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Interactive Associations of Vascular Risk and β-Amyloid Burden With Cognitive Decline in Clinically Normal Elderly Individuals

Findings From the Harvard Aging Brain Study

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IMPORTANCE Identifying asymptomatic individuals at high risk of impending cognitive decline because of Alzheimer disease is crucial for successful prevention of dementia. Vascular risk and β-amyloid (Aβ) pathology commonly co-occur in older adults and are significant causes of cognitive impairment.

OBJECTIVE To determine whether vascular risk and Aβ burden act additively or synergistically to promote cognitive decline in clinically normal older adults; and, secondarily, to evaluate the unique influence of vascular risk on prospective cognitive decline beyond that of commonly used imaging biomarkers, including Aβ burden, hippocampal volume, fludeoxyglucose F18–labeled (FDG) positron emission tomography (PET), and white matter hyperintensities, a marker of cerebrovascular disease.

DESIGN, SETTING, AND PARTICIPANTS In this longitudinal observational study, we examined clinically normal older adults from the Harvard Aging Brain Study. Participants were required to have baseline imaging data (FDG-PET, Aβ-PET, and magnetic resonance imaging), baseline medical data to quantify vascular risk, and at least 1 follow-up neuropsychological visit. Data collection began in 2010 and is ongoing. Data analysis was performed on data collected between 2010 and 2017.

MAIN OUTCOMES AND MEASURES Vascular risk was quantified using the Framingham Heart Study general cardiovascular disease (FHS-CVD) risk score. We measured Aβ burden with Pittsburgh Compound-B PET. Cognition was measured annually with the Preclinical Alzheimer Cognitive Composite. Models were corrected for baseline age, sex, years of education, and apolipoprotein E ε4 status.

RESULTS Of the 223 participants, 130 (58.3%) were women. The mean (SD) age was 73.7 (6.0) years, and the mean (SD) follow-up time was 3.7 (1.2) years. Faster cognitive decline was associated with both a higher FHS-CVD risk score (β = −0.064; 95% CI, −0.094 to −0.033; $P < .001$) and higher Aβ burden (β = −0.058; 95% CI, −0.079 to −0.037; $P < .001$). The interaction of the FHS-CVD risk score and Aβ burden with time was significant (β = −0.040, 95% CI, −0.062 to −0.018; $P < .001$), suggesting a synergistic effect. The FHS-CVD risk score remained robustly associated with prospective cognitive decline (β = −0.055; 95% CI, −0.086 to −0.024; $P < .001$), even after adjustment for Aβ burden, hippocampal volume, FDG-PET uptake, and white matter hyperintensities.

CONCLUSIONS AND RELEVANCE In this study, vascular risk was associated with prospective cognitive decline in clinically normal older adults, both alone and synergistically with Aβ burden. Vascular risk may complement imaging biomarkers in assessing risk of prospective cognitive decline in preclinical Alzheimer disease.

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Supplemental content

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Identifying asymptomatic individuals at high risk of impending cognitive decline because of Alzheimer disease (AD) is crucial to the success of clinical trials aimed at preventing dementia. The advent of in vivo measures of β-amyloid (Aβ) burden highlighted a preclinical phase of AD,[1,2] allowing for the identification of clinically normal individuals with objective evidence of AD pathology. However, a substantial portion of individuals who are amyloid positive do not show clear evidence of cognitive decline in available longitudinal follow-up data.[3-5] This is consistent with autopsy data indicating that approximately 30% of clinically normal elderly individuals have signs of elevated Aβ burden on pathological examination.[6,7] These findings have prompted the search for additional biomarkers that can be used with Aβ burden to identify individuals at maximal risk of cognitive decline.[4,5,8,9] Most commonly, these additional biomarkers capture early signs of neurodegeneration, including alterations in cerebrospinal fluid tau, fludeoxyglucose F18-labeled (FDG) positron emission tomography (PET), and hippocampal volume.[8]

Multiple studies have demonstrated that cardiovascular risk factors, such as hypertension and hyperlipidemia (which often occur together[10]), are also risk factors for cognitive decline and AD.[11-15] Consistent with this, recent epidemiological data suggest that declining dementia incidence may be partially because of advances in the treatment of cardiovascular disease.[13,16] Neuropathological studies indicate that vascular brain changes frequently co-occur with AD pathology in late-onset dementia and that vascular pathology may lower the threshold for cognitive impairment.[17-21] Neuroimaging studies examining the combined impact of Aβ burden and increased white matter hyperintensities (WMH; an imaging measure thought to reflect small vessel ischemic changes) and/or cerebral infarcts have generally demonstrated additive effects of Aβ burden and cerebrovascular pathology on cognition.[22-26] However, markers of cerebrovascular disease provided by conventional neuroimaging (eg, WMH, infarcts) may capture only a portion of total cerebrovascular disease burden, since many cerebrovascular changes are not well visualized on magnetic resonance imaging (MRI).[27-31]

The goal of the present study was to examine whether a well-validated, multivariable measure of vascular risk is associated with prospective cognitive decline in a large cohort of clinically normal elderly individuals, either additively or synergistically with Aβ burden. A secondary goal was to investigate whether vascular risk is associated with cognitive decline even after controlling for commonly used imaging biomarkers, including Aβ burden, FDG-PET, hippocampal volume, and WMH.

Key Points

Question Is vascular risk associated with prospective cognitive decline in a cohort of clinically normal older adults, additively or synergistically with β-amyloid?

Findings In this study, Framingham and other vascular risk algorithms were associated with longitudinal cognitive decline, both alone and synergistically with β-amyloid burden. Vascular risk maintained a strong association with cognitive decline beyond that of commonly used imaging biomarkers, including β-amyloid, hippocampal volume, fludeoxyglucose F18–labeled positron emission tomography, and white matter hyperintensities.

Meaning Vascular risk may complement other imaging biomarkers in assessing risk of cognitive decline in older adults with preclinical Alzheimer disease.

Methods

Participants

Participants were drawn from the Harvard Aging Brain Study (HABS), an ongoing longitudinal study of aging and preclinical AD. Participants provided written informed consent prior to study procedures, which used protocols approved by the Partners Healthcare institutional review board. Exclusionary criteria included a Hachinski score of 5 or more, history of stroke with residual deficits, and history of intracranial hemorrhage. At study entry, all participants had scores of 0 on the Clinical Dementia Rating,[32] 11 or less on the Geriatric Depression Scale,[33] and 27 or more on the education-adjusted Mini-Mental State Examination,[34] and performed within education-adjusted norms on Logical Memory-delayed recall.[35] Participants were required to have baseline imaging data from all modalities (MRI, FDG-PET, and Aβ-PET), baseline medical data to quantify vascular risk, and at least 1 follow-up neuropsychological visit. Apolipoprotein E (APOE) ε4 status was determined by the presence of at least 1 ε4 allele. **Table 1** summarizes baseline participant characteristics.

Cardiovascular Disease Risk

Our primary measure of cardiovascular disease risk was the office-based Framingham Heart Study general cardiovascular disease (FHS-CVD) risk score.[36] The FHS-CVD risk score was calculated on baseline data and represents a weighted sum of age, sex, antihypertensive treatment (yes or no), systolic blood pressure (millimeters of mercury), body mass index, history of diabetes (yes or no), and current cigarette smoking status (yes or no). The FHS-CVD risk score provides a 10-year probability of future cardiovascular events (defined as coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure). In this sample, scores ranged from 4% to 88%, with higher scores representing greater risk of cardiovascular events. For stratified analyses and visualization purposes, participants were divided into high and low FHS-CVD risk groups based on a median split (at a FHS-CVD risk score of 29%). To confirm the findings with the FHS-CVD risk score, supplemental analyses examined alternate measures of vascular risk, including the lipid-based FHS-CVD risk score,[36] the Revised Framingham Stroke Risk Profile,[37] and the QRISK2-2016 (https://qrisk.org/2016/; eMethods in the Supplement).

Amyloid PET

Baseline Aβ burden was measured with carbon 11-labeled Pittsburgh compound-B (PiB) PET using previously described protocols.[38] Data were expressed as a distribution

Table 1. Participant Characteristics Overall and by β-Amyloid Status[a]

Characteristic	Mean (SD) Overall (N = 223)	Aβ Negative (n = 166)	Aβ Positive (n = 57)	*P* Value
Age, y	73.7 (6.0)	73.3 (6.0)	74.7 (5.9)	.13
Education, y	15.9 (2.9)	15.8 (2.9)	16.3 (2.9)	.36
Female, No. (%)	130 (58.3)	93 (56.0)	37 (64.9)	.31
β-Amyloid positive, No. (%)	57 (25.6)	NA	57 (100.0)	NA
APOE ε4 carriers, No. (%)	65 (29.1)	29 (17.5)	36 (63.2)	<.001
PiB FLR DVR	1.17 (0.2)	1.07 (0.05)	1.46 (0.2)	<.001
FHS-CVD risk score	32.8 (18.1)	32.8 (18.8)	32.7 (16.2)	.94
Treatment with hypertension medication, No. (%)	120 (53.8)	88 (53.0)	32 (56.1)	.80
Systolic blood pressure, mm Hg	140.5 (17.6)	139.8 (18.0)	142.8 (16.2)	.23
BMI	26.9 (4.6)	27.1 (4.5)	26.4 (4.6)	.33
History of diabetes, No. (%)	23 (10.3)	18 (10.8)	5 (8.7)	.85
Current smoker, No. (%)	10 (4.4)	7 (4.2)	3 (5.3)	.99
Hippocampal volume, mm^3	7441 (874.2)	7523 (836.3)	7201 (943.7)	.02
FDG-PET standardized uptake value ratio	1.24 (0.1)	1.25 (0.1)	1.21 (0.1)	.009
Log-transformed white matter hyperintensities volume, mm^3	7.64 (0.9)	7.55 (0.9)	7.89 (1.1)	.03
Follow-up, y	3.7 (1.2)	3.6 (1.2)	3.9 (1.2)	.18

Abbreviations: Aβ, β-amyloid; APOE ε4, apolipoprotein E ε4; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FDG-PET, fludeoxyglucose-F18–labeled positron emission tomography; FHS-CVD, Framingham Heart Study general cardiovascular disease; NA, not applicable; PiB DVR FLR, Pittsburgh compound B distribution volume ratio of frontal, lateral parietal and temporal, and retrosplenial regions.

[a] Unless otherwise indicated, data are expressed as mean (SD).

volume ratio using cerebellar gray as the reference region. A composite measure of cortical Aβ burden within frontal, lateral temporal and parietal, and retrosplenial cortices (FLR regions) was used to represent neocortical Aβ burden in statistical models. When needed, a Gaussian mixture modeling approach was used to classify participants as Aβ positive or Aβ negative using a previously published cutoff level of PiB FLR distribution volume ratio equal to 1.2.[3]

Fludeoxyglucose F18–Labeled PET

Baseline fludeoxyglucose F18–labeled (FDG) PET imaging was performed using previously described protocols.[4] The mean FDG uptake was extracted from a previously published composite reflecting AD-vulnerable regions (lateral parietal, lateral inferior temporal, and posterior cingulate cortices)[39] and was normalized using a pons and vermis reference region.

Structural MRI

Baseline structural MRIs were collected on a 3-T Trio TIM MRI scanner (Siemens) using a 12-channel phased-array head coil according to previously described protocols.[4] Measurements of bilateral hippocampal volume based on FreeSurfer version 5.1 (Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging)[40] were adjusted for total intracranial volume prior to analysis.[4]

WMH Analysis

Baseline cortical WMH were assessed using fluid-attenuated inversion recovery MRI (repetition time = 6000 milliseconds; echo time = 454 milliseconds; inversion time = 2100 milliseconds; 1 × 1 × 1.5-mm voxels; 2 × acceleration). All WMH were identified using an automated algorithm[41] and previously described methods.[42] Total WMH volume in millimeters cubed was estimated within a cortical mask defined by the Johns Hopkins University White Matter Atlas.[43] Prior to analysis, WMH values were log-transformed to account for a positive skew.

Cognitive Measures

HABS is an ongoing study, and enrollment is staggered; therefore not all participants had the same number of neuropsychological follow-up visits. Cognitive data were available for 223 participants at baseline and at the first annual follow-up, 213 at the second follow-up, 177 at the third follow-up, 139 at the fourth follow-up, and 72 at the fifth follow-up. The mean (SD) follow-up period was 3.7 (1.2) years. The cognitive outcome variable was the Preclinical Alzheimer Cognitive Composite (PACC), a continuous measure optimized to detect Aβ-associated cognitive decline.[44,45] The PACC consists of the Mini-Mental State Examination,[34] Digit Symbol Coding,[46] Logical Memory–delayed recall,[35] and free recall plus total recall from the Free and Cued Selective Reminding Test.[47] Raw scores were *z*-transformed based on the mean and SD from the baseline data and a combined mean was determined. Higher PACC scores indicate better performance.

Statistical Analyses

Linear mixed-effects models (*nlme* package, R version 3.2.4 [R Foundation for Statistical Computing]) with random intercept and slope were used to assess associations between the FHS-CVD risk score, Aβ burden, and longitudinal PACC decline. All models included age at baseline, sex, years of education, and their interactions with time. We also controlled for APOE ε4 status and its interaction with time, given previously described associations with vascular risk, Aβ burden, and cognitive decline.[3,48,49] Time was operationalized as years from baseline for each participant. To facilitate comparison across measures, continuous variables were *z*-transformed prior to

model entry. The presence or absence of microbleeds was investigated as a potential covariate in models that included Aβ burden, but was dropped from final models because of nonsignificant results. As indicated earlier, age and sex are incorporated into the FHS-CVD risk score. The primary analyses included age and sex as covariates; secondary analyses omitting age and sex as covariates yielded similar results (eTable 1 in the Supplement).

To investigate the associations of the FHS-CVD risk score and Aβ burden with prospective cognitive decline, we examined interactions of the FHS-CVD risk score with time and Aβ burden with time in a single model (model 1: PACC ~ FHS-CVD × time + Aβ × time + covariates × time). Next, we added an interaction term between the FHS-CVD risk score, Aβ burden, and time to examine whether these 2 factors increase the likelihood of cognitive decline beyond their separate effects (ie, synergistic effect; model 2: PACC ~ FHS-CVD × Aβ × time + covariates × time). To confirm the findings with the FHS-CVD risk score, a parallel set of analyses were computed using alternate measures of vascular risk (eTable 2 in the Supplement).

A secondary goal of the present study was to evaluate the unique influence of the FHS-CVD risk score on prospective cognitive decline while simultaneously controlling for commonly used imaging biomarkers, including Aβ burden, hippocampal volume, FDG-PET uptake, and WMH. To do so, we assessed the relative association of each biomarker with cognitive decline by including all biomarkers within a single model (model 3: PACC ~ FHS-CVD × time + Aβ × time + hippocampal volume × time + FDG-PET × time + WMH × time + covariates × time). For comparison purposes, we also examined whether each of these biomarkers was associated with prospective PACC decline in separate models that controlled for Aβ burden. All models included lower-order effects. Nominal *P* values (< .05) were considered significant.

Results

Cross-sectional Associations of the FHS-CVD Risk Score, Imaging Biomarkers, and Cognition

Prior to longitudinal analyses, we examined the cross-sectional associations between the FHS-CVD risk score and imaging biomarkers. After controlling for age and sex, a higher FHS-CVD risk score was associated with greater WMH (r = 0.21; P = .002) and lower FDG-PET uptake (r = −0.20; P = .002). There was no significant association of the FHS-CVD risk score with Aβ burden (r = −0.07; P = .30) or hippocampal volume (r = −0.08; P = .30; eFigure 1 in the Supplement). A secondary analysis omitting correction for age and sex strengthened the associations between the FHS-CVD risk score and WMH (r = 0.34; P < .001), hippocampal volume (r = −0.24; P < .001), and Aβ burden (r = −0.13; P = .06), although the association of the FHS-CVD risk score with Aβ burden was only marginally significant. The association of the FHS-CVD risk score with FDG-PET uptake was largely unchanged by the omission of age and sex as covariates (r = −0.18; P = .006; eFigure 1 in the Supplement).

Table 2. Association of the Framingham Heart Study General Cardiovascular Disease (FHS-CVD) Risk Score With β-Amyloid Burden, Imaging Biomarkers, and Prospective Cognitive Decline

Model Term	Standardized Estimate (95% CI)	*t* Value	*P* Value
Model 1[a]			
FHS-CVD × time	−0.064 (−0.094 to −0.033)	−4.094	<.001
Aβ × time	−0.058 (−0.079 to −0.037)	−5.367	<.001
Model 2[a]			
FHS-CVD × Aβ × time	−0.040 (−0.062 to −0.018)	−3.583	<.001
Model 3[a]			
FHS-CVD × time	−0.055 (−0.086 to −0.024)	−3.421	<.001
Aβ × time	−0.054 (−0.075 to −0.033)	−5.020	<.001
Hippocampal volume × time	0.033 (0.010 to 0.056)	2.841	.005
FDG-PET × time	0.009 (−0.013 to 0.030)	0.787	.432
WMH × time	−0.002 (−0.025 to 0.022)	−0.145	.885

Abbreviations: *APOE* ε4, apolipoprotein E ε4; FDG-PET, fludeoxyglucose-F18–labeled positron emission tomography; WMH, white matter hyperintensities.

[a] Full models are noted in the text.

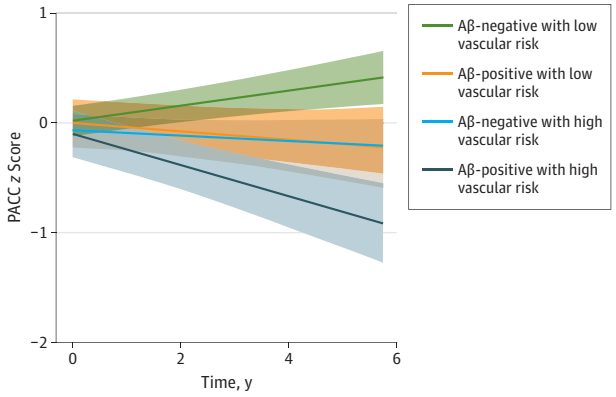
We next examined independent and interactive associations of the FHS-CVD risk score and Aβ burden with baseline cognition, covarying for age, sex, years of education, and APOE ε4 status. The FHS-CVD risk score was marginally associated with baseline cognition (β = −0.09; 95% CI, −0.20 to 0.01; P = .09), whereas Aβ burden was not (β = 0.01; 95% CI, −0.07 to 0.09; P = .87). There was no interaction between the FHS-CVD risk score and Aβ burden with baseline cognition (β = 0.03; 95% CI, −0.06 to 0.12; P = .48).

Associations of the FHS-CVD Risk Score and Aβ Burden With Prospective Cognitive Decline

Of primary interest was whether an elevated FHS-CVD risk score and higher Aβ burden were additive or synergistic in their associations with faster cognitive decline (model 1). Both a higher FHS-CVD risk score and higher Aβ burden were associated with faster PACC decline (**Table 2**). Possible synergistic effects were tested in a separate model that included the interaction between the FHS-CVD risk score, Aβ burden, and time (model 2). The presence of a significant interaction term suggests that an elevated FHS-CVD risk score together with a higher Aβ burden increases the likelihood of cognitive decline beyond their separable effects (**Figure 1** and Table 2; eFigure 2 in the Supplement). Participant APOE ε4 status was not associated with cognitive decline in any of the above models. Alternate vascular risk scores (the lipid-based FHS-CVD risk score, Revised Framingham Stroke Risk Profile, and QRISK2-2016) in place of FHS-CVD risk score yielded similar results with respect to the main and Aβ interactive associations with prospective cognitive decline (eTable 2 in the Supplement).

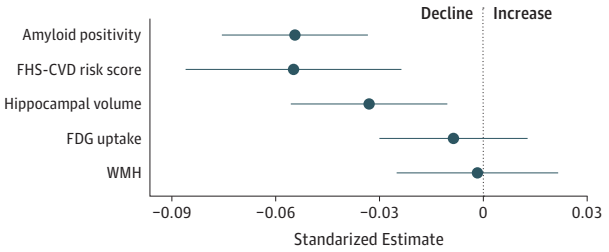
We next examined whether a higher FHS-CVD risk score was associated with cognitive decline in both Aβ-positive and Aβ-negative groups. The FHS-CVD risk score was associated with decline in both groups, but the effect was larger in the Aβ-positive group (Aβ-positive: β = −0.101; 95% CI, −0.184 to −0.018; P = .02; Aβ-negative: β = −0.03; 95% CI, −0.055 to

Figure 1. Comparison of Longitudinal Cognitive Trajectories of Participants Classified According to Joint β-Amyloid Status and a High or Low Framingham Heart Study General Cardiovascular Disease (FHS-CVD) Risk Score



Estimates are from a linear mixed model predicting change in the Preclinical Alzheimer Cognitive Composite (PACC) for groups based on a binary assessment of β-amyloid burden (Aβ positive or Aβ negative) and a high or low FHS-CVD risk score (based on a median split at a score of 29%). Trajectories of cognitive decline were significantly different across the 4 groups. Shaded regions show 95% CIs.

Figure 2. Model Estimates of the Longitudinal Change in the Preclinical Alzheimer Cognitive Composite



The Framingham Heart Study–general cardiovascular disease (FHS-CVD) risk score remained a strong predictor of cognitive decline even after adjusting for commonly used imaging markers in the same model (model 3). Standardized values for each measure are shown. Hippocampal volume and fludeoxyglucose-F18–labeled positron emission tomography estimates and CIs were reversed to facilitate comparisons. Estimates represent the decline in Preclinical Alzheimer Cognitive Composite per year according to a standardized unit increase in each measure. WMH indicates white matter hyperintensities.

−0.001; P = .05), consistent with the observed synergism between the FHS-CVD risk score and Aβ burden on cognitive decline.

To visualize these interactions, we compared the cognitive trajectories of participants classified dichotomously as Aβ positive or Aβ negative and a high or low FHS-CVD risk score. This resulted in 4 groups: (1) Aβ-positive individuals with high FHS-CVD risk scores (n = 29); (2) Aβ-negative individuals with high FHS-CVD risk scores (n = 82), (3) Aβ-positive individuals with low FHS-CVD risk scores (n = 28), and (4) Aβ-negative individuals with low FHS-CVD risk scores (n = 84). Using this grouping, we observed a significant association of group with prospective cognitive decline after adjusting for covariates (β = 0.042; 95% CI, 0.013 to 0.070; P = .005; Figure 1). Post hoc analyses revealed significantly faster cognitive decline in the group that was Aβ-positive with a high FHS-CVD risk score compared with all other groups (vs Aβ-positive with a low FHS-CVD risk score: β = 0.10; 95% CI, 0.02 to 0.19; P = .02; Aβ-negative with a high FHS-CVD risk score: β = 0.12; 95% CI, 0.05 to 0.19; P = .001; Aβ-negative with a low FHS-CVD risk score: β = 0.21; 95% CI, 0.14 to 0.29; P < .001). The group that was Aβ-negative with a low FHS-CVD risk score demonstrated significantly improved performance over time compared with all other groups, likely indicating a practice effect (vs Aβ-positive with a low FHS-CVD risk score: β = −0.11; 95% CI, −0.16, −0.06, P < .001; Aβ-negative with a high FHS-CVD risk score: β = −0.08; 95% CI, −0.13 to −0.04; P < .001; Aβ-positive with a high FHS-CVD risk score: β = −0.20; 95% CI, −0.25 to −0.14; P < .001). There was no difference between the cognitive trajectories of the group that was Aβ-positive with a low FHS-CVD risk score and the group that was Aβ-negative with a high FHS-CVD risk score.

Association of the FHS-CVD Risk Score With Prospective Cognitive Decline, Controlling for Imaging Biomarkers

A secondary goal was to examine whether the FHS-CVD risk score was associated with PACC decline after adjusting for imaging biomarkers, including Aβ burden, hippocampal volume, FDG-PET uptake, and WMH (model 3). As summarized in Table 2 and **Figure 2**, the FHS-CVD risk score remained strongly associated with PACC decline even after including these imaging biomarkers in the model. Hippocampal volume and Aβ burden were also significantly associated with cognitive decline in model 3. When each biomarker was considered in a separate model that controlled for Aβ burden, all biomarkers were significantly associated with PACC decline, with the exception of WMH (eTable 3 in the Supplement).

Discussion

We examined whether a well-validated summary measure of vascular risk was associated with prospective cognitive decline in clinically normal elderly, either additively or synergistically with Aβ burden. The FHS-CVD risk score and Aβ burden each was associated with longitudinal cognitive decline when entered together into a single model. These findings underscore the importance of both vascular risk and Aβ burden to cognitive decline in clinically normal older adults. Additionally, we observed a robust interaction between the FHS-CVD risk score and Aβ burden in association with prospective cognitive decline, whereby individuals with both higher vascular risk and higher Aβ burden showed the steepest decline in cognition on longitudinal follow-up. Supplemental analyses using alternate vascular risk algorithms showed a similar pattern of results. Finally, the FHS-CVD risk score remained strongly associated with cognitive decline after accounting for commonly used imaging biomarkers, suggesting that vascular risk may complement existing biomarkers of neurodegeneration and molecular pathology in assessing risk of cognitive decline.

Notably, we did not observe a clear association of the baseline FHS-CVD risk score with Aβ burden in our study sample. The association of measures of cerebrovascular disease with Aβ pathology have been inconsistently observed in prior studies,[50] with some authors suggesting that cerebrovascular disease may promote Aβ deposition by impairing Aβ clearance.[49,51] Additionally, recent work suggests that midlife but not late-life vascular risk factors are associated with elevated Aβ burden.[52] Notably, when correction for age and sex was omitted, a marginally significant negative association emerged between the FHS-CVD risk score and Aβ burden, perhaps reflecting the exclusion of impaired individuals from this sample. As such, it remains quite possible that a positive association of vascular risk with Aβ burden is discernible in later, symptomatic phases of the disease.[53,54]

While we did not observe a positive association of the FHS-CVD risk score with Aβ burden at baseline, our results indicated a synergism between these 2 factors in promoting cognitive decline. This observed synergy is consistent with neuropathological studies, suggesting that the presence of substantial cerebrovascular disease may lower the threshold at which AD pathology leads to cognitive decline.[17-19] Some prior studies examining the combined impact of Aβ burden and WMH and/or cerebral infarcts on cognition in clinically normal older adults have found additive rather than synergistic effects.[22,23] One possible explanation for this difference is that the FHS-CVD risk score may capture aspects of vascular burden that are not well represented by WMH and/or infarcts. This idea is consistent with the relatively weak association of the FHS-CVD risk score with WMH in the current sample, and the observation that the FHS-CVD risk score remained strongly associated with cognitive decline even after adjusting for WMH in statistical models. Prior studies suggest that many cerebrovascular changes observed at autopsy are not well visualized on MRI, including arteriosclerosis, microinfarcts, and disruptions of the blood brain barrier.[27-31] Further work is needed to examine potential interactions between vascular pathology and Aβ burden using more comprehensive markers of cerebrovascular disease, as such measures may better reflect the results seen here with multivariable vascular risk scores.

Limitations

The present results are best understood in the context of the study sample composition. Because HABS excludes participants with unstable hypertension and uncontrolled diabetes, as well as symptomatic stroke or intracranial hemorrhage, the higher range of vascular risk may be underrepresented in the study sample. This consideration affects the interpretation of our stratified models, because the median level of vascular risk within the general population is likely higher than the median level of vascular risk within the HABS sample. Similarly, individuals with both high vascular risk and high Aβ burden are likely underrepresented in our sample because they are more likely to be cognitively impaired and thus excluded from study participation. However, our results do suggest that even relatively modest levels of vascular risk can interact with Aβ burden to hasten cognitive decline. Another potential limitation is that the age range in HABS (maximum age of 89 years) extends beyond the age range of the sample used to initially validate the FHS-CVD risk score (which was 30 to 74 years),[36] perhaps affecting the estimation of vascular risk in older participants. It remains an open question whether or not to separately control for age and sex when using multivariable vascular risk algorithms, such as the FHS-CVD risk score, because these demographic variables are incorporated into these risk prediction models. As a practical matter, we observed that there was little difference between models that included age and sex as separate covariates (as in the main text) from those that did not (eTable 1 in the Supplement). Finally, most HABS participants have at least some advanced education and may have substantial cognitive reserve, factors that may affect the generalizability of these findings.

Conclusions

In summary, our results suggest that vascular risk has a potent association with longitudinal cognitive decline, both alone and synergistically with Aβ burden in clinically normal older adults. Vascular risk remained strongly associated with prospective cognitive decline even after accounting for commonly used imaging biomarkers, suggesting that measures of vascular risk may complement imaging biomarkers in assessing risk of cognitive decline in clinically normal elderly. Finally, the observed synergy between vascular risk and Aβ burden in promoting cognitive decline is consistent with neuropathological findings suggesting that the presence of vascular pathology may shorten the preclinical phase of AD[17-21] and also with epidemiological studies suggesting that improved cardiovascular health may be partially responsible for declining dementia incidence over the past 30 years.[16] Together, these results bolster the scientific rationale for aggressively targeting vascular risk factors, either alone or in concert with anti-amyloid therapies, as a potential approach to delay cognitive decline in older adults.

ARTICLE INFORMATION

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Author Contributions: Drs Chhatwal and Rabin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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