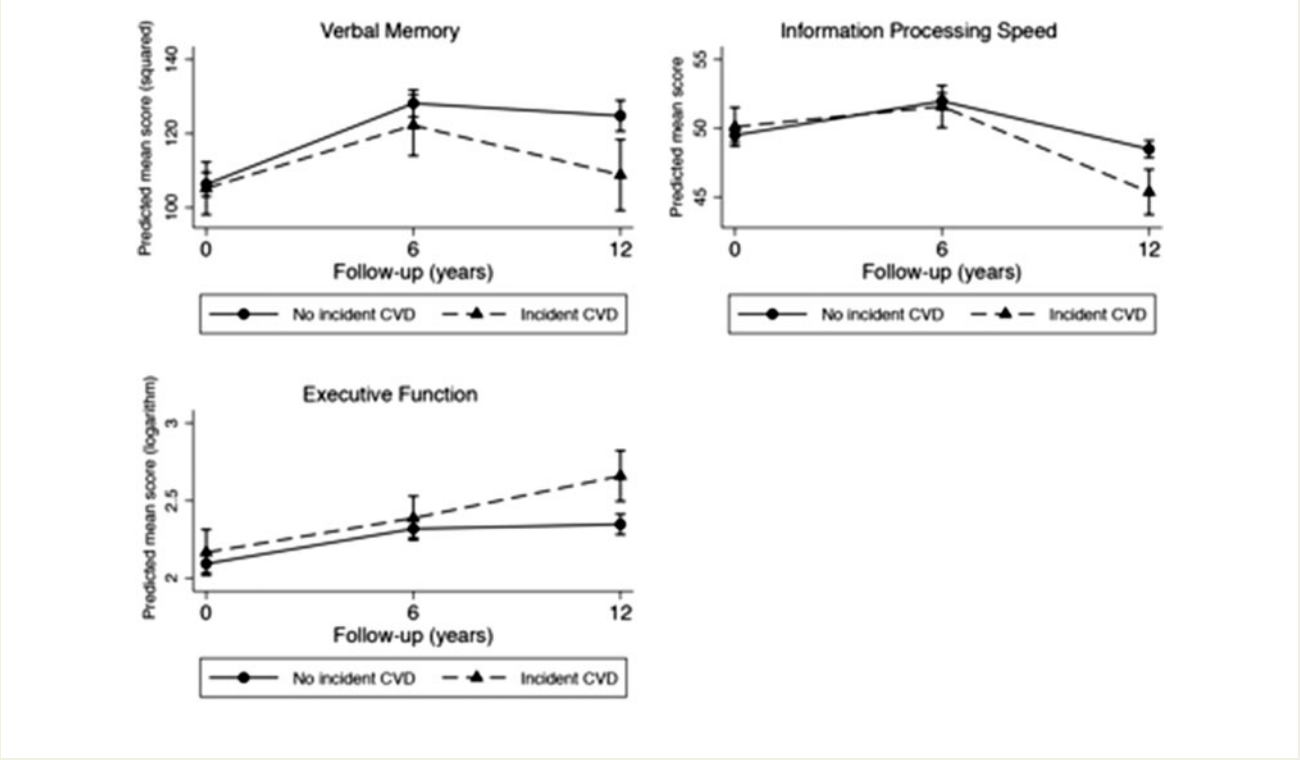

Figure 2 Cognitive trajectories of individuals with incident CVD ($n = 204$) and those without ($n = 1138$). CVD, cardiovascular disease. For the domains verbal memory and information processing speed, a higher score means a better performance. However, for executive function, a higher score means a worse performance.

Effect modification by sex and age

For information processing speed, incident CVD was associated with more decline in both sexes. Stratification by age showed that decline was statistically significant only in younger individuals (*Table 3*). Large standard errors in the older group suggest more heterogeneity in individual cognitive trajectories. Stratified effects in other cognitive domains were statistically inconclusive.

Post hoc analysis: prevalent angina pectoris, myocardial infarction, other cardiovascular disease, and cognitive decline

Since AP and MI were most common in prevalent CVD, their individual effects were studied in *post hoc* analysis. We analysed those with AP only ($n = 67$), those with MI (with or without AP, $n = 68$), and those with other CVD ($n = 60$) relative to the no CVD group ($n = 1\,628$). AP and other CVD were significantly associated with decline in information processing speed and MI with decline in verbal memory. To increase power, we then combined the MI/AP group as suggested by directionally similar individual effects. The interaction effects were significant for verbal memory and for information processing speed, but again not for executive function (see Supplementary material online, *Table S4*).

Discussion

The present study investigated the effect of prevalent and incident CVD on cognitive decline over 12 years. Prevalent CVD predicted faster decline in memory and processing speed. The effect on memory was stronger in men and below age 65. For processing speed, the effect was stronger in both sexes and below 65. Incident CVD showed a faster decline in memory and processing speed over time, but this effect was more modest and only evident during the period between the 6- and 12-year follow-up, i.e. after onset of CVD. Incident CVD predicted decline in processing speed only in the younger age group.

Comparison with other studies is hampered by differences in the definition and severities of CVD, choice of cognitive measures, and study design. In general, our findings are in line with previous studies[5,8,12] and a recent systematic review,[2] but not all,[7,16] and suggest that CVD is associated with worse cognitive test performance and faster decline.

Other studies also found a decline in executive function.[24,25] Rostamian *et al.*[25] used the LDST to measure executive functions, which we consider a test for information processing speed for which the present study found an association, too. To test executive function, we used the CST shifting index, which might not have been sensitive enough for decline. Notably, this is similar to our previous findings in MAAS.[17,18]

The effect of incident CVD on cognition was not examined before. In the present study, cognitive decline in incident CVD showed an

Table 3 Mean differences (and 95% confidence intervals) in baseline cognition and in rate of cognitive decline (slopes) from baseline between those with incident cardiovascular disease ($n = 204$) and those without ($n = 1138$)

	Time						
	Baseline difference		Change baseline to 6-year FU		Change baseline to 12-year FU		
Parameter	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	CVDxTime[a]
Verbal memory							
Total	-1.07	-8.87 to 6.74	-4.85	-13.10 to 3.40	-14.91**	-25.69 to - 4.12	7.37*
Women	1.67	-10.16 to 13.50	-2.78	-16.85 to 11.29	-16.68	-35.90 to 2.54	3.51
Men	-3.98	-14.14 to 6.18	-6.29	-15.83 to 3.25	-11.40*	-22.78 to - 0.03	4.48
Aged <65 years	-4.24	-13.49 to 5.01	1.05	-9.38 to 11.48	-8.18	-20.68 to 4.32	2.26
Aged ≥65 years	-4.49	-18.60 to 9.63	-8.82	-21.87 to 4.22	1.01	-23.12 to 25.13	2.58
Executive function							
Total	0.07	-0.09 to 0.23	0.00	-0.17 to 0.16	0.24*	0.02 to 0.46	5.56
Women	0.17	-0.06 to 0.41	-0.02	-0.27 to 0.23	0.09	-0.27 to 0.46	0.35
Men	-0.03	-0.24 to 0.18	0.01	-0.22 to 0.23	0.39**	0.12 to 0.66	12.36**
Aged <65 years	0.04	-0.14 to 0.22	-0.04	-0.22 to 0.15	0.24	-0.00 to 0.48	5.79
Aged ≥65 years	0.22	-0.08 to 0.51	-0.06	-0.40 to 0.28	-0.16	-0.74 to 0.42	0.36
Information processing speed							
Total	0.61	-0.91 to 2.13	-1.00	-2.25 to 0.25	-3.72***	-5.43 to - 2.02	24.02***
Women	0.02	-2.43 to 2.46	-1.30	-3.53 to 0.94	-3.74*	-6.88 to - 0.60	7.93*
Men	1.08	-0.73 to 2.88	-0.79	-2.09 to 0.51	-3.79***	-5.54 to - 2.03	19.61***
Aged <65 years	-0.75	-2.57 to 1.08	0.25	-0.78 to 1.28	-1.65*	-2.93 to - 0.37	10.92**
Aged ≥65 years	1.63	-0.93 to 4.20	-1.14	-3.82 to 1.54	-1.76	-6.65 to 3.14	0.72

Estimates from different cognitive domains are on different scales and cannot be directly compared. Model: CVD, time, CVDxTime, sex, age, age^2, education, baseline smoking, baseline alcohol abuse, body mass index, diabetes, depressive symptoms.
CI, confidence interval; CVD, cardiovascular disease; FU, follow-up.
[a]χ^2 test (2 degrees of freedom) of interaction between CVD (yes, no) and time (baseline, 6-year, 12-year FU); omnibus test of the null hypothesis of no difference in rate of change over time between CVD groups.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

insidious onset after 6 years and declined from that moment. We previously reported similar findings for incident hypertension.[17] This trajectory indicates a window of opportunity for slowing of cognitive decline by timely preventive measures. Indeed, recent studies showed that an approach targeting multiple risk factors simultaneously is most promising.[2] For instance, the recent FINGER study[26] used a multifactorial approach including diet, exercise, cognitive training, and vascular risk monitoring in at-risk elderly to investigate whether cognition can be improved or maintained by targeting health and lifestyle factors relating to CVD. While the 6-year preDIVA trial[27] did not result in reduced dementia risk through a nurse-led intensive vascular care program in adults aged 70–78 years, intervention effects were observed in participants without a history of CVD, which is in line with our finding of no significant decline in the prediagnostic phase (from baseline to 6-year follow-up). Taken together, these findings imply that primary prevention and timely management of CVD can reduce dementia risk from a lifetime perspective. This heart-brain connection makes a strong case that prevention of CVD and prevention of dementia should go hand in hand.

A dementia diagnosis requires impairment in two or more domains, next to interference with independence in activities of daily living due to these impairments. In this regard, our finding that CVD leads to decline in both memory as well as information processing speed is noteworthy. Processing speed is sensitive to damage to the brain's connectivity and white matter integrity, which is a hallmark of late-onset Alzheimer's disease, next to the aggregation of amyloid plaques and neurofibrillary tangles. Dementia and CVD share many risk factors related to vascular health, including hypertension, obesity, cholesterol, diabetes, healthy diet, and physical activity.[2] CVD may lead to cerebrovascular changes, reduced cognitive functioning and dementia through vascular insufficiency caused by atherosclerosis. Other underlying pathophysiological mechanisms such as cerebral hypoperfusion and low-cardiac output[28] lower cerebral perfusion and affect the neurovascular unit that ascertains constancy of cerebral blood flow, leading to blood-brain barrier damage and cerebral small vessel disease.[3] Indeed, previous studies found MI to be associated with presence of white matter lesions.[29] In addition, other risk factors for white matter lesions might exert stronger effects in people with a history of MI, including high diastolic blood pressure.[30] Besides this, inflammation and oxidative stress compromise repair mechanisms of damaged white matter.[31,32]

Above findings were more pronounced in midlife. This is in line with our previous studies,[17,18] and supports current recommendation to start health- and lifestyle interventions aimed at reducing

dementia risk in midlife or earlier.[33] Possibly, midlife CVD exert stronger effects because they impact on a relatively intact brain, which leads to sharper contrasts with unexposed norm groups. In later life, multimorbidity and wear-and-tear forces (oxidative stress, low-grade inflammation) are prevalent and may cause brain damage that dilutes the effect of any specific risk factor. Since large differences exist in severity and duration of such exposures, this causes inter- and intra-individual variability in cognitive performance as people age, as has been reported with increasing age for choice reaction time,[34] memory, and fluid cognitive abilities.[35,36] Alternatively, selective attrition could have led to an underestimation of the associations between CVD and cognitive decline because older participants were more likely to drop out of the study.[37] Even though the maximum-likelihood estimate and the attrition weights were used to minimize the effect of loss to follow-up, this possibility cannot be excluded.

This study provides weak evidence for sex differences in the association between CVD and cognitive decline. Sex-stratified analyses showed that associations were inconclusive in men with prevalent CVD, whereas a significant decline in memory was found in women. In contrast, decline in processing speed after prevalent CVD and decline in memory and processing speed after incident CVD was equal in both sexes. More research into this important topic is warranted.

This study has several strengths, including its large sample size, broad age range, long follow-up, serial assessment of several cognitive domains, and the ascertainment of relevant confounders. However, limitations should be mentioned. Cardiovascular disease and some covariates were based on self-report, which may have led to non-differential misclassification. Also, information on severity of the CVDs is lacking although this may affect the association differentially. Furthermore, some selection bias may have occurred by loss of older participants, as discussed. And due to the explorative nature of the study, we did not control for multiple comparisons and should therefore carefully interpret the results.

To conclude, this study indicates that individuals with prevalent CVD show more cognitive decline in memory and processing speed than controls. In incident CVD, decline is insidious and more modest, which might provide an opportunity for prevention of cognitive deficits.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton H, Gillespie C, Hailpern S, Heit J, Howard V, Kissela B, Kittner S, Lackland D, Lichtman J, Lisabeth L, Makuc D, Marcus G, Marelli A, Matchar D, Moy C, Mozaffarian D, Mussolino M, Nichol G, Paynter N, Soliman E, Sorlie P, Sotoodehnia N, Turan T, Virani S, Wong N, Woo D, Turner M; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update a report from the American heart association. *Circulation* 2012;**125**:e2–e220.
2. Deckers K, Van Boxtel MP, Schiepers OJ, De Vugt M, Muñoz Sánchez JL, Anstey KJ, Brayne C, Dartigues JF, Engedal K, Kivipelto M, Ritchie K, Starr J, Yaffe K, Irving K, Verhey FR, Köhler S. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry* 2015;**30**:234–246.
3. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider J, Tzourio C, Arnett DK, Bennet DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;**42**:2672–2713.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs RF, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter MJ, Sattar N, Smulders Y, Tiberi M, Van Der Worp BH, Van Dis I, Verschuren MW. 2016 European Guidelines on cardiovascular disease prevention in clinical practice The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
5. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. *BMJ* 1994;**308**:1604–1608.
6. Zuccala G, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, Cocchi A; GIFA-ONLUS Study Group [Grupo Italiano di Farmacoepidemiologia nell'Anzanio]. Hypotension and cognitive impairment: selective association in patients with heart failure. *Neurology* 2001;**57**:1986–1992.
7. Verhaegen P, Borchelt M, Smith J. Relation between cardiovascular and metabolic disease and cognition in very old age: cross-sectional and longitudinal findings from the berlin aging study. *Health Psychol* 2003;**22**:559–569.
8. Halling A, Berglund J. Association of diagnosis of ischaemic heart disease, diabetes mellitus and heart failure with cognitive function in the elderly population. *Euro J Gen Pract* 2006;**12**:114–119.
9. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S, Gona P, Salton CJ, DeCarli C, O'Donnell CJ, Benjamin E, Wolf P, Manning W. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation* 2010;**122**:690–697.
10. Aronson M, Ooi W, Morgenstern H, Hafner A, Masur D, Crystal H, Frishman W, Fisher D, Katzman R. Women, myocardial infarction, and dementia in the very old. *Neurology* 1990;**40**:1102–1106.
11. Launer L, Feskens E, Kalmijn S, Kromhout D. Smoking, drinking, and thinking. The Zutphen Elderly Study. *Am J Epidemiol* 1996;**143**:219–227.
12. Singh-Manoux A, Britton AR, Marmot M. Vascular disease and cognitive function: evidence from the Whitehall II Study. *J Am Geriatr Soc* 2003;**51**:1445–1450.
13. Zhu L, Viitanen M, Guo Z, Winblad B, Fratiglioni L. Blood pressure reduction, cardiovascular diseases, and cognitive decline in the mini-mental state examination in a community population of normal very old people: a three-year follow-up. *J Clin Epidemiol* 1998;**51**:385–391.
14. Petrovitch H, White L, Masaki KH, Ross GW, Abbott RD, Rodriguez BL, Lu G, Burchfiel CM, Blanchette PL, Curb JD. Influence of myocardial infarction, coronary artery bypass surgery, and stroke on cognitive impairment in late life. *Am J Cardiol* 1998;**81**:1017–1021.
15. Grubb NR, Simpson C, Fox KA. Memory function in patients with stable, moderate to severe cardiac failure. *Am Heart J* 2000;**140**:E1–E5.
16. Singh-Manoux A, Sabia S, Lajnef M, Ferrie JE, Nabi H, Britton AR, Marmot MG, Shipley MJ. History of coronary heart disease and cognitive performance in midlife: the Whitehall II study. *Eur Heart J* 2008;**29**:2100–2107.
17. Köhler S, Baars MA, Spauwen P, Schievink S, Verhey FR, Van Boxtel MP. Temporal evolution of cognitive changes in incident hypertension: prospective cohort study across the adult age span. *Hypertension* 2014;**63**:245–251.
18. Spauwen PJ, Köhler S, Verhey FR, Stehouwer CD, Van Boxtel MP. Effects of type 2 diabetes on 12-year cognitive change: results from the Maastricht Aging Study. *Diabetes Care* 2013;**36**:1554–1561.
19. Jolles J. *Maastricht Aging Study: Determinants of Cognitive Aging*. Maastricht: Neuropsych Publishers; 1995.
20. Van Der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc* 2005;**11**:290–302.
21. Van Der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The concept shifting test: adult normative data. *Psychol Assess* 2006;**18**:424–432.
22. Van Der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The letter digit substitution test: normative data for 1,858 healthy participants aged 24–81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. *J Clin Exp Neuropsychol* 2006;**28**:998–1009.
23. Arrindell WA, Ettema JHM. *SCL-90. handleiding bij een multidimensionele psychopathologie-indicator [SCL-90. Manual of a Multidimensional Psychopathology-Indicator]*. Lisse, The Netherlands: Swets Test Publishers; 2003.
24. Roberts RO, Knopman DS, Geda YE, Cha RH, Roger VL, Petersen RC. Coronary heart disease is associated with non-amnestic mild cognitive impairment. *Neurobiol Aging* 2010;**31**:1894–1902.

25. Rostamian S, Van Buchem MA, Westendorp RG, Jukema JW, Mooijaart SP, Sabayan B, De Craen AJ. Executive function, but not memory, associates with incident coronary heart disease and stroke. *Neurology* 2015;**85**:783–789.
26. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, Mangialasche F, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015;**385**:2255–2263.
27. Moll Van Charante EP, Richard E, Eurelings LS, Van Dalen J-W, Ligthart SA, Van Bussel EF, Hoevenaar-Blom MP, Vermeulen M, Van Gool WA. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 2016;**388**:797–805.
28. Bursi F, Rocca WA, Killian JM, Weston SA, Knopman DS, Jacobsen SJ, Roger VL. Heart disease and dementia: a population-based study. *Am J Epidemiol* 2006;**163**:135–141.
29. Breteler M, Van Swieten J, Bots M, Grobbee D, Claus J, Van Den Hout J, Van Harskamp F, Tanghe H, De Jong P, Van Gijn J. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology* 1994;**44**:1246–1252.
30. De Leeuw FE, De Groot JC, Oudkerk M, Witteman J, Hofman A, Van Gijn J, Breteler M. A follow-up study of blood pressure and cerebral white matter lesions. *Ann Neurol* 1999;**46**:827–833.
31. Tan Z, Beiser A, Vasan R, Roubenoff R, Dinarello C, Harris T, Benjamin E, Au R, Kiel D, Wolf P, Seshadri S. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. *Neurology* 2007;**68**:1902–1908.
32. Tan ZS, Beiser AS, Fox CS, Au R, Himali JJ, Debette S, DeCarli C, Vasan RS, Wolf PA, Seshadri S. Association of metabolic dysregulation with volumetric brain magnetic resonance imaging and cognitive markers of subclinical brain aging in middle-aged adults: the Framingham Offspring Study. *Diabetes Care* 2011;**34**:1766–1770.
33. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol* 2016;**15**:455–532.
34. Anstey KJ, Dear K, Christensen H, Jorm AF. Biomarkers, health, lifestyle, and demographic variables as correlates of reaction time performance in early, middle, and late adulthood. *Q J Exp Psychol A* 2005;**58**:5–21.
35. Hultsch DF, MacDonald SW, Dixon RA. Variability in reaction time performance of younger and older adults. *J Gerontol B Psychol Sci Soc Sci* 2002;**57**:101–115.
36. Christensen H, Mackinnon A, Jorm A, Henderson A, Scott L, Korten A. Age differences and interindividual variation in cognition in community-dwelling elderly. *Psychol Aging* 1994;**9**:381–390.
37. Euser SM, Schram MT, Hofman A, Westendorp RG, Breteler MM. Measuring cognitive function with age: the influence of selection by health and survival. *Epidemiology* 2008;**19**:440–447.