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Association of midlife vascular risk and AD biomarkers with subsequent cognitive decline

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Neurology® 2020;95:e3093-e3103. doi:10.1212/WNL.0000000000010946

Abstract

Objective

To determine whether vascular risk and Alzheimer disease (AD) biomarkers have independent or synergistic effects on cognitive decline and whether vascular risk is associated with the accumulation of AD pathology as measured by change in biomarkers over time.

Methods

At baseline, participants (n = 168) were cognitively normal and primarily middle-aged (mean 56.4 years, SD 10.9 years) and had both vascular risk factor status and proximal CSF biomarkers available. Baseline vascular risk was quantified with a composite vascular risk score reflecting the presence or absence of hypertension, hypercholesterolemia, diabetes, current smoking, and obesity. CSF biomarkers of β-amyloid $(A\beta)_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau) were used to create dichotomous high and low AD biomarker groups (based on $A\beta_{1-42}$ and tau). Linear mixed-effects models were used to examine change in a cognitive composite score (mean follow-up 13.9 years) and change in CSF biomarkers (mean follow-up 4.2 years).

Results

There was no evidence of a synergistic relationship between the vascular risk score and CSF AD biomarkers and cognitive decline. Instead, the vascular risk score (estimate −0.022, 95% confidence interval [CI] −0.043 to −0.002, $p = 0.03$) and AD biomarkers (estimate −0.060, 95% CI −0.096 to −0.024, $p = 0.001$) were independently and additively associated with cognitive decline. In addition, the vascular risk score was unrelated to levels of or rate of change in CSF $A\beta_{1-42}$, t-tau, or p-tau.

Conclusions

The results of this observational cohort study suggest that vascular risk and biomarkers of AD pathology, when measured in midlife, act along independent pathways and underscore the importance of accounting for multiple risk factors for identifying cognitively normal individuals at the greatest risk of cognitive decline.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **BIOCARD** = Biomarkers for Older Controls at Risk for Dementia; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **CVD** = cerebrovascular disease; **JHU** = Johns Hopkins University; **MCI** = mild cognitive impairment; **p-tau** = phosphorylated tau; **t-tau** = total tau.

When measured in midlife, vascular risk factors (e.g., hypertension, diabetes)[1–4] and biomarkers of amyloid and tau pathology[5,6] are each associated with cognitive decline and increased risk of developing clinical symptoms of dementia. However, few studies have examined whether these measures independently or synergistically affect cognitive decline with mixed results.[7–9] In addition, the extent to which vascular risk factors affect cognitive trajectories of cognitively normal individuals in the presence of both amyloid and tau pathology remains to be determined.

It is also unclear whether vascular risk factors accelerate Alzheimer disease (AD) pathology. While some studies among cognitively normal participants and those without dementia have found more abnormal AD biomarker levels among individuals with higher vascular risk, findings have been inconsistent.[10–19] In addition, longitudinal studies have failed to find relationships between vascular risk and changes in amyloid.[20–22] Moreover, little is known about the impact of vascular risks on changes in tau.[22] This question is particularly important given the accumulating evidence that amyloid is necessary but not sufficient to cause cognitive decline and dementia.[23]

This study examined (1) whether midlife vascular risk and CSF amyloid and tau biomarkers, measured among cognitively normal, primarily middle-aged individuals, independently or synergistically affect long-term cognitive trajectories and (2) whether vascular risk is associated with change in CSF biomarkers. The focus on primarily middle-aged participants is particularly important because AD pathology begins to develop in midlife[24,25] and midlife (vs late-life) vascular risk factors may be differentially related to dementia risk.[26]

Methods

Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent. This study was approved by the Johns Hopkins University (JHU) Institutional Review Board.

Study design and participant selection

Data for these analyses were derived from the Biomarkers for Older Controls at Risk for Dementia (BIOCARD) study, an ongoing longitudinal study designed to identify variables among cognitively normal individuals that predict subsequent development of mild to moderate symptoms of AD. As described previously,[27] the study was initiated in 1995 at the NIH, with recruitment conducted between 1995 and 2005 by the staff of the Geriatric Psychiatry Branch of the intramural program of the National Institute of Mental Health. Participants were recruited through various sources, including printed materials, informational lectures, and word of mouth. Approximately 75% of the cohort had a first-degree relative with dementia of the Alzheimer type by design. At enrollment, participants completed a comprehensive evaluation consisting of a physical and neurologic examination, neuropsychological testing, an ECG, and standard laboratory studies. Individuals with cognitive impairment (as determined by the cognitive testing or evidence of clinical symptoms based on reports by the participant and collateral sources) or with significant medical problems (e.g., cardiovascular disease), severe cerebrovascular disease (CVD), chronic psychiatric or neurologic disorders, or alcohol or drug abuse were excluded from participation.

A total of 349 primarily middle-aged (mean 57.3 years, SD 10.4 years) individuals were enrolled in the study. While the study was at the NIH, participants were administered a comprehensive neuropsychological battery and clinical assessments annually; blood, CSF, and MRI scans were obtained biennially. The study was stopped in 2005 and re-established in 2009 by a research team from JHU, at which point annual clinical and cognitive assessments and collection of blood specimens were reinitiated. Collection of CSF and MRI scans was reinitiated in 2015.

The analyses presented here included 168 participants who had both baseline vascular risk scores and CSF collected in the same time frame (i.e., CSF within 14 months of the baseline vascular risk score; mean time between baseline vascular risk score and matched CSF data −0.02 years, SD 0.17 years). Participants were excluded from analyses for the following reasons: (1) participants have not yet re-enrolled or had not given permission to use their previously acquired data (n = 28); (2) participants' estimated age at onset of clinical symptoms of mild cognitive impairment (MCI) was determined to be at or before their baseline vascular risk score (n = 14); (3) baseline vascular risk scores were missing (n = 70); and (4) no CSF draw was done within 14 months of baseline vascular risk score (n = 69). Table 1 shows the characteristics of participants excluded from the analyses due to incomplete data (i.e., missing vascular risk scores or no matching CSF measures) relative to the whole BIOCARD cohort and those included in the analyses.

Clinical assessment

The clinical assessments in the BIOCARD study have been completed annually, first at the NIH and subsequently at JHU.[27] Clinical assessments include a physical and neurologic

Table 1 Participant characteristics at first BIOCARD visit

	Cohort as a whole	Included in analyses	Excluded from analyses due to incomplete data
No.	349	168	139
Age, mean (SD) [range], y	57.3 (10.4) [20–86]	56.3 (10.7) [22–86]	57.5 (13.8) [20–82]
Female sex, n (%)	201 (57.6)	100 (59.5)	82 (59.0)
White race/ethnicity, n (%)	339 (97.1)	162 (96.4)	136 (97.8)
Education, mean (SD) [range], y	17.0 (2.4) [12–20]	17.4 (2.2) [12–20]	16.6 (2.5) [12–20][a]
***APOE* ε4 carrier, n (%)**	117/348 (33.6)	50 (29.8)	53 (38.1)
MMSE score, mean (SD)	29.5 (0.9)	29.6 (0.7)	29.5 (1.0)
Paired Associates immediate recall score, mean (SD)	20.2 (3.4)	20.8 (2.8)	20.1 (3.3)[a]
Logical Memory delayed recall score, mean (SD)	12.3 (4.0)	13.1 (3.9)	11.9 (4.1)[a]
Boston Naming Test score, mean (SD), % correct	96.0 (5.3)	96.5 (5.5)	95.5 (5.3)
Digit-Symbol Substitution score, mean (SD)	52.2 (11.7)	53.3 (11.5)	51.9 (12.3)

Abbreviations: BIOCARD = Biomarkers for Older Controls at Risk for Dementia; MMSE = Mini-Mental State Examination.
[a] $p \leq 0.05$ assessing group difference between participants included vs excluded from the analyses using t tests or χ^2 tests.

examination, record of medication use, behavioral and mood assessments, family history of dementia, history of symptom onset, neuropsychological testing, and a Clinical Dementia Rating[28] (CDR) based on a semistructured interview.

All consensus diagnoses used in study analyses are based on procedures implemented by the staff of the JHU BIOCARD Clinical Core, with diagnoses completed prospectively for all JHU visits and retrospectively for all NIH visits. All cases are handled in a manner comparable with those used in the National Institute on Aging Alzheimer's Disease Centers program. First, a syndromic diagnosis is established (e.g., normal, MCI, dementia) from 3 sources of information: (1) clinical data pertaining to the medical, neurologic, and psychiatric status of the individual; (2) reports of changes in cognition by the individual and by collateral sources based on a semistructured interview (the CDR); and (3) decline in cognitive performance based on review of longitudinal testing from multiple domains (and comparison to published norms). Second, if a participant is deemed to be impaired, a decision is made about the likely etiology of the syndrome on the basis of the medical, neurologic, and psychiatric information collected at each visit, as well as medical records obtained from the participant when necessary. More than 1 etiology can be endorsed for each participant (e.g., AD and vascular disease; Parkinson disease and depression).

This consensus diagnosis procedure follows the diagnostic recommendations incorporated in the National Institute on Aging/Alzheimer's Association working group reports for the diagnosis of MCI[29] and dementia due to AD.[30] A diagnosis of impaired not MCI is also used, reflecting this incorporation in the AD Centers Program diagnostic procedures. Within the context of this study, this diagnosis typically reflects contrasting information from the CDR interview and the cognitive test scores (i.e., the participant or collateral source expressed concerns about cognitive changes in daily life but the cognitive testing did not show changes or vice versa). Diagnoses (and determination of likely etiology) are made without knowledge of biomarker measures.

Cognitive assessment

The annual cognitive assessment consisted of a comprehensive battery of neuropsychological tests. Four tests from this battery were used to create a composite score to examine longitudinal cognitive trajectories using previously published procedures.[6] This a priori–derived cognitive composite score included 4 measures previously identified to be the best combination of cognitive predictors of time to progress from normal cognition to clinical symptom onset in this cohort.[27] These measures included Paired Associates immediate recall (Wechsler Memory Scale–Revised), Logical Memory delayed recall score (Story A; Wechsler Memory Scale–Revised), Boston Naming, and Digit-Symbol Substitution (Wechsler Adult Intelligence Scale–Revised). The cognitive composite score was calculated by transforming the individual measures to z scores and then averaging them. Thus, the standardized score has a mean of 0 at baseline. To maximize the amount of data available for modeling, at least 2 of the 4 scores were required to be present at a given time point (78% of the longitudinal composites were calculated with all 4 test scores). Cognitive test scores before an individual's baseline vascular risk score (described below) were excluded from analysis.

Table 2 Participant characteristics at baseline

Variable	Participants in analyses
No.	168
Age, mean (SD), y	56.4 (10.9)
Female sex, n (%)	100 (59.5)
White race/ethnicity, n (%)	162 (96.4)
Education, mean (SD), y	17.4 (2.2)
APOE ε4 carrier, n (%)	50 (29.8)
MMSE score, mean (SD)	29.6 (0.7)
Paired associates immediate recall score, mean (SD)	20.8 (2.7) (n = 158)
Logical memory delayed recall score, mean (SD)	13.1 (3.9) (n = 161)
Boston naming score, mean % correct (SD)	96.4 (5.7)
Digit-symbol substitution score, mean (SD)	53.2 (11.6) (n = 158)
Standardized cognitive composite score, mean (SD)	0.0 (0.7)
Cognitive follow-up, mean (SD) [range], y	13.9 (3.9) [0.9–20.9]
Cognitive measures over time, mean (SD) [range], n	9.0 (3.6) [2–18]
Progress to MCI or dementia over follow-up, n (%)	39 (23.2)
Composite vascular risk score, mean (SD) [range]	0.5 (0.7) [0–3]
Composite vascular risk score ≥1, n (%)	66 (39.3)
Hypertension, n (%)	16 (9.5)
Hypercholesterolemia, n (%)	21 (12.5)
Diabetes, n (%)	2 (1.2)
Current smoking, n (%)	10 (6.0)
Body mass index >30 kg/m^2, n (%)	36 (21.4)
AD biomarker indicator, low Aβ_{1-42} and high t-tau, n (%)	19 (11.3)
AD biomarker indicator, low Aβ_{1-42} and high p-tau, n (%)	20 (11.9)
CSF Aβ_{1-42}, pg/mL	405.1 (95.4)
CSF t-tau, pg/mL	67.1 (28.9)
CSF p-tau, pg/mL	34.8 (14.8)
CSF measures over time, n	2.6 (1.5) [1–7]
Participants with ≥2 CSF measures over time, n (%)	111 (66.1)
Participants with ≥3 CSF measures over time, n (%)	73 (43.5)
CSF measures over time for participants with ≥2 CSF measures, n	3.4 (1.3)
Time between first and last CSF measures for participants with ≥2 CSF measures, y	4.2 (2.5) [0.2–10.0]

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; p-tau = phosphorylated tau; t-tau = total tau.

Composite vascular risk score

Vascular risk factors were established by medical records or self-report during a medical history interview. A composite vascular risk score was calculated with a previously published algorithm,[11] which sums 5 dichotomous vascular risk factors (each coded as 0 = absent vs 1 = recent/remote): hypertension, hypercholesterolemia, diabetes, current smoking (i.e., within the last 30 days), and obesity based on body mass index >30 kg/m^2. For the majority of participants, vascular risk scores were calculated at their first study visit; for the remaining participants, the first available vascular risk data were used (mean time between baseline vascular risk score and first study visit 0.08 years, SD 0.70 years, range −0.97 to 5.98 years). For the purposes of this study, baseline is therefore defined as first available vascular risk score. Because very few individuals had ≥3 risk factors, composite vascular risk scores were coded dichotomously (0 vs ≥1).

CSF AD biomarkers

Lumbar punctures were conducted after an overnight fast. A maximum of 30 mL CSF was drawn with a 20- or 22-gauge needle (1995–2000) or 25-gauge Whiteacre-point needle (starting in 2000) and divided into aliquots in polypropylene cryotubes, which were kept on dry ice (≈0.5 mL CSF per tube). Immediately after the collection, the cryotubes were transferred to a −80°C freezer for long-term storage. These samples were thawed for the first time after collection to run the assays described below.

The CSF assays used the xMAP-based AlzBio3 kit (Innogenetics, Ghent, Belgium) run on the Bioplex 200 system. The AlzBio3 kit contains monoclonal antibodies specific for β-amyloid (Aβ)$_{1-42}$ (4D7A3), total tau (t-tau; AT120), and phosphorylated tau (p-tau181p; AT270), each chemically bonded to unique sets of color-coded beads, and analyte-specific detector antibodies (HT7, 3D6). Samples (run in triplicate) were analyzed on the same plate. Calibration curves, coefficients of variation, and comparison to published norms have been published previously.[5,31]

CSF measures were analyzed in 2 ways. (1) To examine the combined impact of the composite vascular risk score and biomarkers of both amyloid and tau pathology on cognitive trajectories, we used a previously published approach to create a dichotomous AD biomarker indicator variable that reflects the presence of both low Aβ_{1-42} and high t-tau (or low Aβ_{1-42} and high p-tau) at baseline on the basis of tertiles.[6] Using all available baseline CSF, AD biomarker group status was coded as 1 if Aβ_{1-42} was in the lower one-third of the distribution and t-tau (or p-tau) was in the upper one-third of the distribution, reflecting the high AD biomarker group, or otherwise coded as 0 (low AD biomarker group). (This is conceptually similar to the stage 2 hypothetical preclinical AD group defined by significant alterations in biomarkers for both amyloid and tau, which has been proposed as 1 of 3 stages for categorizing cognitively normal individuals along a continuum of preclinical AD.[32]) Although the present study did not use clinically derived cut points for determining biomarker abnormality, in prior publications, we have found that the relationship between these biomarker groupings and

Table 3 Results of linear mixed-effects models with cognitive performance as the outcome

	High AD biomarker indicator based on low $A\beta_{1-42}$ and high t-tau		High AD biomarker indicator based on low $A\beta_{1-42}$ and high p-tau	
Model predictor	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**
Time	0.016 (−0.003 to 0.034)	0.09	0.015 (−0.003 to 0.033)	0.10
Age	−0.026 (−0.039 to −0.012)	<0.001	−0.025 (−0.038 to −0.011)	<0.001
Age × time	−0.003 (−0.004 to −0.002)	<0.001	−0.003 (−0.004 to −0.002)	<0.001
Sex (F)	0.290 (0.016 to 0.565)	0.04	0.314 (0.039 to 0.589)	0.04
Sex (F) × time	0.012 (−0.008 to 0.033)	0.24	0.013 (−0.007 to 0.034)	0.20
***APOE* ε4**	−0.068 (−0.357 to 0.222)	0.65	−0.067 (−0.356 to 0.222)	0.65
***APOE* ε4 × time**	−0.002 (−0.023 to 0.020)	0.89	−0.002 (−0.023 to 0.019)	0.86
Years of education	0.054 (−0.007 to 0.115)	0.08	0.053 (−0.008 to 0.113)	0.09
Years of education × time	0.002 (−0.002 to 0.007)	0.34	0.002 (−0.003 to 0.006)	0.45
Composite vascular risk score (dichotomous)	−0.154 (−0.425 to 0.117)	0.27	−0.155 (−0.425 to 0.116)	0.26
Composite vascular risk score (dichotomous) × time	−0.022 (−0.043 to −0.002)	0.03	−0.023 (−0.043 to −0.003)	0.03
AD biomarker indicator (dichotomous)	−0.288 (−0.728 to 0.152)	0.20	−0.363 (−0.792 to 0.066)	0.10
AD biomarker indicator (dichotomous) × time	−0.060 (−0.096 to −0.024)	0.001	−0.057 (−0.092 to −0.023)	0.001

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; CI = confidence interval; p-tau = phosphorylated tau; t-tau = total tau.

longitudinal cognitive outcomes is fairly robust to variations in cut points (e.g., using quintiles).[6] Note that the primary goal of these groupings was to dichotomize the variables as high vs low AD biomarker groups for statistical purposes, as opposed to using clinically defined cut points (e.g., normal vs abnormal). The impact of the composite vascular risk score and CSF biomarkers on cognitive trajectories was also evaluated with continuous CSF biomarker measures (as opposed to the AD biomarker indicator), as described in the sensitivity analyses below. (2) To examine the relationship between the composite vascular risk score and change in CSF biomarkers over time, CSF $A\beta_{1-42}$, t-tau, and p-tau values were modeled as continuous variables with the use of CSF acquired at the NIH (CSF acquired at JHU was not included because biomarker harmonization is still ongoing).

APOE genotype

APOE genotypes were determined by restriction endonuclease digestion of PCR-amplified genomic DNA (performed by Athena Diagnostics, Worcester, MA). Genotypes were coded dichotomously (*APOE* ε4 carriers = 1, noncarriers = 0).

Statistical Analyses

The data were analyzed with longitudinal linear mixed-effects models that included random intercepts and slopes with unstructured covariance.[33] Baseline age and education were centered using baseline means, and time (from baseline) was modeled in the unit of years. All other continuous variables (including dependent variables) were standardized as *z* scores before model fitting.

The first set of models examined the combined impact of the baseline composite vascular risk score and baseline CSF AD biomarker indicators (low vs high) on longitudinal change in cognition. Separate models were run with the AD biomarker indicator defined by $A\beta_{1-42}$ and t-tau and by $A\beta_{1-42}$ and p-tau. The model predictors included time, as well as baseline age, sex, *APOE* ε4 genotype, education (years), vascular risk score, AD biomarker indicator, their interaction (cross-product) with time, vascular risk score × AD biomarker indicator interaction, and vascular risk score × AD biomarker indicator × time interaction. The 3-way interactions examined the possible synergism between baseline vascular risk and AD biomarkers on cognitive trajectories. If this term was not significant, we ran reduced models that excluded this term (and the vascular risk score × AD biomarker indicator term) to examine the independent associations between vascular risk and AD biomarkers with the rate of change in cognition (as indicated by the composite vascular risk score × time and AD biomarker indicator × time interaction term, respectively). In sensitivity analyses, these models were rerun using continuous measures of $A\beta_{1-42}$, t-tau, p-tau, and the ratios of t-tau/$A\beta_{1-42}$ and p-tau/$A\beta_{1-42}$ (as opposed to the AD biomarker indicators).

The second set of linear mixed-effects models tested the relationship between the composite vascular risk score and longitudinal change in CSF AD biomarkers. Separate models were run with $A\beta_{1-42}$, t-tau, and p-tau as outcome variables. The model predictors included time, as well as baseline age, sex, *APOE* ε4 genotype, vascular risk score, and their interactions with time. In sensitivity analyses, these models were rerun using the log-transformed ratios of t-tau/$A\beta_{1-42}$ or p-tau/$A\beta_{1-42}$ (to

correct for skewness) as outcome variables to assess the association with combined $A\beta_{1-42}$ and tau/p-tau. All analyses were run in Stata/IC (version 15.1; StataCorp, College Station, TX). Estimates and 95% confidence intervals (CIs) are reported for final models, and values of $p \leq 0.05$ were considered significant.

Data availability

Anonymized data used in the analyses presented in this report are available on request from qualified investigators (biocard-se.org).

Results

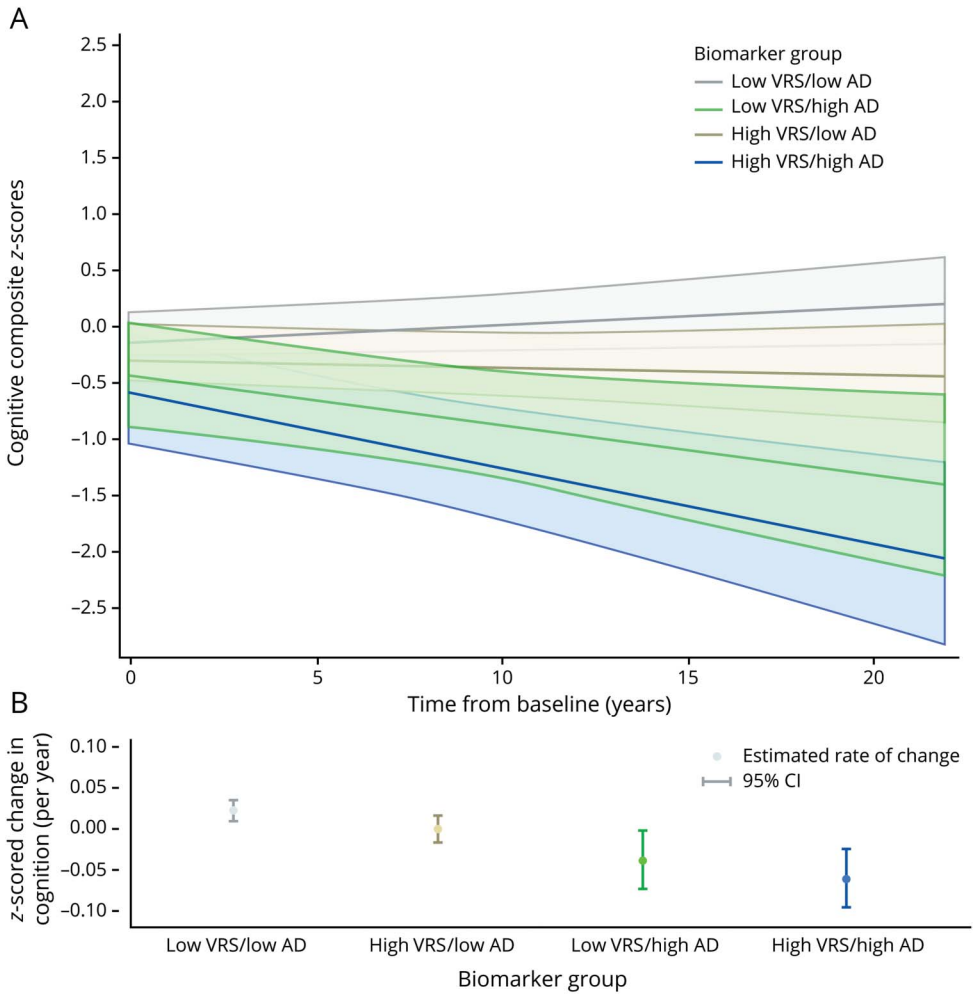
At baseline, participants were primarily middle-aged; the majority were white and highly educated (table 2).

Vascular risk, AD biomarkers, and change in cognition

On average, participants had 9.0 occasions of cognitive assessments over time, with 13.9 years of follow-up. Results examining longitudinal cognitive trajectories as the outcome were identical whether CSF $A\beta_{1-42}$ and t-tau or $A\beta_{1-42}$ and p-tau were used to define AD biomarker group membership. There were no significant 3-way vascular risk score × AD biomarker indicator × time interactions (all $p > 0.50$, data not shown), providing no statistical evidence that the association between the AD biomarker indicator and cognitive trajectories differed by baseline vascular risk. In the reduced models (table 3), there were significant effects of age and age × time (indicating lower cognitive performance and steeper cognitive decline among older individuals) and sex (indicating higher cognitive performance among women). Of primary interest, the vascular risk score and AD biomarker indicator were each independently associated with steeper cognitive decline (figure; table 4 provides models stratified by vascular risk).

The patterns of results were similar in sensitivity analyses that used continuous measures of $A\beta_{1-42}$, t-tau, and p-tau (as opposed to the AD biomarker indicators; table 5) or the ratios of t-tau/$A\beta_{1-42}$ and p-tau/$A\beta_{1-42}$ (data not shown). For each set of analyses, there were no significant 3-way vascular risk score × CSF

Figure Estimates of longitudinal cognitive change based on the composite vascular risk score (0 vs ≥1) and AD biomarker group defined by $A\beta_{1-42}$ and t-tau (low vs high; see text for details)



(A) Adjusted estimates from linear mixed-effects models predicting cognitive composite scores (95% confidence interval [CI]) over time. (B) Adjusted estimates of annual rate of change in cognitive composite scores (95% CI). Predicted marginal rates of global cognitive change were as follows: low vascular risk score (VRS)/low Alzheimer disease (AD) biomarker group estimate 0.022 (95% CI 0.010–0.035); high VRS/low AD biomarker group estimate 0.000 (95% CI −0.016 to 0.016); low VRS/high AD biomarker group estimate −0.038 (95% CI −0.073 to −0.002); and high VRS/high AD biomarker group estimate −0.060 (95% CI −0.096 to −0.024). Corresponding rates of global cognitive change for the CSF biomarker indicator based on β-amyloid$_{1-42}$ and phosphorylated tau (p-tau) are nearly identical (data not shown). Estimates are adjusted for age, sex, education, *APOE* ε4 genotype, and their interactions with time. t-tau = total tau.

biomarker × time interactions (all $p > 0.16$), and the reduced models showed significant vascular risk score × time and CSF biomarker × time interactions (with the exception of p-tau × time, estimate −0.010 [95% CI −0.021 to 0.001], $p = 0.076$). Patterns of results were also unchanged in sensitivity analyses that excluded the *APOE* ε4 and *APOE* ε4 × time covariates (data not shown). Likewise, similar results were obtained when the vascular risk score was treated as a continuous variable (data not shown).

Vascular risk and change in AD biomarkers

On average, participants had 2.6 CSF measures over time; 66% (111 of 168) of participants had ≥2 CSF measures with an average of 3.4 CSF measures. Results of the models examining the relationship of the vascular risk score to level of and rate of change in the CSF biomarkers are shown in table 6. There were main effects of age, indicating more abnormal baseline CSF biomarkers levels among older participants. For CSF p-tau, there was also a main effect of time (indicating an increase in p-tau over time). (In reduced models that excluded nonsignificant interaction terms, the main effect of time was also significant for $A\beta_{1-42}$—estimate −0.035 [95% CI −0.064 to −0.006], $p = 0.019$—indicating a decrease in $A\beta_{1-42}$ over time.) The main effects of the composite vascular risk score and the vascular risk score × time interactions were not significant, indicating no relationship between vascular risk and baseline levels of or rate of change in CSF biomarkers over time. The patterns of results were the same when the log-transformed ratio of t-tau/$A\beta_{1-42}$ or p-tau/$A\beta_{1-42}$ was used as the dependent variable and when the *APOE* ε4 and *APOE* ε4 × time covariates were excluded (data not shown).

Discussion

In this longitudinal study of individuals who were cognitively normal and primarily middle-aged at baseline, the composite vascular risk score and CSF AD biomarkers were each independently associated with cognitive decline over 13.9 years on average. Because there were no significant 3-way interactions, these results suggest that vascular risks and CSF AD biomarkers have additive effects on cognitive trajectories whereby the combined effects of these variables are not greater than the sum of their parts. In addition, the composite vascular risk score was unrelated to levels of or short-term rate of change in AD biomarkers (over 4.2 years on average), as measured by CSF $A\beta_{1-42}$, t-tau, or p-tau. Taken together, these results suggest that vascular risk and AD biomarkers, when measured in midlife, appear to act in an independent and additive manner rather than synergistically.

The results of this study suggest that vascular risk, measured among primarily middle-aged cognitively normal individuals, affects longitudinal cognitive trajectories independently from the combined effects of biomarkers of amyloid and tau pathology. This is important given that cognitively normal individuals with biomarker evidence of both amyloid and tau pathology/neurodegeneration (sometimes referred to as hypothetical stage 2[32]) are at the greatest risk for cognitive decline compared to those with only 1 or no abnormal AD biomarkers.[6,34,35] Similar to a prior study that measured AD pathology with amyloid imaging among cognitively normal individuals in their 70s,[9] we found that vascular risk and CSF measures of AD pathology are each associated with cognitive decline. However, unlike that prior study, we found that these effects were not synergistic but additive. There are several possible reasons for these differences, including differences in baseline age (56.4 vs 73.7 years), duration of follow-up (13.9 vs 3.7 years), level of vascular risk, and method of AD biomarker measurement (CSF amyloid and tau vs amyloid PET). Nonetheless, together, these studies emphasize that even low levels of vascular risk affect the cognitive trajectories of

Table 4 Relationship of AD biomarker groups to cognitive trajectories based on level of vascular risk

	High AD biomarker indicator based on low $A\beta_{1-42}$ and high t-tau		High AD biomarker indicator based on low $A\beta_{1-42}$ and high p-tau	
Model predictor	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**
Vascular risk score 0				
Time	0.017 (−0.004 to 0.035)	0.06	0.017 (−0.001 to 0.035)	0.06
AD biomarker indicator (dichotomous)	−0.513 (−1.08 to 0.052)	0.08	−0.579 (−1.13 to −0.032)	0.04
AD biomarker indicator (dichotomous) × time	−0.045 (−0.091 to 0.002)	0.06	−0.046 (−0.089 to −0.004)	0.03
Vascular risk score ≥1				
Time	−0.016 (−0.047 to 0.016)	0.34	−0.016 (−0.047 to 0.016)	0.34
AD biomarker indicator (dichotomous)	−0.037 (−0.723 to 0.648)	0.92	−0.037 (−0.723 to 0.648)	0.92
AD biomarker indicator (dichotomous) × time	−0.079 (−0.136 to −0.021)	0.008	−0.079 (−0.136 to −0.021)	0.008

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; CI = confidence interval; p-tau = phosphorylated tau; t-tau = total tau.
Mixed-effects models examined the relationship of the AD biomarker groups to cognitive trajectories, stratified by individuals with vascular risk score 0 and vascular risk score ≥1. The models were fit as described in the Statistical Analyses section except that the vascular risk score terms were excluded to directly examine the relationship of the AD biomarker groups and the outcomes of interest by level of vascular risk.

Table 5 Results of linear mixed-effects models with cognitive performance as the outcome and individual CSF biomarkers as predictors

	CSF $A\beta_{1-42}$		CSF t-tau		CSF p-tau	
Model predictor	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**
Time	0.011 (−0.008 to 0.029)	0.25	0.010 (−0.008 to 0.028)	0.29	0.009 (−0.010 to 0.028)	0.35
Age	−0.025 (−0.038 to −0.013)	<0.001	−0.030 (−0.044 to −0.017)	<0.001	−0.026 (−0.039 to −0.014)	<0.001
Age × time	−0.003 (−0.004 to −0.002)	<0.001	−0.003 (−0.004 to −0.002)	<0.001	−0.003 (−0.004 to −0.002)	<0.001
Sex (F)	0.279 (0.006 to 0.551)	0.045	0.283 (0.007 to 0.558)	0.04	0.324 (0.049 to 0.599)	0.02
Sex (F) × time	0.010 (−0.011 to 0.030)	0.36	0.012 (−0.008 to 0.033)	0.24	0.013 (−0.009 to 0.034)	0.24
***APOE* ε4**	−0.057 (−0.345 to 0.231)	0.70	−0.089 (−0.379 to 0.201)	0.55	−0.059 (−0.347 to 0.230)	0.69
***APOE* ε4 × time**	−0.002 (−0.024 to 0.019)	0.83	−0.002 (−0.023 to 0.020)	0.87	−0.003 (−0.025 to 0.019)	0.81
Years of education	0.050 (−0.010 to 0.111)	0.10	0.055 (−0.006 to 0.116)	0.08	0.054 (−0.007 to 0.115)	0.08
Years of education × time	0.002 (−0.003 to 0.006)	0.49	0.002 (−0.003 to 0.006)	0.44	0.002 (−0.003 to 0.006)	0.43
Composite vascular risk score (dichotomous)	−0.162 (−0.432 to 0.107)	0.24	−0.143 (−0.415 to 0.129)	0.30	−0.168 (−0.438 to 0.103)	0.22
Composite vascular risk score (dichotomous) × time	−0.024 (−0.044 to −0.003)	0.02	−0.025 (−0.045 to −0.005)	0.02	−0.024 (−0.045 to −0.003)	0.02
CSF biomarker	0.142 (0.008 to 0.276)	0.038	0.057 (−0.090 to 0.203)	0.45	−0.133 (−0.269 to 0.004)	0.06
CSF biomarker × time	0.010 (0.000 to 0.021)	0.050	−0.016 (−0.027 to −0.004)	0.006	−0.010 (−0.021 to 0.001)	0.076

Abbreviations: Aβ = β-amyloid; CI = confidence interval; p-tau = phosphorylated tau; t-tau = total tau.

cognitively normal individuals, after accounting for levels of AD biomarkers.

Notably, our results are also consistent with prior studies among cognitively normal individuals that have found that biomarkers of AD and CVD (e.g., infarcts, white matter hyperintensities) have independent effects on longitudinal cognitive outcomes[36–38] and with neuropathologic studies suggesting that cerebrovascular and AD pathologies have additive effects on the threshold for dementia.[39,40]

Providing additional support for the independence of vascular risk and biomarkers of AD pathology, we found no evidence that vascular risk promoted the short-term accumulation of amyloid or tau pathology as measured by CSF biomarkers. Similar findings have been reported in other studies examining short-term rates of change in biomarkers of amyloid pathology.[20–22] Consistent with the present results, a recent study reported that midlife atherosclerosis, measured among cognitively normal individuals, was associated with cerebral small vessel disease measured ≈20 years later but not with CSF biomarkers of AD pathology.[41] However, other studies have reported associations between midlife vascular risk and amyloid abnormality ≈20 years later.[11,15] Prior studies examining cardiovascular risk in relationship to short-term change in biomarkers of tau pathology among individuals who were cognitively normal at baseline are limited. Contrary to our results, Bos et al.[22] found that higher vascular risk, particularly hypertension, was associated with an increase in CSF t-tau and p-tau over a mean of follow-up of 2.1 years (mean baseline age 68 years), with the strongest effects in the small subset of individuals classified as amyloid and tau positive at baseline (n = 23 with mean 1.7 years of follow-up). The authors interpreted these associations as reflecting hypertension-related changes in neurodegeneration, raising the possibility that relationships may differ for individual vascular risk factors vs composite vascular risk scores. Although it is unclear why findings differ across studies with respect to CSF t-tau and p-tau, the reason might be related to differences in study design (i.e., use of a composite vascular

Table 6 Results of linear mixed-effects models with CSF biomarkers as the outcome

	CSF $A\beta_{1-42}$		CSF t-tau		CSF p-tau	
Model predictor	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**
Time	−0.024 (−0.074 to 0.026)	0.35	−0.007 (−0.034 to 0.020)	0.61	0.071 (0.004 to 0.138)	0.04
Age	−0.020 (−0.033 to −0.006)	0.004	0.029 (0.016 to 0.041)	<0.001	0.014 (0.001 to 0.028)	0.037
Age × time	−0.001 (−0.005 to 0.002)	0.55	0.001 (−0.001 to 0.003)	0.38	−0.003 (−0.007 to 0.001)	0.17
Sex (F)	0.055 (−0.237 to 0.348)	0.71	0.114 (−0.161 to 0.389)	0.42	0.222 (−0.072 to 0.516)	0.14
Sex (F) × time	−0.027 (−0.084 to 0.031)	0.36	0.016 (−0.016 to 0.048)	0.32	0.033 (−0.043 to 0.110)	0.40
***APOE* ε4**	−0.123 (−0.437 to 0.192)	0.45	0.075 (−0.221 to 0.371)	0.62	0.156 (−0.160 to 0.473)	0.33
***APOE* ε4 × time**	−0.016 (−0.077 to 0.046)	0.62	−0.013 (−0.047 to 0.021)	0.46	−0.019 (−0.101 to 0.062)	0.65
Composite vascular risk score	0.040 (−0.255 to 0.335)	0.79	−0.080 (−0.357 to 0.197)	0.57	−0.059 (−0.355 to 0.238)	0.70
Composite vascular risk score × time	0.027 (−0.034 to 0.080)	0.39	−0.017 (−0.052 to 0.017)	0.33	−0.010 (−0.090 to 0.070)	0.80

Abbreviations: Aβ = β-amyloid; CI = confidence interval; p-tau = phosphorylated tau; t-tau = total tau.

risk score vs individual risk factors), baseline age among participants, and levels of cardiovascular risk. Because AD pathology accumulates over years to decades, it will be important to examine the association between midlife vascular risk and longitudinal rates of change of AD pathology over longer periods of follow-up using both composite vascular risk scores and individual vascular risk factors.

In addition, several neuropathologic studies have found no relationship between vascular risk and levels of AD pathology at autopsy,[42–44] although this is not universally true.[45,46] Notably, it has been suggested that vascular risk factors, when measured among population-based, prospective studies, are not associated with the subsequent degree of AD pathology at autopsy but instead appear to affect cognitive outcomes through concomitant CVD and vascular brain injury.[47]

As reviewed elsewhere, there are a number of ways by which AD pathology and measures related to vascular risk may combine on a pathophysiologic level to exert additive effects on cognitive outcomes, which may include downstream effects on neuronal function, cerebral perfusion, and cortical atrophy.[48,49] More work is needed to better understand the independent and shared mechanisms by which these risk factors affect cognitive trajectories and the time course of these processes. Nonetheless, targeting modifiable midlife vascular risk factors to lower the burden of CVD may be a promising avenue for interventions designed to reduce late-life cognitive decline and dementia risk.

In line with prior work in this cohort,[6] the model indicators reflecting AD biomarker status had a significant relationship with longitudinal cognitive decline. More abnormal levels of amyloid and tau were associated with a marked decline in cognition, regardless of whether the AD biomarker indicator was defined using CSF $A\beta_{1-42}$ and t-tau or $A\beta_{1-42}$ and p-tau. Although p-tau levels are thought to be more directly related to the neurofibrillary tau tangle pathology found in AD and levels of t-tau are thought to reflect more general neurodegeneration/neuronal injury (i.e., due to both AD and non-AD causes such as CVD), they tend to be strongly correlated among individuals with limited coexisting pathologies.[50] In this study, there was a strong correlation between these measures $[r(166) = 0.67, p < 0.001]$ and therefore high concordance in the 2 AD biomarker groups. We hypothesize that this is because much of this cohort's elevation in t-tau is due to AD-related processes given the cohort's relatively young age, strong family history of AD, and proportion of *APOE* ε4 carriers.

This study has a number of strengths. For example, the cohort's characteristics allowed us to examine associations between vascular risk and AD biomarkers in a younger cohort with longer follow-up and a more comprehensive set of AD biomarkers than has been done previously. The current study also has limitations. First, BIOCARD participants are highly educated and primarily white and have a strong family history of AD dementia, which limits the generalizability of these findings to the population at large. Second, participants had very low levels of vascular risk, and the individual vascular risk factors were dichotomized and determined during the medical history interview rather than objective measurements or medication use. This limits the generalizability of these

findings, and we cannot rule out the possibility that vascular risk was underestimated or that the results would have been different with the use of objectively determined vascular risk scores, with the use of continuous measures of vascular risk, or in a sample with greater variability in vascular risk or clinical evidence of CVD. Third, the sample size was limited, and we therefore may have been underpowered to detect a 3-way interaction between vascular risk and CSF biomarkers on cognitive trajectories. Fourth, although participants were largely middle-aged at baseline (i.e., 83% were 40–69 years of age), the sample included a large age range (22–86 years). Of note, sensitivity analyses demonstrated comparable results when the age range excluded individuals <45 years of age. Lastly, although participants had undergone 13.9 years of cognitive follow-up, on average, the duration of CSF follow-up was more limited. Future studies examining the relationship of vascular risk factors to biomarker trajectories over longer intervals are critically needed given that the pathologic process underlying cognitive decline likely occurs over decades.

These results underscore the importance of accounting for multiple risk factors for identifying cognitively normal individuals at the greatest risk of cognitive decline and the need for interventions designed to reduce the burden of midlife vascular risks.

Acknowledgment

The authors acknowledge the contributions of the Geriatric Psychiatry Branch of the intramural program of National Institute of Mental Health who initiated the study (principal investigator, Dr. Trey Sunderland). The authors are particularly indebted to Dr. Karen Putnam, who has provided ongoing documentation of the Geriatric Psychiatry Branch study procedures and the data files received from National Institute of Mental Health.

Study funding

This work was supported by the NIH (grants U19-AG033655, P50-AG005146). The BIOCARD Study consists of 7 cores with the following members: (1) the Administrative Core (Marilyn Albert, Rostislav Brichko); (2) the Clinical Core (Marilyn Albert, A. Soldan, C. Pettigrew, R.F. Gottesman, Ned Sacktor, Scott Turner, Leonie Farrington, Jules Gilles, Maura Grega, Gay Rudow, Scott Rudow); (3) the Imaging Core (Michael Miller, Susumu Mori, Tilak Ratnanather, Timothy Brown, Andrea Faria, Anthony Kolasny, Kenichi Oishi, Laurent Younes); (4) the Biospecimen Core (A. Moghekar, Jacqueline Darrow, Richard O'Brien); (5) the Informatics Core (Roberta Scherer, David Shade, Ann Ervin, Jennifer Jones, Hamadou Coulibaly, Kathy Moser); (6) the Biostatistics Core (M.-C. Wang, Daisy Zhu, J. Wang); and (7) the Neuropathology Core (Juan Troncoso, Olga Pletnikova, Gay Rudow, Karen Fisher). The authors are grateful to the members of the BIOCARD Scientific Advisory Board who provide continued oversight and guidance regarding the conduct of the study, including Drs. John Csernansky, David Holtzman, David Knopman, Walter Kukull, and Kevin Grimm, and Drs. John Hsiao and Laurie Ryan, who provide oversight on behalf of the National Institute on Aging. The authors thank the members of the BIOCARD Resource Allocation Committee who provide ongoing guidance regarding the use of the biospecimens collected as part of the study, including Drs. Constantine Lyketsos, Carlos Pardo, Gerard Schellenberg, Leslie Shaw, Madhav Thambisetty, and John Trojanowski.

Disclosure

C. Pettigrew, A. Soldan, J. Wang, M.-C. Wang, and K. Arthur report no disclosures relevant to the manuscript. A. Moghekar has a research grant from Fujirebio Diagnostics. R.F. Gottesman is an associate editor for *Neurology*. M. Albert is an advisor to Eli Lily. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* March 30, 2020. Accepted in final form July 22, 2020.

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Mei-Cheng Wang, PhD	Johns Hopkins University, Baltimore, MD	Supervised the analysis of the data; interpretation of the data; revised the manuscript for content
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