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Original Contribution

Associations Between Midlife (but Not Late-Life) Elevated Coronary Heart Disease Risk and Lower Cognitive Performance: Results From the Framingham Offspring Study

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It is unclear how coronary heart disease (CHD) risk across the adult life span affects late-life cognition. We estimated associations of midlife and late-life elevated CHD risk with cognitive trajectories (general cognitive performance, processing speed/executive function, memory) in later life (after age 55 years or age 70 years) among 2,892 Framingham Offspring Study participants who had completed CHD risk assessments approximately every 4 years since 1971 and had undergone neuropsychological testing between 1999 and 2014. We stratified analyses by apolipoprotein E gene (*APOE*) ε4 allele carrier status. Using linear mixed-effects models, elevated CHD risk in midlife (age 55 years) was associated with lower levels of general cognitive performance ($\beta = -0.560$ standard deviation (SD) units, 95% confidence interval (CI): −0.874, −0.246), executive function ($\beta = -0.624$ SD units, 95% CI: −0.916, −0.332), and memory ($\beta = -0.560$ SD units, 95% CI: −0.907, −0.213) at age 70 years but not with rates of cognitive change. Late-life (age 70 years) elevated CHD risk, however, was associated with somewhat better levels of general cognitive performance and memory. There were associations between duration of elevated CHD risk during midlife and levels (but not trajectories) of later-life cognitive outcomes. Associations were not modified by *APOE*-ε4 status. These findings suggest that midlife elevated CHD risk is associated with lower cognition, independently of *APOE*-ε4 status, suggesting that risk of vascular disease may not contribute a "second hit" to AD risk.

Alzheimer disease; apolipoprotein E ε4; cognition; coronary heart disease; life course

Abbreviations: AD, Alzheimer disease; *APOE*, apolipoprotein E gene; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; SD, standard deviation.

Identifying risk factors for preclinical Alzheimer disease (AD) may represent the best strategy for reducing AD risk. Cardiovascular disease (CVD) risk factors, including diabetes (1–3) and hypertension (4, 5), are associated with poorer cognition, particularly problems with executive function (6, 7) and memory (4, 7–9). Yet, CVD risk factors are seldom present in isolation (10, 11); combinations thereof could be more impactful for risk of incident AD, particularly before AD symptom onset. In previous studies, investigators have reported associations of aggregations of midlife CVD risk factors (12–18) with cognitive decline, yet associations of late-life CVD risk factors are unclear, with some authors reporting null (19–21) or even protective (22, 23) findings.

A hypothesized mechanism linking multiple CVD risk factors to AD is the "2-hit" vascular hypothesis of AD (24), which postulates that microvascular damage, partly attributable to cardiovascular factors, leads to neuronal injury and dysfunction (hit 1). This vascular injury triggers multiple neurotoxic molecules and/or diminished brain capillary flow, which then leads to breakdowns in the blood-brain barrier that affect amyloid β clearance, resulting in amyloid β accumulation (hit 2). Although the timing of this cascade is unclear, it could be accelerated by the number and duration of modifiable CVD risk factors present during adulthood, as well as genetic profile.

Our primary goal was to determine how longitudinal CVD risk affects the trajectory of cognitive performance across

adulthood and to examine whether the relationship varies by apolipoprotein E (*APOE*) genotype, given previous work showing that these factors modify associations between vascular risk and cognition (1, 25, 26). Some modifiable CVD risk factors may be associated with AD risk in midlife, yet some (i.e., hypertension (23) and obesity (22)) may become protective in later life. We hypothesized that longer duration of elevated CHD risk accelerates cognitive deterioration, such that CHD risk in midlife, not late life, is more strongly associated with lower cognition and steeper declines in general cognitive performance and cognitive domains, including processing speed/executive function and memory.

METHODS

Study sample

Participants were members of the Offspring Cohort ($n = 5{,}124$) of the Framingham Heart Study. The Framingham Heart Study, initiated in Framingham, Massachusetts, in 1948, is a community-based prospective cohort study of CVD risk factors. The Offspring Cohort includes children of original cohort members and spouses and has been followed with health examinations approximately quadrennially since 1971. Between study cycle examinations, information is obtained via interim mailed questionnaires and regular telephone calls, thereby maintaining continuous surveillance (27). The present study used data on 2,892 participants who completed up to 9 health assessments and underwent neuropsychological testing during 1999–2014 as part of an ancillary study. The number of visits with neuropsychological testing ranged from 1 to 10 (mean = 2.2 visits). The examination schedule, shown in Web Figure 1 (https://academic.oup.com/aje), describes the relative timing of the administration of CHD risk evaluations and cognitive assessments during the life course. The protocol was approved by the institutional review board of Boston University Medical Center, and participants provided written informed consent.

CHD risk

To measure cumulative CHD risk, we used the Framingham Risk Score, a composite index of age, blood pressure, diabetes mellitus status, smoking status, and high-density lipoprotein (HDL) cholesterol and total cholesterol levels (28). Variables in the index were weighted using coefficients from sex-specific regressions predicting 10-year onset of CHD. The average of 2 blood pressure measurements taken while the participant sat for ≥5 minutes was used. We did not include information on use of antihypertension medication because neither definitions based on JNC-V criteria (fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure) nor the original Framingham Risk Score incorporate such information. Additionally, the Framingham Offspring Study started in 1971 (see Web Figure 1), prior to the availability of many cholesterol medications and statins. Diabetes was defined as elevated fasting plasma glucose level ≥100 mg/dL, hemoglobin A_{1c} concentration ≥5.7%, or self-reported history of type 2 diabetes or diabetes treatment (use of insulin or oral hypoglycemic agents). Smoking status was reported by the participant if the person had smoked regularly during the past year. Total cholesterol level was determined through the Abell-Kendall technique. This risk score was derived from 5,573 participants aged 30–74 years without CHD from the Framingham Heart Study and the Framingham Offspring Study (29).

Neuropsychological assessment

Using confirmatory factor analysis, we derived scores for processing speed/executive function, memory, and general cognition (30–37). A description of the tests and their domains is given in Web Table 1. Factor scores for each domain were estimated from 2-parameter logistic graded-response item response theory models and scaled to have a mean value of 50 and a standard deviation (SD) of 10 (38).

Adjustment covariates

The adjustment covariates were age at the first examination visit with CHD risk data (centered at 70 years so that cognitive intercepts would be interpretable at that age), sex, and educational level (less than high school diploma, high school graduation, some college, or college graduation).

Statistical analyses

We compared sample characteristics between participants with and without elevated CHD risk, using *t* tests for continuous variables and χ^2 tests for categorical variables. We measured CHD risk for each participant at available study visits using the time-varying information available from its components. Using linear mixed-effects models of cognitive trajectories, we leveraged time-varying information about CHD risk in 3 ways. We first examined the duration of elevated CHD risk during midlife; we then evaluated continuous CHD risk at specific ages in midlife and later life, followed by elevated CHD risk during midlife and late life.

Association of duration of elevated midlife CHD risk with cognitive trajectory. To evaluate whether duration of elevated CHD risk is associated with late-life levels of and changes in cognitive outcomes, we used linear mixed-effects models to regress random intercepts and random slopes for cognitive growth processes on duration of elevated CHD risk. To calculate duration of elevated CHD risk, we subtracted from 60 the first age at which CHD risk was found to be elevated (in the top 20th percentile, consistent with previous studies (39)). We used 60 years as the minuend to ensure that the assessment of CHD risk preceded the first cognitive assessment. The linear mixed-effects model modeled cognitive outcomes as a function of age, age^2, adjustment variables, and interactions of adjustment variables with age. We used age as the time scale in analyses because of its biological relevance, and we adjusted for baseline age to anchor everyone to their age at entry (40). The intercept and linear age term were random effects, while

the age^2 term was a fixed effect to accommodate nonlinear trajectories.

Association of CHD risk in midlife and late life with cognitive trajectory. To evaluate associations of CHD risk at ages 55 and 70 years with cognition in linear mixed models, we calculated the maximum continuous CHD score among visits occurring within 3 years of ages 55 and 70 years, respectively. This treatment of CHD risk is independent of CHD risk at other ages. The models for each cognitive outcome were otherwise the same as the corresponding component of the joint models described above. We divided the CHD risk score by 10, so that parameter estimates would reflect a 10% difference in CHD risk.

Association of midlife and late-life elevated CHD risk with cognitive trajectory. To evaluate associations of elevated CHD risk with cognition in linear mixed models, we generated a binary indicator of whether continuous CHD risk scores at ages 55 and 70 years were in the top 20th percentile. We entered this CHD risk predictor into the same type of linear mixed model as that described above. Further, we fitted the models in subgroups stratified by *APOE* ε4 allele carrier status to evaluate effect modification.

Secondary analyses. To evaluate which components of CHD risk may drive associations with cognition, we examined associations of CHD risk score components, high low-density lipoprotein cholesterol level (≥160 mg/dL), and low HDL cholesterol level (<40 mg/dL in men or <50 mg/dL in women) with cognitive trajectories using linear mixed models.

Sensitivity analyses. To evaluate whether results were driven by associations between survival and old age, we reran the primary analyses using a subsample of participants who had CHD risk scores calculated at both age 55 years and age 70 years. To evaluate the sensitivity of results to individuals with extremely long periods of cognitive follow-up, we refitted linear mixed-effects models after excluding study visits that took place more than 10 years (5 visits) after the first cognitive examination. To determine the sensitivity of our findings to the choice of cutpoint for elevated CHD risk (80th percentile), we compared analyses using the 75th and 85th percentiles.

All analyses adjusted for age at first cognitive assessment, sex, and years of education. We used maximum likelihood estimation with robust standard error estimation under the expectation maximization algorithm in Mplus software for statistical models (41). Maximum likelihood estimation assumes that data are missing at random, conditional on variables in the model.

RESULTS

Sample characteristics

On average, participants were followed for CHD risk for 36.8 years beginning at age 34.8 years (range, 18–63 years) and for cognition starting at age 62.3 years (range, 34–93 years) (Table 1). The duration of elevated CHD risk in the full sample was 9.3 (SD, 11.1) years. Of 2,892 participants, 1,306 (45.2%) had elevated CHD risk at some visit during follow-up. Among persons who had ever been found to have elevated CHD risk, the duration of elevated CHD risk was 18.6 (SD, 8.6) years. Compared with those who had never had elevated CHD risk, persons with a history of elevated CHD risk tended to be male; to be older at the first examination with data on both CHD and age at first neuropsychological assessment; to be demented; to be an *APOE*-ε4 carrier; and to have lower educational attainment, fewer study visits, a higher Framingham CHD risk score, and lower performance for all cognitive outcomes (Table 1). The mean follow-up time was 30.2 years, with 83,912.5 person-years at risk. Table 2 includes information comparing persons with and without elevated CHD risk at ages 55 and 70 years. The correlation between CHD risk scores at ages 55 and 70 years was 0.52 based on continuous versions of the scores and 0.59 based on discretized versions of the scores at the 80th percentile. Web Figure 2 shows scatterplots of the continuous CHD risk score at 55 years of age with the cognitive factors.

All participants contributed data on CHD risk. Of the 2,892 participants, 809 contributed 1 study visit. Persons with 2 or more visits contributed to the estimation of change in cognitive performance and predictors thereof, while those with 1 visit contributed to the estimation of baseline cognitive performance and its correlates.

Associations of duration of elevated CHD risk with cognitive trajectory

Table 3 shows associations of duration of elevated CHD risk with level and slope of cognitive trajectories for general cognition, executive function, and memory. There were associations of duration of elevated CHD risk with levels, but not change, for all cognitive outcomes. Magnitudes of differences in cognitive levels per unit difference in duration of CHD risk were approximately 0.09 SD units for all outcomes.

Associations of midlife and late-life CHD risk with cognitive trajectory

Table 4 shows results from linear mixed-effects models of associations of midlife and late-life CHD risk score with cognitive level and change. Elevated CHD risk during midlife (age 55 years) was associated with lower levels of general cognition at age 70 years based on both the continuous version of the CHD risk score ($\beta = -0.560$ SD units per 10% difference in CHD risk, 95% confidence interval (CI): −0.874, −0.246) and the categorical version indicating elevated levels at age 55 years ($\beta = -0.665$ SD unit difference between elevated and nonelevated CHD risk, 95% CI: −1.327, −0.003). These associations represent an approximately 0.05-SD difference in cognition per 10% difference in CHD risk and between elevated and nonelevated CHD risk. The same was true for executive functioning (Table 4). The continuous CHD risk score at age 55 years, but not the categorical version, was associated with lower memory at age 70 years. In contrast, late-life

Table 1. Characteristics of Participants in a Study of Coronary Heart Disease Risk and Cognitive Trajectories, Overall and by Elevated Coronary Heart Disease Risk[a] Status, Framingham Offspring Study ($n = 2,892$), 1971–2014

Characteristic	Total Sample ($n = 2,892$)			CHD Risk Status					
				Ever Had Elevated CHD Risk ($n = 1,306$)			Never Had Elevated CHD Risk ($n = 1,586$)		
	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)
Demographic characteristics									
Age at first examination visit, years			34.8 (9.2)			38.6 (8.2)[b]			31.7 (8.9)[b]
Age at first neuropsychological assessment, years			62.3 (9.7)			66.2 (8.2)[b]			59.1 (9.7)[b]
Educational level[c]									
Less than high school diploma	110	3.8		78[b]	6.0[b]		32[b]	2.0[b]	
High school diploma	766	26.5		377[b]	28.9[b]		389[b]	24.5[b]	
Some college	749	25.9		325[b]	24.9[b]		424[b]	26.7[b]	
College degree or more	1,260	43.6		522[b]	40.0[b]		738[b]	46.5[b]	
Female sex	1,553	53.7		345[b]	26.4[b]		1,208[b]	76.2[b]	
APOE-ε4 carrier[d]	638	22.1		306[b]	23.4[b]		332[b]	20.9[b]	
Ever having dementia	180	6.2		105[b]	8.0[b]		75[b]	4.7[b]	
Ever having Alzheimer disease	121	4.2		65	5.0		56	3.5	
Duration of time in study, years			36.8 (3.9)			36.2 (4.1)[b]			37.3 (3.6)[b]
No. of study visits			10.1 (2.2)			10.2 (2.1)[b]			10.0 (2.3)[b]
Duration of time in study with cognitive testing, years			5.5 (4.1)			5.5 (4.2)			5.5 (4.1)
No. of study visits with cognitive testing			2.2 (1.2)			2.3 (1.2)			2.2 (1.1)
Framingham Risk Score			0.08 (0.05)			0.11 (0.06)[b]			0.06 (0.02)[b]

Table continues

Table 1. Continued

Characteristic	Total Sample ($n = 2,892$)			CHD Risk Status					
				Ever Had Elevated CHD Risk ($n = 1,306$)			Never Had Elevated CHD Risk ($n = 1,586$)		
	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)
Components of Framingham Risk Score									
Ever having elevated total cholesterol level	2,218	76.7		1,088[b]	83.3[b]		1,130[b]	71.3[b]	
Ever being a smoker[e]	1,777	61.5		969[b]	74.2[b]		808[b]	51.0[b]	
Ever having low HDL cholesterol level[f]	2,187	75.6		1,149[b]	88.0[b]		1,038[b]	65.5[b]	
Ever having high blood pressure[g]	2,414	83.5		1,259[b]	96.4[b]		1,155[b]	72.8[b]	
Ever having elevated fasting glucose level[h]	2,608	90.2		1,283[b]	98.2[b]		1,325[b]	16.0[b]	
Cognitive function									
General cognitive performance[i]			54.0 (7.5)			52.1 (7.5)[b]			55.6 (7.2)[b]
Executive functioning[j]			53.8 (6.8)			52.6 (7.2)[b]			54.9 (6.3)[b]
Memory[k]			53.9 (8.2)			52.0 (8.0)[b]			55.5 (8.0)[b]

Abbreviations: *APOE*, apolipoprotein E gene; CHD, coronary heart disease; HDL, high-density lipoprotein; SD, standard deviation.
[a] Elevated CHD risk was defined as the upper 20th percentile of the Framingham Risk Score.
[b] $P < 0.01$ for ever having elevated CHD risk versus never having elevated CHD risk.
[c] Data were missing for 7 participants.
[d] Data were missing for 111 participants.
[e] Data were missing for 104 participants.
[f] Data were missing for 675 participants.
[g] Data were missing for 458 participants.
[h] Data were missing for 278 participants.
[i] Cognitive factor scores characterize performance at the first cognitive assessment and are internally scaled.
[j] Data were missing for 8 participants.
[k] Data were missing for 6 participants.

Table 2. Characteristics of Participants by Elevated Coronary Heart Disease Risk[a] Status and Age, Framingham Offspring Study ($n = 2{,}892$), 1971–2014[b]

Characteristic	Age and CHD Risk Status											
	Age 55 Years						Age 70 Years					
	Elevated CHD Risk ($n = 595$)			Nonelevated CHD Risk ($n = 2{,}121$)			Elevated CHD Risk ($n = 599$)			Nonelevated CHD Risk ($n = 598$)		
	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)
Demographic characteristics												
Age at first examination visit, years			N/A			N/A			N/A			N/A
Age at first neuropsychological assessment, years			64.4 (8.0)			61.6 (9.6)			74.5 (3.7)			73.4 (3.6)
Educational level[c]												
Less than high school diploma	36	6.1		64	3.0		52	8.7		32	5.4	
High school diploma	179	30.1		541	25.5		181	30.2		174	29.1	
Some college	169	28.4		542	25.6		137	22.9		174	29.1	
College degree or more	208	35.0		970	45.7		228	38.1		216	36.1	
Female sex	133	22.4		1,327	62.6		135	22.5		483	80.8	
APOE-ε4 carrier[d]	144	24.2		462	21.8		144	24.0		115	19.2	
Ever having dementia	35	5.9		119	5.6		83	13.9		78	13.0	
Ever having Alzheimer disease	21	3.5		86	4.1		54	9.0		58	9.7	
Duration of time in study, years			36.1 (4.3)			37.3 (3.5)			35.9 (4.2)			37.0 (3.7)
No. of study visits			10.4 (2.0)			10.5 (2.1)			10.4 (2.0)			10.5 (2.1)
Duration of time in study with cognitive testing, years			5.1 (4.1)			5.9 (4.1)			6.4 (4.0)			7.0 (4.3)
No. of study visits with cognitive testing			2.1 (1.2)			2.3 (1.2)			2.6 (1.3)			2.8 (1.5)
Framingham Risk Score			2.83 (0.79)			0.98 (0.45)			3.52 (1.35)			1.01 (0.36)

Table continues

Table 2. Continued

Characteristic	Age and CHD Risk Status											
	Age 55 Years						Age 70 Years					
	Elevated CHD Risk ($n = 595$)			Nonelevated CHD Risk ($n = 2,121$)			Elevated CHD Risk ($n = 599$)			Nonelevated CHD Risk ($n = 598$)		
	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)	No. of Persons	%	Mean (SD)
Components of Framingham Risk Score												
Ever having elevated total cholesterol level	500	84.0		1,426	67.2		508	84.8		508	85.0	
Ever being a smoker[e]	514	86.4		1,153	54.4		416	69.5		296	49.5	
Ever having low HDL cholesterol level[f]	468	78.7		1,020	48.1		460	76.8		317	53.0	
Ever having high blood pressure[g]	492	82.7		1,066	50.3		540	90.2		454	75.9	
Ever having elevated fasting glucose level[h]	509	85.6		1,403	66.2		571	95.3		485	81.1	
Cognitive function												
General cognitive performance[i]			52.3 (7.3)			54.7 (7.2)			49.5 (8.0)			50.8 (8.5)
Executive functioning[j]			52.9 (6.9)			54.3 (6.4)			49.9 (8.5)			50.9 (8.2)
Memory[k]			52.2 (7.7)			54.6 (8.0)			49.3 (8.2)			50.4 (8.8)

Abbreviations: *APOE*, apolipoprotein E gene; CHD, coronary heart disease; HDL, high-density lipoprotein; N/A, not applicable; SD, standard deviation.

[a] Elevated CHD risk was defined as the upper 20th percentile of the Framingham Risk Score.

[b] All differences between groups were significant at $P < 0.01$ for elevated CHD risk at ages 55 and 70 years, except for duration of time in the study with cognitive testing.

[c] Data were missing for 7 participants.

[d] Data were missing for 111 participants.

[e] Data were missing for 104 participants.

[f] Data were missing for 675 participants.

[g] Data were missing for 458 participants.

[h] Data were missing for 278 participants.

[i] Cognitive factor scores characterize performance at the first cognitive assessment and are internally scaled.

[j] Data were missing for 8 participants.

[k] Data were missing for 6 participants.

Table 3. Associations of Duration of Elevated Coronary Heart Disease Risk[a] With Cognitive Trajectories in Linear Mixed-Effects Models, Framingham Offspring Study ($n = 2,885$), 1971–2014[b]

Cognitive Outcome	Association Between Duration of Elevated CHD Risk and Cognitive Slope[c]		Association Between Duration of Elevated CHD Risk and Cognitive Level (Age 70 Years)[d]	
	β	95% CI	β[e]	95% CI
General cognitive performance	−0.003	−0.009, 0.003	−0.094	−0.157, −0.031
Executive function	−0.005	−0.011, 0.001	−0.097	−0.156, −0.038
Memory	−0.002	−0.010, 0.006	−0.097	−0.166, −0.028

Abbreviations: CHD, coronary heart disease; CI, confidence interval.

[a] Elevated CHD risk was defined as the upper 20th percentile of the Framingham Risk Score.

[b] Results were adjusted for age (centered at mean age at first cognitive assessment), education, and sex.

[c] Coefficients for cognitive slope represent the difference in the annual rate of cognitive decline per difference in duration (years) of elevated CHD risk up to age 60 years.

[d] Coefficients for cognitive level represent the model-estimated difference in cognition at age 70 years per difference in duration (years) of elevated CHD risk up to age 60 years.

[e] $P < 0.05$.

CHD risk (at age 70 years) was not associated with level of cognitive performance (coefficients even indicated a positive relationship between CHD risk and cognition).

Effect modification by *APOE*-ε4 carrier status

Associations of duration of elevated CHD risk with cognitive trajectories did not differ by *APOE*-ε4 carrier status (Table 5). From stratified linear mixed models, associations between categorical CHD risk and levels of all domains of cognition were larger among individuals without an *APOE* ε4 allele; however, differences were not remarkably different (Web Table 2). The continuous CHD risk score was not associated with cognitive levels or trajectories (Web Table 2).

Secondary analyses

To determine whether a specific component of the CHD risk score at either midlife or late life was driving associations found between CHD risk and level of cognitive performance, we tested associations of midlife and late-life components of CHD risk with cognition (Web Table 3). High blood pressure in both midlife and late life was associated with lower levels of all cognitive factors. Low midlife HDL cholesterol was associated with lower levels of executive function (Web Table 3). Midlife diabetes was associated with decline in executive function (β = −0.064, 95% CI: −0.123, −0.005).

Sensitivity analyses

We fitted linear mixed-effects models (Web Tables 4 and 5) among the 1,860 individuals who had risk scores at both age 55 years and age 70 years. Results from these tables correspond to Tables 3 and 4, respectively. Associations between duration of elevated CHD risk and levels of all cognitive outcomes were maintained (Web Table 4), as were findings from models examining continuous CHD risk at age 55 years and levels of executive function (β = −0.547, 95% CI: −1.047, −0.047) and memory (β = −0.709, 95% CI: −1.385, −0.033) (Web Table 5). Although the association with general cognitive performance in Web Table 5 did not reach statistical significance (β = −0.531, 95% CI: −1.105, 0.043), the point estimate was close to the corresponding estimate in Table 4 (β = −0.560, 95% CI: −0.874, −0.246).

Web Table 6 presents results from linear mixed-effects models using examinations taking place within 5 visits of the first examination with cognitive data. Consistent with findings from main analyses (Table 4), continuous CHD risk at age 55 years was associated with lower cognitive levels in all domains, while elevated CHD risk, treated categorically, at age 55 years was associated with lower levels of executive functioning at age 70 years (Web Table 6).

When elevated CHD risk was defined by the 75th or 85th percentile, null findings from models of duration of elevated midlife CHD risk were unchanged (Web Table 7). Consistent with findings in Table 4, midlife (age 55 years) elevated CHD risk, as defined by the 75th percentile, was associated with lower cognitive levels (Web Table 8).

DISCUSSION

In this study, we evaluated the interplay of CHD risk in midlife and later life with cognitive impairment and decline in later life. Elevated CHD risk during midlife, but not later life, was associated with lower levels of all cognitive domains. Importantly, we detected associations between the Framingham Risk Score and levels of cognitive performance that were not evident for each component of CHD risk, which underscores the importance of considering aggregations of CHD risk. These main findings were comparable among subgroups of individuals defined by *APOE*-ε4 status, which is consistent with the notion that vascular pathologies may affect cognition in late life but are not necessarily

Table 4. Associations of Elevated Coronary Heart Disease Risk[a] at Ages 55 and 70 Years with Cognitive Trajectories in Linear Mixed-Effects Models, Framingham Offspring Study, 1971–2014[b]

Risk Measure, Age, and Cognitive Outcome	No. of Persons	Association of CHD Risk With Cognitive Slope[c]		Association of CHD Risk With Cognitive Level (Age 70 Years)[d]		Mean Cognitive Level[e]		Mean Cognitive Slope[f]	
		β	95% CI	β	95% CI	β	95% CI	β	95% CI
CHD risk score (continuous) at age 55 years									
General cognitive performance	2,431	−0.013	−0.044, 0.018	−0.560[g]	−0.874, −0.246	47.706	46.653, 48.759	−0.282	−0.390, −0.174
Executive function	2,430	−0.009	−0.040, 0.022	−0.624[g]	−0.916, −0.332	48.088	47.067, 49.109	−0.421	−0.533, −0.309
Memory	2,428	−0.005	−0.040, 0.030	−0.560[g]	−0.907, −0.213	47.510	46.363, 48.657	−0.223	−0.345, −0.101
CHD risk score (continuous) at age 70 years									
General cognitive performance	1,120	−0.032	−0.087, 0.023	0.401	−0.046, 0.848	45.871	43.67, 48.072	−0.573	−0.863, −0.283
Executive function	1,119	−0.004	−0.069, 0.061	0.136	−0.336, 0.608	47.923	45.62, 50.226	−0.897	−1.228, −0.566
Memory	1,118	−0.024	−0.089, 0.041	0.408	−0.092, 0.908	45.369	42.87, 47.868	−0.486	−0.815, −0.157
Elevated CHD risk (binary) at age 55 years									
General cognitive performance	2,431	0.017	−0.050, 0.084	−0.665[g]	−1.327, −0.003	46.788	45.957, 47.619	−0.319	−0.407, −0.231
Executive function	2,430	0.019	−0.050, 0.088	−0.793[g]	−1.450, −0.136	47.090	46.263, 47.917	−0.451	−0.541, −0.361
Memory	2,428	−0.089	−0.293, 0.115	0.431	−1.119, 1.981	46.611	45.704, 47.518	−0.247	−0.345, −0.149
Elevated CHD risk (binary) at age 70 years									
General cognitive performance	1,120	−0.123	−0.303, 0.057	0.533	−0.849, 1.915	46.915	45.067, 48.763	−0.587	−0.842, −0.332
Executive function	1,119	−0.021	−0.225, 0.183	−0.186	−1.558, 1.186	48.600	46.665, 50.535	−0.893	−1.175, −0.611
Memory	1,118	−0.089	−0.293, 0.115	0.431	−1.119, 1.981	46.524	44.407, 48.641	−0.498	−0.780, −0.216

Abbreviations: CHD, coronary heart disease; CI, confidence interval.

[a] Elevated CHD risk was defined as the upper 20th percentile of the Framingham Risk Score.

[b] Separate models were fitted for CHD risk at each age and for each cognitive outcome. Results were adjusted for age (centered at mean age at first cognitive assessment), education, and sex. Cognitive tests were internally scaled within the Framingham Offspring Study.

[c] Coefficients for cognitive slope regressed on continuous CHD risk represent the 0.1–standard-deviation unit difference in the annual rate of cognitive decline per 10% difference in CHD risk. Coefficients for the binary elevated CHD risk score represent the difference in cognitive level between elevated CHD risk and nonelevated CHD risk.

[d] Coefficients for cognitive level regressed on continuous CHD risk represent the difference in cognitive score at age 70 years per 10% difference in CHD risk score. Coefficients for the binary elevated CHD risk score represent the difference in cognitive level between elevated CHD risk and nonelevated CHD risk.

[e] Mean of the random intercept from each model.

[f] Mean of the random slope from each model.

[g] $P < 0.05$.

Table 5. Associations of Duration of Elevated Coronary Heart Disease Risk[a] With Level and Slope of Cognitive Performance, by *APOE* ε4 Carrier Status, Dementia Status, and Alzheimer Disease Status, in Linear Mixed-Effects Models, Framingham Offspring Study, 1971–2014[b]

Cognitive Outcome and *APOE*-ε4 Status	No. of Persons	Intercept Regressed on Duration of CHD Risk[c]		Slope Regressed on Duration of CHD Risk[d]	
		β	95% CI	β	95% CI
General cognitive performance					
Carrier	636	−0.112	−0.265, 0.041	0.004	−0.012, 0.020
Noncarrier	2,140	−0.068	−0.137, 0.001	−0.004	−0.010, 0.002
Difference	2,776	−0.044	−0.212, 0.124	0.008	−0.009, 0.025
Executive function					
Carrier	636	−0.096	−0.235, 0.043	0.000	−0.016, 0.016
Noncarrier	2,140	−0.080[e]	−0.145, −0.015	−0.005	−0.011, 0.001
Difference	2,776	−0.016	−0.169, 0.137	0.005	−0.012, 0.022
Memory					
Carrier	636	−0.145	−0.323, 0.033	0.003	−0.015, 0.021
Noncarrier	2,140	−0.060	−0.136, 0.016	−0.002	−0.010, 0.006
Difference	2,776	−0.085	−0.279, 0.109	0.005	−0.014, 0.024

Abbreviations: *APOE*, apolipoprotein E gene; CHD, coronary heart disease; CI, confidence interval.

[a] Elevated CHD risk was defined as the upper 20th percentile of the Framingham Risk Score.

[b] Results were adjusted for age centered at mean age at first cognitive assessment, education, and sex. Elevated CHD risk was defined as the upper 20th percentile of the Framingham Risk Score. Cognitive tests were internally scaled within the Framingham Offspring Study.

[c] Coefficients for cognitive level represent the model-estimated difference in cognition at age 70 years per difference in duration (years) of elevated CHD risk up to age 60 years.

[d] Coefficients for cognitive slope represent the difference in the annual rate of cognitive decline per difference in duration (years) of elevated CHD risk up to age 60 years.

[e] $P < 0.05$.

causally linked to AD pathology. Importantly, we did not find associations between CHD risk at age 55 years and cognitive change, which would provide stronger evidence for an effect of CHD on development of dementia.

Despite the low prevalence of CHD risk factors during midlife, levels of these factors during middle age instead of late life might be more salient correlates of lower later-life cognitive performance (42). Other studies have found that aggregations of CVD risk factors are associated with cognitive decline (12–17). The null but slightly positive associations we observed between late-life elevated CHD risk and high levels of cognitive performance have been reported in other studies (43, 44) and might be attributable to survival bias, as individuals are more likely to experience a CVD-related event with increasing age. Participants would not be assessed for later-life CHD risk if they experienced a fatal CVD-related event prior to 70 years of age. However, sensitivity analyses conducted in this study using the subset of individuals seen during both midlife and late life revealed a similar pattern of findings, suggesting that the small associations of CHD risk with higher cognitive levels are not entirely attributable to healthy survivor bias.

As for the components of CHD risk, we found that elevated risks of high blood pressure in both midlife and late life were associated with lower levels of all cognitive factors. Additionally, low HDL cholesterol levels in midlife were associated with lower levels of executive function, consistent with prior findings regarding dementia risk (45). The timing of cholesterol measurements may play a role in dementia risk, as evidenced by the associations of low HDL cholesterol and elevated total cholesterol with levels of cognitive performance. We found no associations of current smoking status at ages 55 and 70 years with the cognitive factors, but this could be attributed to the low frequency of current smoking in the Framingham Offspring Study: Many participants quit smoking prior to midlife.

While these findings support the first hit of the vascular 2-hit hypothesis of Alzheimer neurodegeneration, the direct link to AD is less clear. Our lack of findings related to *APOE*-ε4 carriers suggests that genetic and other factors may be primary drivers for individuals with earlier onset of AD. Midlife vascular injury resulting from the aggregation of CVD risk factors may affect the blood-brain barrier, resulting in hypoxia and accumulation of neurotoxins (24). This could lead to downstream amyloid β accumulation and eventual development of cognitive impairment. For instance, brains of *APOE*-ε4 noncarriers who will eventually develop AD could be susceptible to the adverse associations with vascular injury (i.e., diabetes (46)), but the lower aggregation rate of AD pathology will not reach the diagnostic

threshold until later in life. This would be consistent with neuropathological studies reporting that vascular pathology may be disproportionate to AD pathology in autopsy cases in which there is a CVD history (47, 48).

There were several strengths of this study. The Framingham cohort is a large, well-characterized, community-based study sample with measurements collected prospectively for over 4 decades and a validated CHD risk score. The frequency of *APOE*-ε4 carriers in the Framingham cohort mirrors that in the general population, suggesting that the sample is representative of the general population with regard to AD risk (49). We leveraged comprehensive neuropsychological assessment at multiple time points and employed modern psychometric and modeling approaches to develop cognitive factors and use them in analyses.

This study also had limitations. The Framingham cohort is predominantly white, healthy, and well-educated, which could have attenuated estimates, given the restricted range of some of the variables in the study. Unmeasured confounding may have affected results. Given that we found associations between midlife CHD risk and cognitive level, confounding by early-life factors that influence both CHD risk and cognitive performance is plausible and should be evaluated in future research; we did not have a good measure of early-life socioeconomic status available in this study. A final limitation is that we leveraged repeated measures from examination visits, which only occurred approximately quadrennially. More intensive follow-up with CHD risk ascertainment and cognitive testing during shorter time periods may have afforded more statistical power to detect associations with cognitive decline (50). However, a more intensive regimen of cognitive assessments brings with it additional challenges, including learning effects and participant fatigue. Between regular examinations in the Framingham Study, interim questionnaires collecting updated details on medical and family history are mailed, and information is obtained via regular phone calls, thereby maintaining continuous surveillance of the participants (27); however, not all variables required for calculation of the CHD risk score are available at such interim time points.

We examined associations of CHD risk in midlife and late life with level of cognitive function and rate of cognitive decline in later life using high-quality cognitive measures. We considered CHD risk in terms of "time to event" as well as CHD risk at particular points in the life course, and we concluded that midlife elevated CHD risk, not later-life CHD risk, is associated with lower levels of all cognitive factors. Associations were invariant to *APOE*-ε4 status. These findings help elucidate our understanding of life-course cardiometabolic health and late-life cognitive health and suggest that elevated levels of CHD risk factors in midlife may negatively affect cognition independently of AD via cerebrovascular injury.

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