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ORIGINAL INVESTIGATIONS

Cognitive Decline Before and After Incident Coronary Events

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ABSTRACT

BACKGROUND Previous studies have suggested that coronary heart disease (CHD) may be associated with accelerated cognitive decline. However, the temporal pattern of cognitive decline before and after incident CHD remains largely unknown.

OBJECTIVES The purpose of this study was to determine the cognitive trajectory before and after incident CHD diagnosis in a national representative cohort age ≥50 years.

METHODS This study included 7,888 participants (mean age 62.1 ± 10.2 years) with no history of stroke or incident stroke during follow-up from the English Longitudinal Study of Ageing. Participants underwent a cognitive assessment at baseline (wave 1, 2002 to 2003), and at least 1 other time point (from wave 2 [2004 to 2005] to wave 8 [2016 to 2017]). Incident CHD was identified as a diagnosis of myocardial infarction and/or angina during follow-up.

RESULTS Incident CHD was associated with accelerated cognitive decline during a median follow-up of 12 years. The annual rate of cognitive decline before CHD diagnosis among individuals who experienced incident CHD was similar to that of participants who remained CHD-free throughout follow-up. No short-term cognitive decline was observed in participants with CHD diagnosis after the event. In the years following CHD diagnosis, global cognition, verbal memory, and temporal orientation scores declined significantly faster than they did before the event, after multivariable adjustment. Sensitivity analyses yielded similar results.

CONCLUSIONS Incident CHD is associated with accelerated cognitive decline after, but not before, the event. Attention should be drawn to the long-term cognitive deterioration related to CHD. Careful monitoring of cognitive function is warranted in CHD patients in the years following the event. (J Am Coll Cardiol 2019;73:3041–50) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Coronary heart disease (CHD) remains 1 of the leading causes of mortality worldwide, and its incidence increases with age (1,2). CHD predisposes individuals to cerebrovascular damage, such as cerebral ischemic lesions, which has been reported to result in cognitive impairment and to be involved in the pathological cascade of vascular dementia and Alzheimer's disease (3,4). Previous

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CI = confidence interval

MI = myocardial infarction

research on the relationship between cardiovascular diseases and cognitive changes has primarily focused on cerebrovascular diseases such as stroke, and only few longitudinal studies have explored the association between CHD and cognitive impairment (5). However, these results have been inconsistent, with some revealing an accelerated cognitive decline after CHD (6–8), and others detecting no such association (9,10).

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The atherosclerotic process and related hypoperfusion have been proposed to underlie vascular-related cognitive impairment (11,12), and these occur during a period prior to the CHD event. Thus, it is reasonable to assume that patients with CHD have faster rates of cognitive decline before the event. At present, the magnitude of short-term cognitive changes in participants with incident CHD is uncertain. Moreover, no studies have measured both the short-term cognitive decline after incident CHD and the cognitive changes occurring in the years before and after CHD; thus, the pattern of cognitive trajectory remains largely unknown.

Because cognitive function deteriorates naturally with age, even in healthy elderly individuals (13,14), it is critical to measure pre-CHD cognitive changes to accurately interpret the influence of CHD on cognitive trajectories. The ELSA (English Longitudinal Study of Ageing) includes multiple phases of cognitive assessment of a large community-based population over a median follow-up of 12 years, and therefore meets the requirement for pre-CHD cognitive assessment and offers the opportunity to evaluate the trajectory of cognitive decline before and after CHD. Therefore, the present study was designed to: 1) explore the trajectories of long-term cognitive decline in stroke-free participants who did or did not have an incident CHD during follow-up; and 2) measure the magnitude of long-term pre- and post-CHD diagnosis cognitive decline as well as short-term decline after CHD diagnosis.

METHODS

STUDY POPULATION. ELSA is a nationally-representative, biannual, ongoing, longitudinal cohort study of community-dwelling older adults living in England (15,16). A flow chart of participant selection is presented in Online Figure 1. We combined the data from wave 1 (2002 to 2003) with wave 8 (2016 to 2017). The baseline survey (wave 1) recruited 12,099 participants, of which 2,567 individuals were excluded from the current study for the following reasons: history of stroke (n = 511), history of myocardial infarction (MI) and/or angina (n = 1,254), did not complete all of the cognitive tests (n = 319), had a confirmed diagnosis of dementia and/or Alzheimer's disease at baseline (n = 28), or had an incident stroke during follow-up (n = 455). The details of stroke assessment have been provided in the Online Appendix. Furthermore, we also excluded participants who were lost to follow-up from waves 2 to 8 (n = 1,644). Therefore, the analytical sample of this study comprised 7,888 participants (3,260 men and 4,628 women) with complete baseline data and at least 1 reassessment of cognitive function (at waves 2 to 8).

Ethical consent has been obtained for all waves of the ELSA from the London Multicentre Research Ethics Committee (MREC/01/2/91) and informed consent has been obtained from all participants.

COGNITIVE ASSESSMENTS. The details of cognitive assessments have been published previously (17,18). At each wave, participants underwent a battery of 3 cognitive tests. First, memory was assessed by testing immediate and delayed recall of 10 unrelated words. Immediate and delayed recall scores ranged from 0 to 10, and a composite verbal memory score was created by summing the scores of the 2 individual memory tests. The validity and consistency of the memory test has been well-documented (19). Second, the animal fluency test was used to assess semantic fluency. Participants were asked to orally name as many different animals as possible in 1 min. The score of semantic fluency is equal to the total number of words produced, excluding repeated words and nonanimal words. The reliability and validity of this task has been well-documented, and it has previously been used as an indicator of executive function in other studies (20,21). Third, 4 questions regarding the date (i.e., day of month, month, year, and day of week) were asked to assess temporal orientation, and a score of 1 point was allocated for each correct answer. Higher scores on the verbal memory, semantic fluency, and temporal orientation tests indicate better cognitive function.

To allow direct comparisons to be made across cognitive tests, we calculated *Z* scores standardized to wave 1 for the individual tests by subtracting the mean score at wave 1 from the participant's test score at each wave and dividing by the SD of the wave 1 scores (18). Then, we generated a composite global cognitive *Z* score for each participant by averaging the *Z* scores of the 3 tests and restandardizing to wave 1 using the mean and SD of the global cognitive *Z* score at wave 1. A *Z* score of 1 would therefore describe cognitive performance that is 1 SD above the mean

score at wave 1. *Z* scores were used in regression analyses to allow for comparisons of regression coefficients across cognitive tests.

ASSESSMENT OF INCIDENT CHD. Participants were classified as incident CHD if they had been diagnosed with MI and/or angina during follow-up. We identified self-reported doctor-diagnosed incident CHD after wave 1 from "heart attack (MI or coronary thrombosis) diagnosis newly reported" and "angina diagnosis newly reported" at waves 2 to 8. The CHD diagnosis date was recorded as being between the date of the last interview and that of the interview reporting an incident CHD.

COVARIATES. The details of covariates are available in the Online Appendix. These covariates included age, sex, education, marital status, body mass index, depressive symptoms, current smoking, alcohol consumption, physical activity, hypertension, diabetes, chronic lung disease, asthma, and cancer.

STATISTICAL ANALYSIS. The results are presented as a number (percentage) for discrete variables and the mean ± SD or the median with interquartile range for continuous variables. Linear mixed models were used to evaluate the differences between slopes of cognitive decline over time (SD/year). Detailed descriptions of the statistical models and sensitivity analyses are provided in the Online Appendix. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). An alpha value of 0.05 (2-sided) was chosen as the threshold for statistical significance.

RESULTS

BASELINE CHARACTERISTICS AND SAMPLE SIZE. Among the 7,888 stroke-free participants (mean age 62.1 ± 10.2 years), 4,628 individuals (58.7%) were women. During the median follow-up of 12 years (interquartile range: 6 to 14 years), we identified 480 (5.6%) incident CHD events (254 MI and 286 angina pectoris). The baseline characteristics of participants according to incident CHD status are presented in Table 1. The participation patterns of this study population are shown in Online Tables 1 to 3. From waves 2 to 8, the cohort size was 7,423, 6,384, 5,670, 5,406, 4,971, 4,360, and 3,826, and the number of participants with incident CHD was 137, 74, 74, 61, 47, 42, and 45, respectively. The median number of cognitive assessments was 7 (interquartile range: 4 to 8).

COGNITIVE DECLINE FROM WAVES 1 TO 8. We compared the average annual cognitive decline from baseline of participants who had an incident CHD with that of CHD-free participants (Online Table 4).

TABLE 1 Baseline Characteristics of the Study Participants, by Whether They Had an Incident CHD During Follow-Up

	No Incident CHD (n = 7,408)	Incident CHD (n = 480)	p Value*	Adjusted p Value†
Age, yrs	61.9 ± 10.2	65.1 ± 9.2	<0.001	NA
Women	4,386 (59.2)	242 (50.4)	<0.001	NA
Body mass index, kg/m^2	27.5 ± 4.6	28.5 ± 4.6	<0.001	<0.001
Systolic blood pressure, mm Hg	136.2 ± 19.5	139.2 ± 19.6	0.001	0.208
Diastolic blood pressure, mm Hg	76.4 ± 11.3	75.2 ± 11.5	0.025	0.083
Education ≥ NVQ3/GCE A level‡	2,435 (32.9)	126 (26.3)	0.003	0.021
Living alone	2,279 (30.8)	166 (34.6)	0.080	0.497
Depressive symptoms	1,000 (13.5)	92 (19.2)	<0.001	<0.001
Current smoking	1,318 (17.8)	107 (22.3)	0.013	<0.001
≥1 alcoholic drink per week	4,593 (62.0)	260 (54.2)	<0.001	<0.001
Moderate-vigorous activity	6,023 (81.3)	362 (75.4)	0.002	0.014
Hypertension	3,714 (47.1)	297 (61.9)	<0.001	0.002
Diabetes	394 (5.3)	55 (11.5)	<0.001	<0.001
Heart failure	13 (0.2)	1 (0.2)	0.868	0.983
Chronic lung disease	359 (4.9)	45 (9.4)	<0.001	<0.001
Asthma	817 (11.0)	49 (10.2)	0.578	0.785
Cancer	400 (5.4)	21 (4.4)	0.333	0.190
Verbal memory scores	10.1 ± 3.4	9.8 ± 3.4	0.081	0.229
Sematic fluency scores	20.3 ± 6.3	19.6 ± 5.9	0.029	0.610
Temporal orientation scores	4 (4–4)	4 (4–4)	0.376	0.085

Values are mean ± SD, n (%), or median (quartile 1 to 3). *Calculated by using the Student's *t*-test, Wilcoxon rank test, or chi-square test. †Calculated by using the analysis of covariance or logistic regression after adjustment for baseline age and sex. ‡NVQ3/GCE A level is equivalent to senior high school.

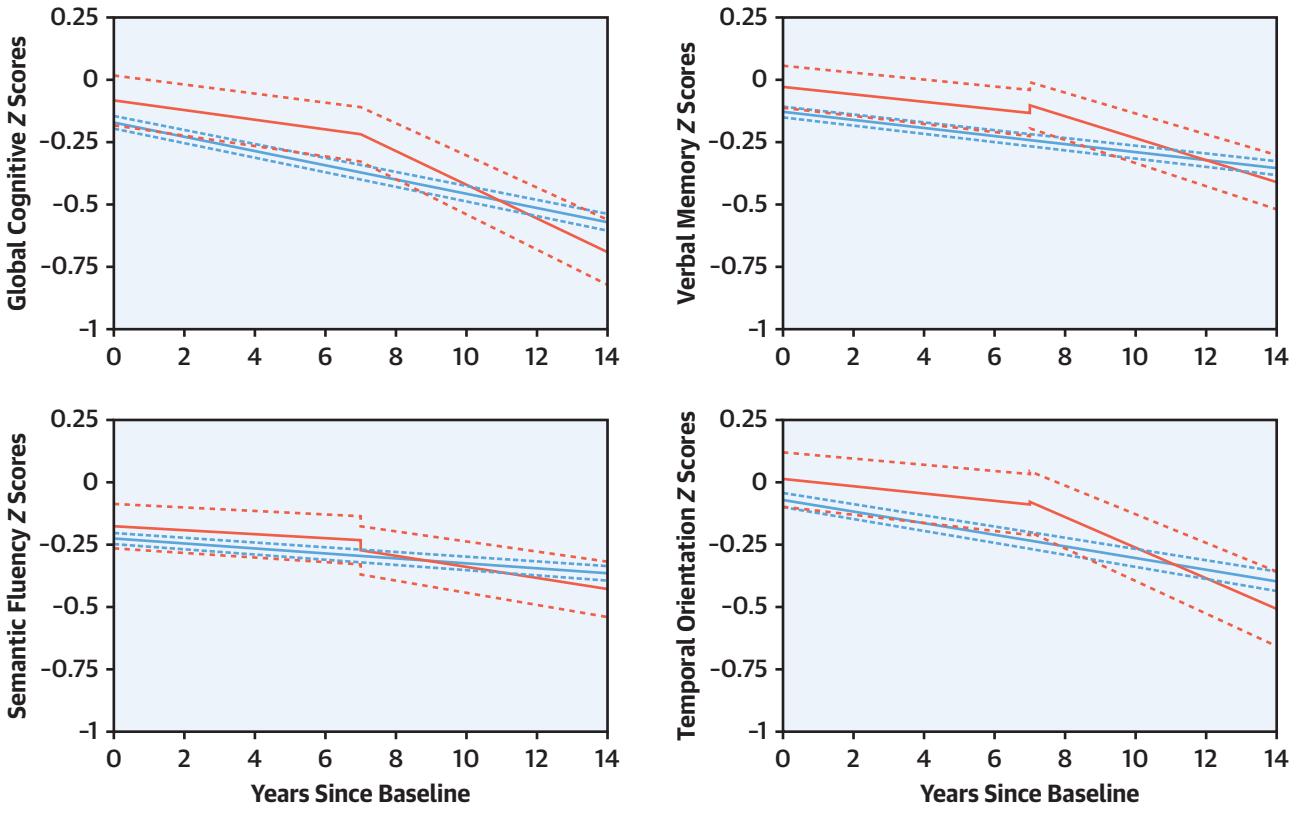
CHD = coronary heart disease; NA = not applicable.

Compared with CHD-free participants, the rate of global cognitive decline was accelerated among the participants in the CHD group (−0.018 SD/year; 95% confidence interval [CI]: −0.029 to −0.007) after multivariable adjustment. Likewise, faster rates of declines in verbal memory (−0.015 SD/year; 95% CI: −0.023 to −0.008), sematic fluency (−0.011 SD/year; 95% CI: −0.019 to −0.003), and temporal orientation (−0.015 SD/year; 95% CI: −0.027 to −0.003) were observed in participants with incident CHD. Stratification by sex showed no evidence of a modifying effect of sex on these estimates.

COGNITIVE DECLINE BEFORE CHD DIAGNOSIS. The annual rate of cognitive decline before CHD diagnosis in individuals who experienced an incident CHD was similar to those in participants who remained CHD-free throughout follow-up (Central Illustration, Table 2).

SHORT-TERM COGNITIVE DECLINE AFTER CHD DIAGNOSIS. As shown in the Central Illustration and Table 3, participants with CHD diagnosis did not experience short-term cognitive decline following CHD diagnosis after adjustment for post-CHD-diagnosis cognitive decline, calendar time, and baseline covariates.

CENTRAL ILLUSTRATION **Cognitive Decline and Incident Coronary Heart Disease**



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Predicted mean change in cognitive *Z* scores (SD) before and after an incident coronary heart disease (CHD) at year 7. Predicted values of cognitive function were calculated for a 70-year-old woman with a body mass index of 28 kg/m^2, education < NVQ3/GCE A level (equivalent to senior high school), ≥1 alcoholic drink per week, moderate or vigorous activity, living with spouse, and hypertension, but without depressive symptoms, current smoking, diabetes, chronic lung disease, asthma, or cancer. **Blue lines** represent the trajectory for CHD-free participants. **Red lines** represent the trajectory for participants with incident CHD. The **dashed lines** represent the 95% confidence intervals. The natural slopes of cognitive decline of CHD-free participants and pre-CHD slopes were estimated using the models in Table 2. The short-term changes in cognitive function and post-CHD slopes were estimated using the models in Table 3.

MEAN DIFFERENCE BETWEEN PRE- AND POST-CHD-DIAGNOSIS SLOPES. In the years following CHD diagnosis, global cognitive function declined significantly faster than it did before the event (−0.039 SD/year; 95% CI: −0.063 to −0.015) after adjustment for calendar time, short-term change in global cognitive function, and baseline covariates (Central Illustration, Table 3). Likewise, the rates of declines in verbal memory (−0.028 SD/year; 95% CI: −0.043 to −0.013) and temporal orientation (−0.038 SD/year; 95% CI: −0.068 to −0.007) were accelerated after CHD diagnosis. The post-CHD-diagnosis slope of sematic fluency also declined faster than its pre-CHD-diagnosis slope, although this difference did not achieve significance (Table 3). Further analyses showed that these estimates of global cognitive function decline were consistent across all major subgroups (all p values for interaction >0.05) (Figure 1).

NONRESPONSE ANALYSES. Of the 9,532 participants who had complete data at baseline, 1,644 (17.2%) were excluded from this study because they were lost to follow-up. These 1,644 participants had poorer cognitive function than those included in this study. Furthermore, the excluded participants had higher percentages of covariates, including male sex, depressive symptoms, living alone, smoking,

hypertension, diabetes, self-reported chronic lung disease, and cancer; they also had lower percentages of alcohol consumption and higher levels of education (Online Table 5).

SENSITIVITY ANALYSES. When we restricted the analyses to the 480 participants with incident CHD, the post-CHD-diagnosis annual declines in global cognition, verbal memory, and temporal orientation were still significant (**Table 4**). Slight differences were observed between the influences of incident MI and angina on cognitive declines. Incident MI was significantly associated with cognitive declines in global cognition, verbal memory, and semantic fluency; meanwhile, incident angina was only significantly associated with decline in temporal orientation, although its associations with declines in global cognition and verbal memory were borderline significant (Online Tables 6 and 7). Nevertheless, both incident MI and angina were significantly associated with post-diagnosis cognitive declines, but not with pre-diagnosis declines or short-term changes after the diagnosis (Online Tables 8 to 11), which is consistent with our main results. Furthermore, we divided the study population into 3 groups: participants with an incident MI including those who reported both MI and angina during follow-up (n = 254), participants with an incident angina (n = 226), and CHD-free participants (n = 7,408). Then, we analyzed the influence of the categorized variable on cognitive declines during follow-up. As shown in Online Table 12, participants with an incident MI had a faster memory decline during follow-up compared with participants with an incident angina (p = 0.045). To assess the stability of our results, we also restricted analyses to participants who had complete data from all 8 waves (n = 3,224), and the analyses yielded results consistent with the main analyses (Online Tables 13 to 15). In the analyses that included patients with stroke, the results were consistent with our main analyses and the post-CHD-diagnosis annual decline in sematic fluency became significant (Online Tables 16 to 18). For the purpose of better understanding how much the original scores would change for each cognitive test, the results of the analyses based on the original cognitive scores remained the same as those based on *Z* scores (Online Tables 19 to 21).

TABLE 2 Pre-CHD-Diagnosis Mean Difference in Rate of Change in Cognitive *Z* Scores (SD/Year) Between Participants Who Did and Did Not Have an Incident CHD

	Mean Difference (95% CI) in Rate of Change*	p Value*	p Value for Interaction
Global cognitive *Z* scores			
Men	0.014 (-0.014 to 0.041)	0.344	0.608
Women	0.004 (-0.023 to 0.030)	0.793	
Total	0.009 (-0.011 to 0.028)	0.384	
Verbal memory *Z* scores			
Men	−0.002 (−0.021 to 0.017)	0.822	0.666
Women	0.004 (−0.016 to 0.023)	0.708	
Total	0.001 (−0.013 to 0.014)	0.930	
Semantic fluency *Z* scores			
Men	0.018 (−0.004 to 0.039)	0.112	0.056
Women	−0.011 (−0.032 to 0.009)	0.289	
Total	0.002 (−0.013 to 0.017)	0.751	
Temporal orientation *Z* scores			
Men	0.014 (−0.015 to 0.043)	0.351	0.636
Women	0.004 (−0.026 to 0.033)	0.799	
Total	0.009 (−0.012 to 0.030)	0.391	

*Using participants who did not have an incident CHD as the reference group, after adjusting for baseline age, sex, body mass index, education, marital status, depression symptoms, current smoking, alcohol consumption, physical activity, hypertension, diabetes, chronic lung disease, asthma, and cancer.

CHD = coronary heart disease; CI = confidence interval.

DISCUSSION

Using data from a large cohort of stroke-free individuals age 50 years or older, we observed a significant association between incident CHD and accelerated cognitive decline across a median follow-up of 12 years. After dividing the long-term cognitive

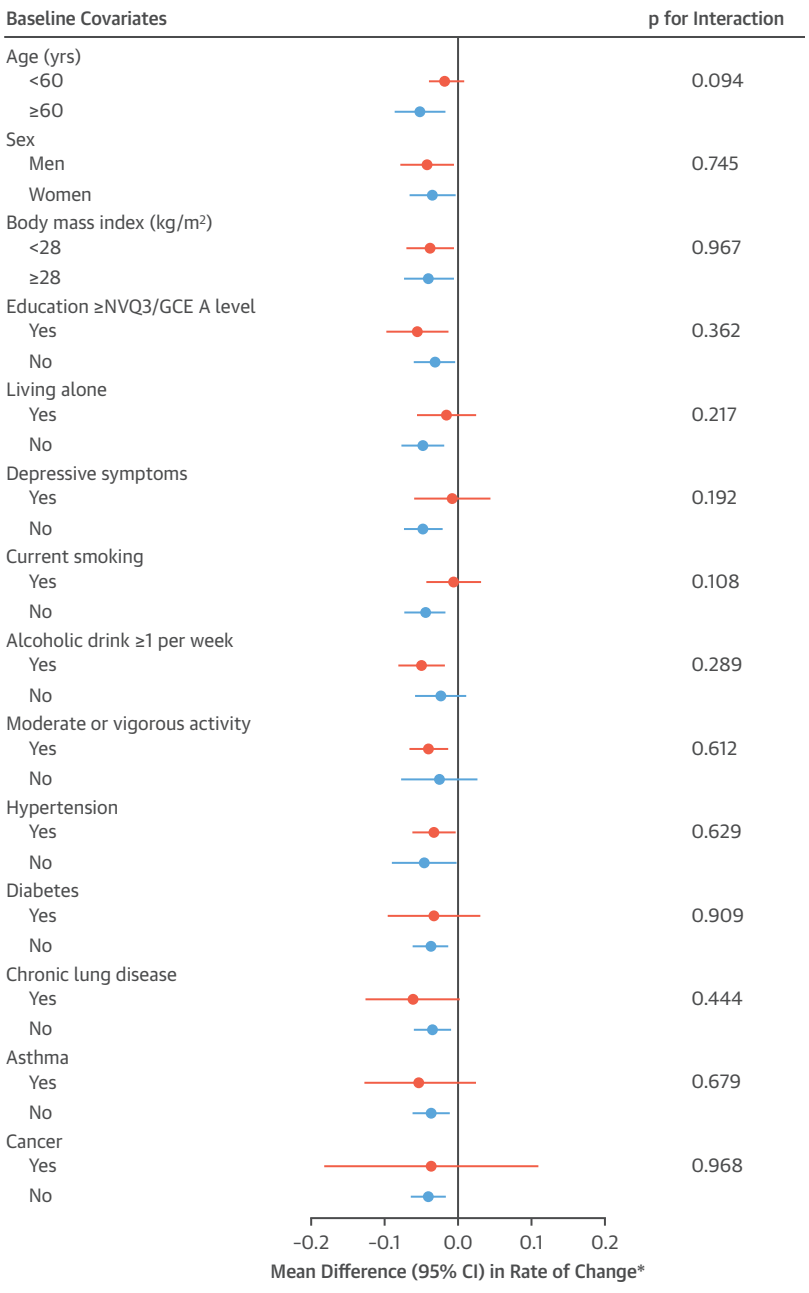
TABLE 3 Short-Term Change in Cognitive *Z* Scores (SD) and Post-CHD Annual Decline in Cognitive *Z* Scores (SD/Year) After CHD Diagnosis

	Short-Term Change After CHD Diagnosis		Post-CHD-Diagnosis Annual Decline*	
	β (95% CI)†	p Value†	β (95% CI)†	p Value†
Global cognitive *Z* scores	0.002 (−0.091 to 0.094)	0.973	−0.039 (−0.063 to −0.015)	0.002
Verbal memory *Z* scores	0.032 (−0.038 to 0.102)	0.370	−0.028 (−0.043 to −0.013)	<0.001
Semantic fluency *Z* scores	−0.042 (−0.116 to 0.033)	0.277	−0.012 (−0.027 to 0.003)	0.111
Temporal orientation *Z* scores	0.011 (−0.097 to 0.118)	0.845	−0.038 (−0.068 to −0.007)	0.016

*Compared with pre-CHD-diagnosis annual decline (reference). †After adjusting for calendar time, baseline age, sex (when analyzing total data), body mass index, education, marital status, depression symptoms, current smoking, alcohol consumption, physical activity, hypertension, diabetes, chronic lung disease, asthma, and cancer.

Abbreviations as in Table 2.

FIGURE 1 Post-CHD Annual Decline in Global Cognitive *Z* Scores (SD/Year) After CHD Diagnosis, According to Subgroups Defined by Covariates



*After adjusting for short-term change in global cognitive *Z* scores after coronary heart disease (CHD) diagnosis, calendar time, baseline age, sex, body mass index, education, marital status, depression symptoms, current smoking, alcohol consumption, physical activity, hypertension, diabetes, chronic lung disease, asthma, and cancer, except where an adjusting variable was itself being tested.

decline into pre-CHD diagnosis, short-term after CHD diagnosis, and post-CHD diagnosis, we found that incident CHD was significantly associated with faster rates of post-CHD-diagnosis cognitive decline, but not with cognitive changes in the years before or short-term changes following the event.

To the best of our knowledge, the current study is one of the largest longitudinal cohort studies to

TABLE 4 Sensitivity Analysis in 480 Participants With Incident CHD: Short-Term Change in Cognitive *Z* Scores (SD) and Post-CHD Annual Decline in Cognitive *Z* Scores (SD/Year) After CHD Diagnosis

	Short-Term Change After CHD Diagnosis		Post-CHD-Diagnosis Annual Decline*	
	β (95% CI)†	p Value†	β (95% CI)†	p Value†
Global cognitive *Z* scores	−0.051 (−0.151 to 0.050)	0.324	−0.039 (−0.067 to −0.011)	0.006
Verbal memory *Z* scores	0.019 (−0.063 to 0.101)	0.648	−0.023 (−0.041 to −0.005)	0.012
Semantic fluency *Z* scores	−0.056 (−0.137 to 0.026)	0.180	−0.010 (−0.028 to 0.008)	0.288
Temporal orientation *Z* scores	−0.010 (−0.022 to 0.016)	0.088	−0.049 (−0.083 to −0.015)	0.005

*Compared with pre-CHD-diagnosis annual decline (reference). †After adjusting for calendar time, baseline age, sex (when analyzing total data), body mass index, education, marital status, depression symptoms, current smoking, alcohol consumption, physical activity, hypertension, diabetes, chronic lung disease, asthma, and cancer.

Abbreviations as in Table 2.

evaluate the association between incident CHD and cognitive decline in stroke-free populations. Based on repeated cognitive measurements over a long follow-up period, this study revealed a reliable and robust trajectory of cognitive decline, and thus examined the influence of the CHD event over the years before and after the event. The influence of incident CHD on cognitive trajectory before the event has not been previously investigated. Compared with individuals who remained CHD-free, no significant increase in the slope of pre-CHD-diagnosis cognitive decline in participants who later had an incident CHD was observed, which suggests that the atherosclerotic process and related hypoperfusion might be compensatory before the clinical manifestation of CHD, and therefore result in no such brain injury that causes cognitive impairment detectable with the methods used in this study. Another possible explanation is that the cognitive assessments used in the present study are not sensitive enough to verify the subtle cognitive deficits present before the CHD event. The present study also adds to previous research by describing the effect of incident CHD on cognitive performance in the short time period after the event. We did not find any sharp short-term cognitive declines in any of the cognitive domains tested among participants with CHD diagnosis. This indicates that, unlike brain damage caused by cerebrovascular diseases (e.g., stroke), the hypoxic-ischemic brain injury induced by CHD might be minor and thus insufficient to cause cognitive impairment in the short-term. Besides, we found that participants with an incident MI had a significantly faster memory decline than those with an incident angina, which might be attributed to the different treatments and prognosis after the events.

Among participants with CHD diagnosis, post-CHD-diagnosis decline was accelerated for memory and temporal orientation compared with the decline rate pre-CHD diagnosis. For sematic fluency, only a borderline significance was found. Although making comparisons with previous studies is difficult given the discrepancies in the definition and severity of CHD, the cognitive function tests used, outcome measurements, and length of follow-up, our present finding is, in general, consistent with a previous study reporting that incident cardiovascular disease is associated with worse cognitive performance, including memory and information processing, but not executive function (6). This previous prospective cohort study with 1,342 participants also found that incident cardiovascular disease was associated with faster cognitive decline in the follow-up period of 6 to 12 years, but not in the pre-diagnostic phase (from baseline to the 6-year follow-up) (6). Similarly, the Whitehall II study also found a significant trend for lower cognitive scores with an increase in the time since the first CHD event (every 5-year increase) for the AH4-I, Mill Hill, and semantic fluency (8). These results are compatible with our finding that accelerated cognitive decline occurs after but not before incident CHD diagnosis. According to previous studies, a clinically significant change has been defined as a decline of ≥50% SD between baseline and follow-up (22,23). Therefore, for the significantly accelerated cognitive decline we observed in the years following CHD, the 95% CIs of cognitive declines in global cognition, verbal memory, and temporal orientation in approximately 10 years would correspond to declines of 50% SD. In addition, even miniscule differences in cognitive function can result in a substantially increased risk of dementia over several years (24). As there is currently no cure for dementia, early detection and intervention, such as multidomain lifestyle interventions (25),

may be the most effective approaches for the prevention of cognitive exacerbation and the delay of the progression to dementia. Taken together, the present findings suggest that careful monitoring for cognitive dysfunction in participants with CHD diagnosis are warranted in the years following their diagnosis.

Although the precise pathophysiological pathways through which incident CHD may cause cognitive decline in the long-term remain to be elucidated, several mechanisms have been proposed. For example, CHD might directly contribute to cognitive decline by causing cerebral hypoxia and silent brain lesions (26). A postmortem study has reported that ischemic heart disease was associated with cerebral microinfarcts, which suggests that CHD may be associated with cerebral small vessel disease and therefore contribute to cognitive impairment (27). Another important mechanism linking CHD to cognitive decline involves the shared vascular risk factors (3,28,29). According to previous systematic reviews, long-term exposure to vascular risk factors starting in early life might contribute to cognitive decline over the life-course through various biological pathways, including oxidative stress, immune responses, and endothelial dysfunction (26,30). Indeed, emerging evidence from imaging studies has demonstrated that vascular risk factors might contribute to the development of neurodegenerative lesions (i.e., β-amyloid deposition) in the brain (26,31,32). Although we controlled for several vascular risk factors in the statistical analysis, it is still possible that other risk factors may cause ongoing vascular brain injury, such as microinfarcts and cerebral small vessel disease, thus contributing to cognitive decline and even dementia later in life (33–35). Interestingly, both the Maastricht Aging Study (6) and our study found that participants with incident CHD had a higher burden of risk factors than a non-CHD group, but the higher burden did not significantly accelerate cognitive decline before an incident CHD. This finding indicates that incident CHD might play a role in triggering faster cognitive decline. In summary, although the underlying pathophysiological mechanisms could be reciprocally synergistic to exacerbate both atherosclerotic and degenerative brain lesions, they may also represent coinciding independent biological cascades that aggregate to cause continuous incremental brain injury, eventually resulting in cognitive disturbances and clinical manifestation of dementia (26,36,37).

STUDY STRENGTHS AND LIMITATIONS. Our study has several strengths. First, this is one of the largest longitudinal studies investigating the progression of cognitive decline before and after CHD diagnosis in a stroke-free population over a long-term follow-up period. Our study design involved repeated assessments of cognitive function during follow-up, which allowed us to generate the precise trajectory of cognitive decline, obtain participants' cognitive performance in the years before CHD diagnosis, and use a sophisticated model to calculate the short-term cognitive decline following CHD diagnosis and the persistent long-term cognitive decline following incident CHD. Despite this, our study also has several limitations. First, the use of self-reported doctor-diagnosed incident CHD might lead to a misclassification of CHD cases and could have biased our findings to a minor extent. However, 77.5% of incident CHD cases identified in this study were confirmed by ELSA researchers according to medical records. Second, due to lack of accurate information on the date of CHD diagnosis, symptom severity, acute treatments, and medications, we were unable to control for these factors in our analyses. For instance, participants with incident CHD tend to take multiple medications during the post-CHD period. For CHD patients, beta-blockers that might be associated with impaired cognitive function (38,39) are commonly prescribed. Therefore, the potential effect of treatments for CHD on cognitive function cannot be excluded. Third, there is a possibility of selection bias, as 1,644 participants (17.2%) with complete baseline data were excluded from the study because of loss during the follow-up. Considering this, we performed nonresponse analyses, which showed that our study sample was healthier than the initial sample of ELSA participants. This might limit the generalization of our findings to the original population. Besides, our analyses using the data of responders might have diluted our results, as nonresponders would have had a higher incidence of CHD and a faster rate of cognitive decline than responders. Fourth, the possibility of residual confounding cannot be ruled out even after adjustment for a number of potential confounders. For example, the lack of serum lipid measurements and ApoE genotyping and use of these unmeasured factors as covariates might have influenced our results. Finally, cognitive function was measured using isolated tasks, some of which might not be sensitive enough to detect subtle changes in cognitive function caused by CHD. A more elaborate and comprehensive

neuropsychological assessment may yield more robust associations.

CONCLUSIONS

We found that incident CHD was significantly associated with faster post-CHD-diagnosis cognitive decline, but not pre-CHD-diagnosis or short-term cognitive decline after the event. Future studies are warranted to determine the precise mechanisms linking incident CHD to cognitive decline.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Accelerated cognitive decline is associated with incident CHD after, but not before or immediately following ischemic events.

TRANSLATIONAL OUTLOOK: Future research should address the mechanisms responsible for cognitive decline that follows coronary events and seek methods that preserve cognitive function in patients with atherosclerosis.

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KEY WORDS cognitive decline, coronary heart disease, English Longitudinal Study of Ageing, linear mixed model

APPENDIX For an expanded Methods section as well as supplemental tables and a figure, please see the online version of this paper.