RESEARCH ARTICLE

Differential Effects of *APOE* and Modifiable Risk Factors on Hippocampal Volume Loss and Memory Decline in Aβ− and Aβ+ Older Adults

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Abstract

Background and Objectives

This prospective study sought to determine the association of modifiable/nonmodifiable components included in the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score with hippocampal volume (HV) loss and episodic memory (EM) decline in cognitively normal (CN) older adults classified as brain β-amyloid (Aβ) negative (Aβ−) or positive (Aβ+).

Methods

Australian Imaging, Biomarkers and Lifestyle study participants (age 58–91 years) who completed ≥2 neuropsychological assessments and a brain Aβ PET scan (n = 592) were included in this study. We computed the CAIDE risk score (age, sex, *APOE* ε4 status, education, hypertension, body mass index [BMI], hypercholesterolemia, physical inactivity) and a modifiable CAIDE risk score (CAIDE-MR; education, hypertension, BMI, hypercholesterolemia, physical inactivity) for each participant. Aβ+ was classified using Centiloid >25. Linear mixed models assessed interactions between each CAIDE score, Aβ group, and time on HV loss and EM decline. Age, sex, and *APOE* ε4 were included as separate predictors in CAIDE-MR models to assess differential associations. Exploratory analyses examined relationships between individual modifiable risk factors and outcomes in Aβ− cognitively normal (CN) adults.

Results

We observed a significant Aβ group × CAIDE × time interaction on HV loss (β [SE] = −0.04 [0.01]; $p < 0.000$) but not EM decline (β [SE] = −2.33 [9.96]; $p = 0.98$). Decomposition revealed a significant CAIDE × time interaction in Aβ+ participants only. When modifiable/nonmodifiable CAIDE components were considered separately, we observed a significant Aβ group × CAIDE-MR × time interaction on EM decline only (β [SE] = 3.03 [1.18]; $p = 0.01$). A significant CAIDE-MR score × time interaction was observed in Aβ− participants only. Significant interactions between *APOE* ε4 and age × time on HV loss and EM decline were observed in both groups. Exploratory analyses in Aβ− CN participants revealed a significant interaction between BMI × time on EM decline (β [SE] = −3.30 [1.43]; $p = 0.02$).

Discussion

These results are consistent with studies showing that increasing age and *APOE* ε4 are associated with increased rates of HV loss and EM decline. In Aβ− CN adults, lower prevalence of modifiable cardiovascular risk factors was associated with less HV loss and EM decline over ∼10 years, suggesting interventions to reduce modifiable cardiovascular risk factors could be beneficial in this group.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **AIBL** = Australian Imaging, Biomarkers and Lifestyle; **BMI** = body mass index; **CAIDE** = Cardiovascular Risk Factors, Aging and Incidence of Dementia risk score; **CAIDE-MR** = Cardiovascular Risk Factors, Aging and Incidence of Dementia modifiable risk score; **CDR** = Clinical Dementia Rating; **CL** = Centiloid; **CN** = cognitively normal; **CVLT-II** = California Verbal Learning Test, Second Edition; **IPAQ** = International Physical Activity Questionnaire; **LM** = Logical Memory; **LM-II** = delayed recall trial of the LM; **LMM** = linear mixed effects model; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MR** = magnetic resonance; **RCFT** = Rey Complex Figure Test; **VIF** = variance inflation factor; **WMS-R** = Wechsler Memory Scale–Revised.

Prospective studies show that in older adults who are cognitively normal (CN), increasing age, carriage of the *APOE* ε4 allele, and elevated brain β-amyloid levels (Aβ+) each increase the risk of cognitive decline, particularly in episodic memory, brain atrophy, particularly in the hippocampus, and ultimately, Alzheimer disease (AD) dementia.[1,2] Although subtle, Aβ accumulation can occur up to 30 years prior to clinical classification of dementia,[3,4] providing opportunity for the implementation of strategies to mitigate this risk. Because risk factors such as *APOE* ε4 carriage and age cannot be modified, it becomes important to identify other risk factors for adverse cognitive outcomes and brain atrophy in CN adults that might be modifiable. Epidemiologic studies have identified risk factors for dementia, although the mechanisms of these are incompletely understood.[5] For example, physiologic characteristics such as elevated blood pressure and cholesterol levels, obesity, and diabetes,[6,7] as well as behavioral characteristics such as smoking[8] and lower educational attainment,[9] each increase dementia risk, with the prognostic utility of these risk factors for dementia improved when their effects are considered in sum. Each of these risk factors can be modified.

The Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) risk score is a well-validated dementia risk score[10] that encapsulates the combined effects of age, sex, *APOE* ε4 status, education, hypertension, body mass index (BMI), hypercholesterolemia, and physical inactivity.[10,11] Predictive utility of the CAIDE risk score varies by population[12,13] but the CAIDE risk score has become important in decision-making about dementia risk and management, including guiding the development of strategies aimed at reducing dementia risk in older CN populations.[14] However, when considered with respect to emerging biological models of the most common form of dementia—AD—strategies to reduce dementia prevalence based on the CAIDE risk score are problematic, as the CAIDE score also includes characteristics that cannot be modified: age, sex, and *APOE* ε4.

Given the centrality of brain Aβ to AD risk, and observations that age and *APOE* ε4 increase AD dementia risk through their influence on Aβ accumulation,[15,16] it is possible that modifiable risk factors contained within the CAIDE risk score operate by adding to, or amplifying, the effects of age or *APOE* ε4 carriage on Aβ.[17] Alternatively, modifiable risk factors contained in the CAIDE score could increase risk for dementia thorugh processes unrelated to Aβ.[18] With AD biomarkers now applied widely, it becomes possible to investigate how modifiable dementia risk factors, operationalized within the CAIDE risk score, contribute to AD dementia risk in addition to the effects of Aβ+, *APOE* ε4, and age. Hippocampal atrophy and episodic memory decline have reliably been shown to be early markers of preclinical AD and can thus be used to examine the effects of different putative AD risk factors in this stage.[19] Thus, the first aim of this study was to determine the nature of relationships between the CAIDE risk score and indices of incipient dementia (hippocampal atrophy, episodic memory decline) over 10 years in preclinical AD (Aβ+). The second aim was to reexamine these relationships with nonmodifiable risk factors removed from risk estimates. Aim 3 was to challenge the specificity of any relationships observed between the modifiable or nonmodifiable risk factors and disease progression in early AD by reexamination in CN older adults with subthreshold Aβ levels (Aβ−).

Methods

Participants

A total of 592 CN older adults (395 Aβ−; 197 Aβ+) from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study who underwent PET neuroimaging for brain Aβ levels and had completed ≥2 neuropsychological assessments at least 18 months apart were included in this study. Cognitive normality was established by a clinical panel consisting of geriatricians, neurologists, and neuropsychologists who examined all medical and neuropsychological information. The clinical panel was blinded to PET neuroimaging and genetic information. Participants were classified as CN if they performed greater than −1 SD on all neuropsychological tests when compared to Australian normative scores, had a Mini-Mental State Examination (MMSE) score ≥26, and had a Clinical Dementia Rating (CDR) score of 0 or 0.5 (CDR score of 0.5 allowed if all neuropsychological test scores fell within normative ranges). The CDR is not used to determine the clinical status of participants within the AIBL study as it is not administered independently of the neuropsychological test battery. This method of administration can potentially overinflate CDR scores assigned. Instead, the AIBL consensus panel considers classification of mild cognitive impairment (MCI) in an individual when there is evidence of performance

of at least 1.5 SD below age-adjusted means on 2 or more cognitive tests, in addition to reported memory difficulties.[20] Thus, in AIBL, a CDR score of 0.5 does not reflect the MCI disease stage, as participants can be rated as CDR 0.5 when they have only a subjective cognitive concern but still be classified as CN in the consensus clinical panel review.[20] Participants had completed neuropsychological assessment on up to 8 timepoints, at retest intervals of 18-months. AIBL recruitment, inclusion and exclusion criteria, and assessments have been described in detail previously.[20,21] For the current study, individuals with a high cardiovascular disease burden, including symptomatic stroke, uncontrolled diabetes, or current regular alcohol use exceeding 2 standard drinks per day for women or 4 per day for men, were excluded from AIBL participation.

Standard Protocol Approvals, Registrations, and Patient Consents

The AIBL study was approved by institutional research/ethics committees in line with the Helsinki Declaration. Informed consent was obtained from all participants prior to any procedures.

Modifiable and Nonmodifiable Dementia Risk

The CAIDE risk score was computed using the following variables: age, sex, *APOE* ε4 status, education, hypertension, BMI, hypercholesterolemia, and physical inactivity (see Table 1 for computation/cut scores).[10] Scores on the CAIDE can range from 0 to 18, with higher scores indicative of increased dementia risk. Next, to separate contributions of modifiable and nonmodifiable risk factors from the CAIDE score on AD risk, a CAIDE score consisting only of modifiable risk factors (CAIDE modifiable risk [CAIDE-MR]) was computed for each participant by restricting indices of risk to education, hypertension, BMI, hypercholesterolemia, and physical activity and combining these with respect to their weighting in the conventional CAIDE risk score. Scores on the CAIDE-MR can range from 0 to 10. All risk factor data used to compute the scores were collected at baseline assessment. Age, sex, and education were self-reported with educational attainment operationalized as years of formal education. Hypertension was assessed using an objective reading of systolic blood pressure. BMI was calculated based on height and weight (kg/m^2). A fasted blood sample was collected from participants to estimate total blood lipid (cholesterol) levels. Physical inactivity was measured using the International Physical Activity Questionnaire (IPAQ), scored following standard recommendations, and operationalized as 7-day activity or metabolic equivalent score (MET min/wk).

APOE genotyping in AIBL has been described previously.[21,22] Briefly, 80 mL of blood was collected from each participant and 10 mL forwarded for large-scale DNA extraction. TaqMan genotyping assays were used to determine *APOE* (rs7412, assay ID: C____904, 973_10; rs429358, assay ID: C___3084793_20). This was performed on a QuantStudio 12K Flex Real-Time PCR system (Applied Biosystems) using the TaqMan GTXpress Master Mix (Life Technologies) as per manufacturer instructions.

Table 1 Versions of the CAIDE Risk Score Used in the Study Including Risk Factor Cut Scores and the Number of Points Assigned for the Presence of Each Risk Factor Criterion

	Risk scores	
Risk factors	**CAIDE**	**CAIDE-MR**
Age, y		
<47	0	—
47–53	3	—
>53	5	—
Sex		
Women	0	—
Men	1	—
***APOE* ε4 allele**		
Noncarrier	0	—
Carrier	2	—
Education, y		
≥10	0	0
7–9	3	2
0–6	4	3
Hypertension, mm Hg		
SBP ≤140	0	0
SBP >140	2	2
BMI, kg/m^2		
≤30	0	0
>30	2	2
Hypercholesterolemia, mmol/L		
≤6.5	0	0
>6.5	1	2
Physical activity, MET min/wk		
Active: ≥600	0	0
Inactive: <600	1	1
Total points, maximum	18	10

Abbreviations: BMI = body mass index; CAIDE = Cardiovascular, Aging and Incidence of Dementia risk score; CAIDE-MR = Cardiovascular, Aging and Incidence of Dementia modifiable risk score; SBP = systolic blood pressure.

Episodic Memory

Episodic memory was defined using the AIBL episodic memory composite score.[23] This was constructed using data from the California Verbal Learning Test, Second Edition (CVLT-II), the Logical Memory (LM) subtest of the Wechsler

Table 2 Demographic and Clinical Characteristics of Each Aβ Group

Baseline differences	Full sample (n = 592)	Aβ− (n = 395)	Aβ+ (n = 197)	*p* Value
Female	348/244 (58.8)	240 (60.8)	108 (54.8)	0.20
Age, y (range)	70.82 (7.44) (58.8–90.7)	69.7 (6.11) (58.8–90.7)	73 (6.84) (60.3–89.1)	<0.000[c]
Premorbid FSIQ	107.7 (8.07)	107.7 (7.17)	107.9 (8.1)	0.68
Years of education	12.46 (3.28)	12.52 (2.96)	12.34 (2.85)	0.49
MMSE	28.72 (1.37)	28.8 (1.17)	28.5 (1.57)	0.007[b]
Hippocampal volume	2.93 (0.29)	2.96 (0.24)	2.88 (0.31)	0.04[a]
Episodic memory	−0.11 (0.92)	−0.04 (0.77)	−0.27 (0.85)	0.000[c]
CDR 0.05	552/40 (6.76)	19 (3.21)	21 (3.55)	0.007[b]
HADS-A	4.49 (3.32)	4.48 (2.91)	4.52 (3.13)	0.87
HADS-D	2.74 (2.5)	2.68 (2.27)	2.85 (2.46)	0.47
BMI	26.51 (4.53)	26.75 (4.04)	26.04 (4.47)	0.05[a]
Total cholesterol, mmol/L	5.51 (1.25)	5.55 (1.13)	5.44 (1.08)	0.26
IPAQ, MET min/wk	4,676 (4,165)	4,905.95 (4,291.66)	4,206.85 (3,881.34)	0.08
CAIDE	7.91 (2.26)	7.67 (1.97)	8.4 (2.05)	<0.000[c]
CAIDE-MR	1.90 (1.95)	1.89 (1.8)	1.93 (1.75)	0.81
***APOE* ε4 carrier**	176 (29.7)	76 (19.2)	100 (50.7)	<0.000[c]
Follow-up time, y	10.34 (2.44)	10.57 (2.33)	9.83 (2.59)	<0.000[c]
Number of HV timepoints	5.85 (1.69)	6 (1.63)	5.52 (1.77)	<0.000[c]
Number of EM timepoints	6.89 (1.63)	7.05 (1.55)	6.55 (1.73)	<0.000[c]

Abbreviations: Aβ = β-amyloid; Aβ− = β-amyloid negative (≤25 Centiloid); Aβ+ = β-amyloid positive (>25 Centiloid); BMI = body mass index; CAIDE = Cardiovascular Risk Factors, Aging and Incidence of Dementia risk score; CAIDE-MR = Cardiovascular Risk Factors, Aging and Incidence of Dementia modifiable risk score; CDR = Clinical Dementia Rating; FSIQ = full-scale IQ; HADS-A = Hospital Anxiety and Depression Scale (Anxiety); HADS-D = Hospital Anxiety and Depression Scale (Depression); IPAQ = International Physical Activity Questionnaire; MET = metabolic equivalent score; MMSE = Mini-Mental State Examination;
Values are n (%) or mean (SD).
[a] $p \leq 0.05$.
[b] $p \leq 0.01$.
[c] $p \leq 0.001$.

Memory Scale–Revised (WMS-R), and the Rey Complex Figure Test (RCFT). The 30-minute-long delayed free recall trial from the CVLT-II, the delayed recall trial of the LM (LM-II), and the 30-minute delayed recall trial from the RCFT were combined to generate an episodic memory composite. Only Story A of the LM test was used in AIBL assessments. Consistent with previous AIBL studies, performance on each test at each postbaseline assessment was standardized using the baseline mean and SD of the entire Aβ− CN sample.[24] The episodic memory composite was then computed by averaging these standardized scores.

Neuroimaging

Brain Aβ burden was measured using PET imaging coupled with one of the following Aβ− binding tracers: ^{11}C Pittsburgh compound B, ^{18}F-NAV4694, ^{18}F-florbetaben, ^{18}F-flutemetamol, or ^{18}F-florbetapir. Methodology for each tracer has been described previously.[25] Briefly, PET images were analyzed using CapAIBL[26] and Aβ burden was expressed in the Centiloid (CL) scale.[26] The CL scale provides a single continuous scale across the different Aβ imaging tracers, where a value of 0 represents the typical Aβ burden in young controls and 100 the typical Aβ burden seen in mild AD.[27] In the current study, the threshold for Aβ+ status was defined as >25 CL, based on a previously defined cut score in a study including CN older adults from the AIBL cohort.[1]

Magnetic resonance (MR) images were spatially normalized to the Montreal Neurologic Institute single-subject MRI brain template.[28] As described elsewhere, T1-weighted MR images for each participant were classified into gray matter, white matter, and CSF using an implementation of the expectation maximization segmentation algorithm.[29] The algorithm computed probability maps for each tissue type and was used to assign each voxel to its most likely tissue type and subsequent segmentation. Hippocampus was extracted using a multi-atlas

Table 3 Summary of Results From the Linear Mixed Effects Models (Longitudinal) Exploring 3-Way Interactions Between Each Composite CAIDE Risk Score (CAIDE, CAIDE-MR), Aβ Group, and Time

	Hippocampal volume			Episodic memory		
Model predictors (term)	**β estimate**	**SE**	***p* Value**	**β estimate**	**SE**	***p* Value**
CAIDE						
CAIDE	−0.01	0.03	0.64	−7.36	2.25	0.00[c]
Aβ status	0.07	0.39	0.85	−3.46	3.21	0.28
Time	−0.15	0.04	0.00[c]	2.40	4.28	0.00[c]
CAIDE × Aβ group × time	−0.04	0.01	0.00[c]	−2.33	9.96	0.98
CAIDE-MR						
CAIDE-MR	0.02	0.03	0.59	−5.04	2.32	0.03[a]
Aβ status	0.07	0.15	0.65	−2.18	1.26	0.08
Time	−0.14	0.02	0.00[c]	1.20	1.86	0.00[c]
Age × time	−0.04	0.01	0.00[c]	−6.53	1.02	0.00[c]
Sex × time	0.03	0.02	0.06	−6.14	1.87	0.97
CAIDE-MR × Aβ group × time	−0.01	0.01	0.44	3.03	1.18	0.01[b]
Aβ group × *APOE* ε4 × time	−0.17	0.04	0.00[c]	−1.41	4.47	0.00[c]

Abbreviations: Aβ = β-amyloid; CAIDE = Cardiovascular Risk Factors, Aging and Incidence of Dementia risk score; CAIDE-MR = Cardiovascular Risk Factors, Aging and Incidence of Dementia modifiable risk score.
[a] $p \leq 0.05$.
[b] $p \leq 0.01$.
[c] $p \leq 0.001$.

approach based on the Harmonized Hippocampus Protocol.[30] Average hippocampal volumes were normalized for head size using total intracranial volume, defined as the sum of the gray matter, white matter, and CSF volumes.

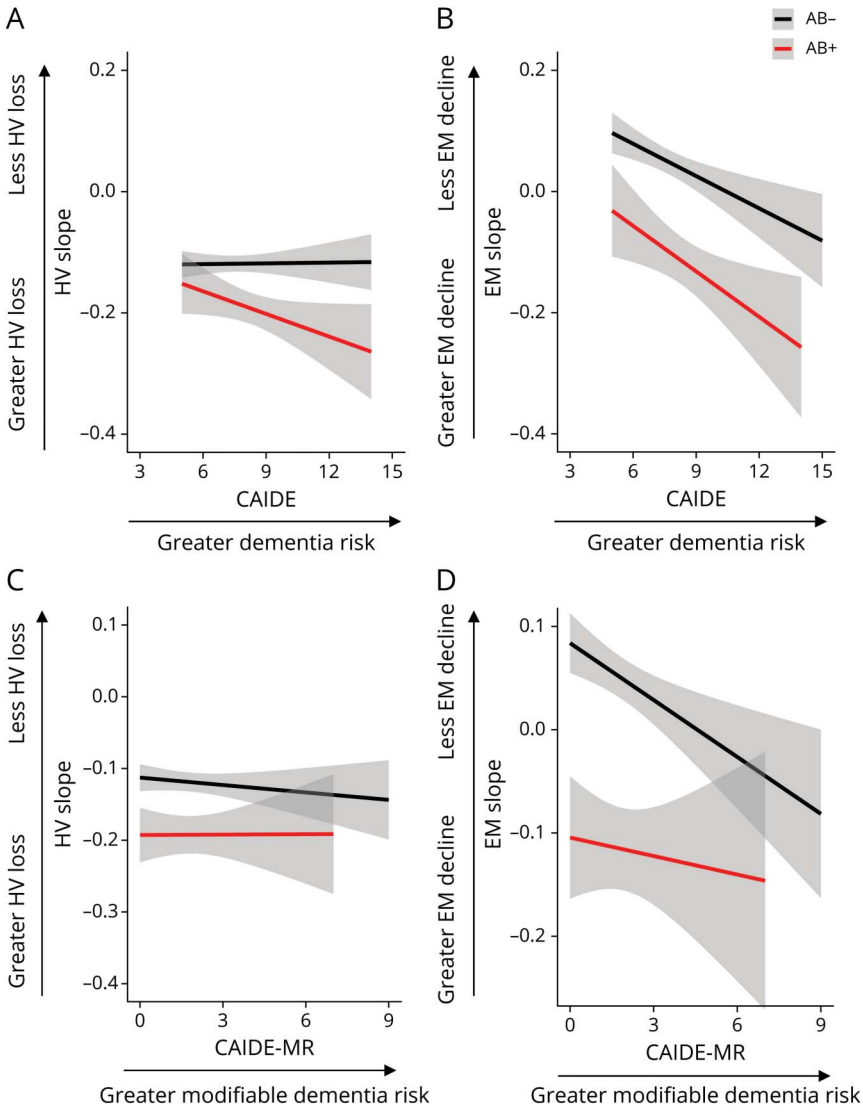
Data Analysis

All analyses/visualizations were conducted in RStudio using the R program (version 3.6.1; RStudio) for statistical computing and the following packages were used: "lme4," "lmerTest," "dplyr," and "ggplot2." Baseline differences in demographic, clinical, and neuropsychological measures across Aβ groups were assessed using a series of linear regressions for continuous variables and χ^2 tests for categorical variables.

A series of linear mixed effects models (LMMs) were applied to determine the extent to which the CAIDE and CAIDE-MR score were related to hippocampal atrophy and episodic memory decline. Each LMM used an unstructured covariance matrix with maximum likelihood estimation and the participant was treated as a random factor. Interactions were assessed between each CAIDE risk score (CAIDE, CAIDE-MR) and change over time in hippocampal volume and episodic memory in the Aβ− and Aβ+ CN groups, as well as between *APOE* ε4 status × Aβ group × time in the CAIDE-MR models. We first computed 3-way interactions between the selected CAIDE risk score × Aβ group × time. If significant, models were decomposed, and each included a 2-way interaction term between the selected CAIDE risk score × time. Nonmodifiable variables (age, sex, *APOE* ε4) included within the CAIDE risk score were included as separate predictors in models assessing interactions between the CAIDE-MR score × time. Each LMM included a random intercept term across participants and a random slope for time. All variables, excluding sex and *APOE* ε4 status, were entered into statistical models as continuous variables. As we sought to understand the relationship between each risk score or factor and change in hippocampal volume and memory, all effects discussed above involve an interaction with time. Models including the CAIDE risk score did not include interaction terms between demographic and baseline clinical characteristics (e.g., age, sex, *APOE* ε4 status) with time, as these variables were included within the computation of the CAIDE risk score (Table 1). The level of probability required for classification of statistical significance was set at $p < 0.05$ as only 2 outcomes were considered, and this was an exploratory investigation involving an adapted risk score with potential to generate new hypotheses about AD progression.

Finally, post hoc exploratory analyses examined interactions between individual modifiable risk factors and episodic memory decline in Aβ− CN participants only, while controlling for the effects of age, sex, and *APOE* ε4. These models included 2-way interactions between each individual

Figure 1 Relationship Between the CAIDE Risk Score, the CAIDE-MR, and the Rate of Change in HV and EM in Aβ− and Aβ+ CN Older Adults Over Time



Relationship between the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) risk score (including both modifiable and non-modifiable risk factor components), Cardiovascular Risk Factors, Aging and Incidence of Dementia modifiable risk score (CAIDE-MR), and the rate of change (slope) in hippocampal volume (HV) (A, C) and episodic memory (EM) (B, D) in Aβ− cognitively normal (CN; black line) and Aβ+ CN (red line) older adults over time. Slope values capture the rate of change in HV and EM for each individual in a single data point. Values on the y-axis that progressively become more negative reflect greater rates of HV loss and EM decline, respectively. Values on the x-axis represent the CAIDE risk score (3–15) or the CAIDE-MR (0–9) score, for which increasingly positive values are indicative of increased dementia risk. CAIDE-MR score models account for the variance associated with age, sex, and *APOE* ε4. Shading indicates 95% CIs.

risk factor × time (e.g., systolic blood pressure × time). For this final exploratory model, the variance inflation factor (VIF) was computed to assess the degree of multicollinearity between modifiable risk factors (predictors) and confirm the appropriateness of these models. VIF threshold cutoffs vary across studies; however, it is generally thought that a predictor with a VIF ≥5 (conservative estimate) indicates that the variable is moderately correlated with other predictor variables and actions to reduce collinearity should be considered.[31]

Data Availability

AIBL data are available at ida.loni.usc.edu. Data are systematically released after a delay (approximately 2 years) to allow AIBL investigators the opportunity to publish main findings. For researchers interested in collaboration, earlier access to data will be considered by the AIBL scientific management committee upon request.

Results

Demographic/Clinical Characteristics

Table 2 summarizes the demographic/clinical characteristics of the Aβ− and Aβ+ groups. On average, the AIBL sample in this study were followed for 10.34 ± 2.44 years. Compared to the Aβ− group at baseline, the Aβ+ group was older, had lower MMSE scores, smaller hippocampal volume, lower episodic memory scores, and higher CAIDE risk scores (Table 2). There was also a higher proportion of *APOE* ε4 carriers in the Aβ+ group and Aβ+ CN participants had a higher BMI than Aβ− CN participants (Table 2). Aβ+ and Aβ− groups were equivalent on all other clinical and demographic characteristics.

Table 4 Summary of Results From the Linear Mixed Effects Model (Longitudinal) Exploring 2-Way Interactions for Each Composite CAIDE Risk Score (CAIDE, CAIDE-MR)

	Aβ− CN (hippocampal volume)			Aβ+ CN (hippocampal volume)		
Model predictors (term)	**β estimate**	**SE**	***p* Value**	**β estimate**	**SE**	***p* Value**
CAIDE						
CAIDE	−0.02	0.03	0.48	−0.07	0.04	0.04[a]
Time	−0.17	0.03	0.00[c]	0.05	0.09	0.62
CAIDE × time	0.01	0.00	0.15	−0.03	0.01	0.00[c]
CAIDE-MR						
CAIDE-MR	0.01	0.03	0.85	−0.02	0.04	0.59
Time	−0.15	0.01	0.00[c]	−0.08	0.04	0.07
Age × time	−0.03	0.01	0.00[c]	−0.10	0.02	0.00[c]
Sex × time	0.05	0.02	0.00[c]	−0.02	0.04	0.60
***APOE* ε4 × time**	−0.04	0.02	0.02[a]	−0.22	0.04	0.00[c]
CAIDE-MR × time	0.01	0.00	0.01[b]	−0.01	0.01	0.68
	Aβ− CN (episodic memory)			**Aβ+ CN (episodic memory)**		
Model predictors (term)	**β estimate**	**SE**	***p***	**β estimate**	**SE**	***p***
CAIDE-MR	−5.80	2.30	0.01[b]	−4.05	3.68	0.27
Time	1.36	2.00	0.00[c]	−8.97	3.28	0.98
Age × time	−6.53	1.20	0.00[c]	−6.40	1.93	0.00[c]
Sex × time	1.84	2.29	0.42	−4.13	3.57	0.25
***APOE* ε4 × time**	−8.84	2.84	0.00[c]	−1.96	3.59	0.00[c]
CAIDE-MR × time	−1.44	6.31	0.02[a]	1.33	1.00	0.19

Abbreviations: Aβ = β-amyloid; Aβ− = β-amyloid negative (≤25 Centiloid); Aβ+ = β-amyloid positive (>25 Centiloid); CAIDE = Cardiovascular Risk Factors, Aging and Incidence of Dementia risk score; CAIDE-MR = Cardiovascular Risk Factors, Aging and Incidence of Dementia modifiable risk score; CN = cognitively normal.
[a] $p \leq 0.05$.
[b] $p \leq 0.01$.
[c] $p \leq 0.001$.

Relationship Between the CAIDE Risk Score and Change in Hippocampal Volume and Episodic Memory in Aβ− and Aβ+ Groups

There was a significant Aβ group × CAIDE risk score × time interaction for hippocampal volume (Table 3 and Figure 1A). Decomposition of this interaction indicated that for the Aβ+ group, a higher CAIDE risk score was negatively associated with a greater rate of hippocampal volume loss (Table 4). In the Aβ− group, there was no relationship between the CAIDE risk score and rate of hippocampal volume loss (Table 4 and Figure 1A).

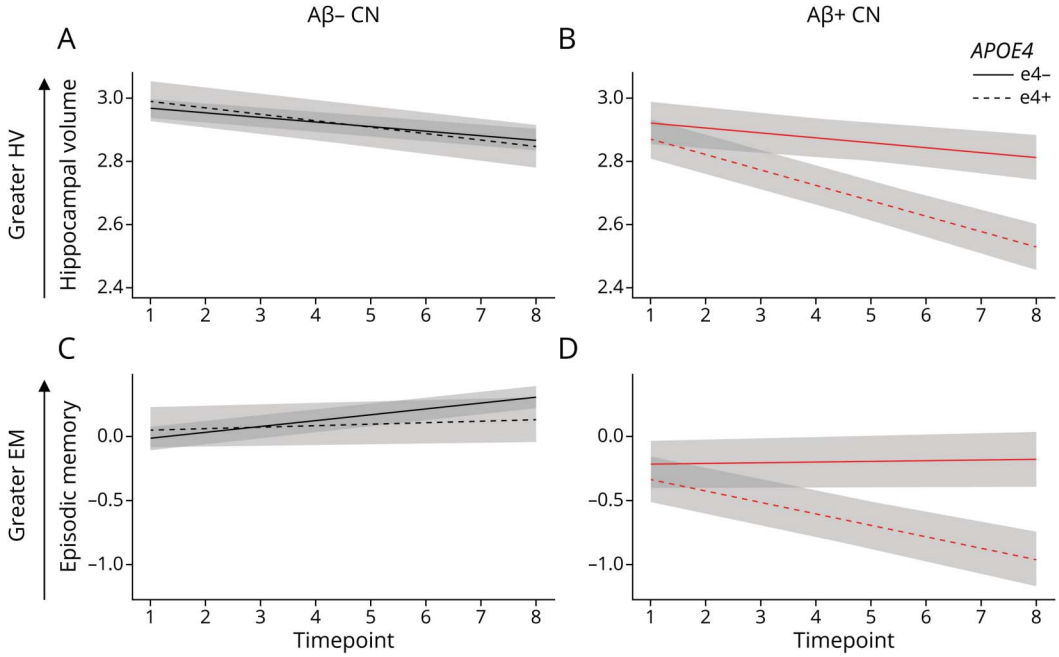
There was no significant Aβ group × CAIDE risk score × time interaction for episodic memory, indicating that the relationship between the CAIDE risk score and episodic memory decline did not differ between the Aβ+ and Aβ− groups (Table 3 and Figure 1B).

Relationship Between CAIDE-MR Score and Change in Hippocampal Volume and Episodic Memory in Aβ− and Aβ+ Groups

There was no significant Aβ group × CAIDE-MR score × time interaction for hippocampal volume, indicating that the relationship between the CAIDE-MR risk score and the rate of hippocampal volume loss was not different between the Aβ+ and Aβ− groups (Table 3 and Figure 1C). However, there was a significant Aβ group × *APOE* ε4 × time interaction for hippocampal volume, where ε4 carriers showed greater rates of hippocampal volume loss than noncarriers (Table 3 and Figure 2).

A significant Aβ group × CAIDE-MR score × time interaction was observed for episodic memory (Table 3 and Figure 1D). Decomposition of this interaction indicated that an increasing CAIDE-MR score was related to faster episodic memory decline in the Aβ− group, but not in the Aβ+ group (Figure 1D

Figure 2 Rates of Change in HV and EM in Aβ− and Aβ+ CN Older Adults Who Are *APOE* ε4 Carriers and Noncarriers Over Time



Rates of change in hippocampal volume (HV) and episodic memory (EM) in Aβ− cognitively normal (CN; black line) and Aβ+ CN (red line) older adults who are *APOE* ε4 carriers (dashed lines) and noncarriers (solid lines) over time (after accounting for variance associated with age, sex, and modifiable risk factors). Higher scores on the y-axis (HV and EM) are indicative of larger HV and better EM performance; lower scores are indicative of smaller HV and poorer EM performance. Timepoints are measured in 18-month intervals. Shading indicates 95% CIs.

and Table 4). Similarly, a significant Aβ group × *APOE* ε4 × time interaction was observed (Table 3 and Figure 2), where ε4 carriers showed greater rates of episodic memory decline than noncarriers.

Contribution of Individual Modifiable Risk Factors to Episodic Memory Decline in Aβ− CN Adults

In Aβ− CN adults, the rate of episodic memory decline was only related to the CAIDE-MR score. Thus, relationships between each modifiable risk factor and episodic memory decline in Aβ− CN adults were explored, with the effects of nonmodifiable risk factors (age, sex, and *APOE* ε4) controlled statistically (Table 5). The VIF assessed the severity of multicollinearity between predictors (modifiable risk factors) (results listed in eTable 1, links.lww.com/WNL/B825). The VIF for all predictor variables fell below a predefined threshold of 5, indicating a moderate correlation between variables, suggesting the analysis was appropriate. Only BMI was significantly associated with episodic memory decline in Aβ− CN participants.

Table 5 Summary of Results From the Linear Mixed Effects Model (Longitudinal) for Individual Modifiable Risk Factors in Aβ− CN Adults

Individual modifiable RFs, model predictors (term)	Aβ− CN (episodic memory)		
	β estimate	SE	*p* Value
Education × time	−9.10	1.34	0.50
BMI × time	−3.30	1.43	0.02[a]
Systolic BP × time	7.49	1.45	0.61
Cholesterol × time	−1.88	1.60	0.24
Physical activity × time	−1.83	1.38	0.18

Abbreviations: Aβ− = β-amyloid negative (≤25 Centiloid); BMI = body mass index; BP = blood pressure; CN = cognitively normal; RF = risk factor.
[a] $p \leq 0.05$.

Discussion

The aim of this study was to determine the contribution of modifiable and nonmodifiable components of the CAIDE risk score to indices of early AD progression, that is, hippocampal atrophy and episodic memory decline. The results of this study showed that in preclinical AD (Aβ+ CN), nonmodifiable dementia risk factors such as age and *APOE* ε4 carriage are related to indices of incipient dementia such as hippocampal volume loss and episodic memory decline. This is most likely due to their established associations with Aβ burden (Figures 1 and 2).[32] However, in this same group, dementia risk estimated only from modifiable risk factors, such as lower educational attainment, higher cholesterol levels, and blood pressure, did not improve predictions of hippocampal volume loss or episodic memory decline over that provided by age and *APOE* ε4

(Figures 1 and 2). In Aβ− CNs, higher ratings on a risk score restricted to modifiable risk factors (CAIDE-MR) were associated with episodic memory decline (Figure 2). Exploration of relationships between each individual modifiable risk factor and episodic memory decline in Aβ− CNs suggested that episodic memory decline was related to higher BMI, a known cardiovascular risk factor (Table 4). Taken together, the results of this study suggest that there are differential effects of common modifiable (e.g., vascular risk) and nonmodifiable (e.g., age, *APOE* ε4) dementia risk factors on indices of incipient dementia such as hippocampal volume loss and memory decline in CN older adults, which are dependent on the presence of abnormal Aβ.

Findings from this study of CN older adults within the AIBL cohort suggest that in preclinical AD, modification of cardiovascular risk factors is unlikely to change the underlying disease course of AD. However, in the absence of abnormal Aβ pathologic processes, modification of cardiovascular risk factors, such as weight, could influence the development of dementia. These results are consistent with findings that the CNS effects of vascular disease and Aβ are independent in CN adults.[18] However, the current findings add to this concept by showing that in the absence of clinically important cardiovascular disease, known modifiable dementia risk factors have no additional influence on disease progression in preclinical AD. The current findings are also important for studies seeking to modify dementia risk in older adults, as they suggest that strategies designed to reduce cardiovascular risk will not influence the development of dementia in Aβ+ CN adults. Therefore, the combination of nonmodifiable/modifiable risk factors into composite dementia risk scores, such as the CAIDE score, to guide preventative risk reduction strategies has limited utility when applied in preclinical AD. However, such scores may prove more useful for computing risk and planning modification strategies in midlife when Aβ remains within subthreshold levels, or in later life, for Aβ− CNs.

The findings of this study are consistent with previous studies in preclinical AD, where we and others have shown that *APOE* ε4 carriage further increases the rate of hippocampal volume loss[33] and episodic memory decline,[16,34] and that in generally healthy CN older adults, Aβ+ is the greatest risk factor for any form of dementia.[35] This finding is also consistent with a small substudy of 48 participants from the FINGER trial, which observed Aβ+ participants (n = 20) to have worse executive function than Aβ− participants, but this association was not explained by higher prevalence of cardiovascular risk factors.[36] The results of our study extend these findings by demonstrating that only nonmodifiable components of the CAIDE risk score that are strong predictors of Aβ accumulation (age, *APOE* ε4) were associated with greater rates of hippocampal atrophy and episodic memory decline in Aβ+ CN adults.

In Aβ− CN adults, the observation that both higher modifiable dementia risk as well as ε4 carriage was associated with greater rates of episodic memory decline (Figures 1 and 2) accords with recent observations that subtle, but discernible, dysfunction in cognition is detectable in Aβ− CN *APOE* ε4 carriers when followed over sufficiently long periods of time (e.g., 9–10 years).[37] While the mechanism by which ε4 increases rates of hippocampal volume loss and memory decline in Aβ− CN adults remains unclear, it is likely through its effects on Aβ and tau accumulation.[15,16,34] Conversely, the modifiable risk factors included in the CAIDE-MR, which are mostly vascular in nature, have previously been shown to not associate with Aβ accumulation,[38,39] although some studies suggest that higher prevalence of vascular risk factors is associated with increased tau accumulation.[39] Although brain Aβ and tau accumulation were not measured in this study, it is also possible that the contribution of modifiable risk factors to memory decline in Aβ− CN adults in this study may reflect unmeasured, underlying cerebrovascular pathology.[38]

As Aβ+ and hippocampal atrophy are defining characteristics of AD,[40] the observation that higher CAIDE-MR scores were associated with faster episodic memory decline but not hippocampal volume loss in Aβ− older adults suggests that this episodic memory decline may reflect non–AD-related brain dysfunction and pathologies. One potential explanation for the memory decline in the Aβ− group is that it reflects cerebrovascular changes, as the CAIDE-MR score is computed from indices such as cholesterol level, blood pressure, and BMI. However, this hypothesis must be challenged in future studies that include neuroimaging indices validated to measure subtle cerebrovascular change, and by determining whether decline in other aspects of cognition, such as attention and executive functions, characteristic of the cognitive impairment arising from subtle cerebrovascular disease,[41] are also associated with an increased CAIDE-MR score. The observation that memory decline occurred in the absence of Aβ+ and hippocampal volume loss does not invalidate the central finding of this study that in preclinical AD, modifiable risk factors are unrelated to disease progression.

Exploratory post hoc analyses were conducted to deconstruct the CAIDE-MR into its individual modifiable risk factors to explore the contribution of each modifiable risk factor to memory decline in Aβ− CNs. After controlling for the effects of age, sex, and *APOE* ε4 over time, only higher BMI was associated with greater memory decline. Recent systematic reviews and meta-analyses have reported that vascular factors, such as higher BMI, can be associated with increased risk or protection depending on the life stage studied (e.g., middle vs late life).[6,42] Nevertheless, vascular risk factors such as increased weight and cerebrovascular pathologies, including cortical and subcortical infarcts, microinfarcts, and white matter hyperintensities, have been shown to increase the rate of hippocampal atrophy[38] and cognitive decline, and may lower the threshold for clinically diagnosed AD dementia.[43] Despite this, our observation that in the absence of abnormal Aβ those with higher BMI demonstrated greater loss of episodic memory over time possibly reflects the cognitive expression of unmeasured/covert cerebrovascular pathology in an aging population. Previous studies have also shown that

cardiovascular risk factors, estimated using the Framingham Heart Study general cardiovascular disease risk score, as well as cerebrovascular disease (white matter hyperintensity burden, stroke), are associated with cognitive decline, but have been shown to operate both independently and synergistically with Aβ burden.[18,44] Other modifiable dementia risk factors, such as years of education, a common sociobehavioral proxy for cognitive reserve and vascular risk, was not associated with longitudinal change in episodic memory, consistent with previous studies demonstrating robust cross-sectional associations between higher educational attainment and cognitive performance, but no association with cognitive decline.[45]

Taken together, these results suggest that there are differential effects of common modifiable (e.g., vascular risk) and nonmodifiable (e.g., age, *APOE* ε4) risk factors on hippocampal atrophy and memory decline in preclinical AD and in CN adults for whom Aβ levels remain subthreshold. In preclinical AD, Aβ levels are already sufficiently high to result in neurodegeneration and cognitive decline.[46] As such, it is likely that modifiable risk factors have little influence on hippocampal volume loss and memory decline because any potential protective effect once incurred is diminished. That is, as age- and Aβ-related pathologic brain burden increases, the brain's ability to withstand increasing levels of pathology declines.[47] This finding conflicts with reports of previous studies showing that Aβ pathologic processes, or *APOE* ε4 carriage, coupled with high cardiovascular risk/burden (midlife hypertension and vascular pathology) may impart greater additive risk for cognitive decline than either pathologic process or risk factor alone.[17,18] In addition, although the Aβ− group was followed up for longer than the Aβ+ group, this difference was not substantial (~7 months). It is thus unlikely that the absence of a significant association between the CAIDE-MR score with episodic memory decline in Aβ+ CN adults is due to any bias arising from differential retention rates. Lastly, in Aβ− CN adults, previous studies have shown that very little change in hippocampal volume and cognition is observed.[3,48] However, these results suggest that when individuals are followed over sufficiently long periods of time, there are subtle but discernible effects of modifiable vascular risk factors on memory. This observation underlines the need for intervention trials focused on modifiable risk reduction and primary prevention to occur early, prior to Aβ abnormality.

There are several caveats to be considered when interpreting the results of this study. Participants enrolled in AIBL were not randomly selected from the community and are generally well-educated, Caucasian, and have fewer vascular risk factors than the broader Australian population. Stringent selection criteria exclude adults younger than 60 and those with comorbid cardio- or cerebrovascular disease. Thus, replication in a younger and more demographically/clinically diverse sample of community-based participants, such as those included in the Mayo Clinic Study of Aging cohort,[49] will be important, particularly when considering the potential effect of these findings for the planning of risk modification strategies across the life course. It will also be important for future studies to explore whether treatment for cardiovascular disease (e.g., antihypertensive medications) mitigates risk of hippocampal atrophy or memory decline, a variable that was not controlled for in this study. Nonetheless, despite the relative cardiovascular health of participants, the observation that vascular risk factors remained an important predictor of memory decline, particularly in Aβ− adults, highlights the significance of vascular risk on cognition. It will also be important for future studies to examine the contribution of modifiable vascular risk factors to Aβ and tau accumulation, as this will provide additional insights into the extent to which modifiable vascular risk factors contribute to the development of AD pathology. Future analyses should also consider how modifiable vascular risk factors relate to imaging markers of cerebrovascular pathology and the extent to which they relate to clinical and cognitive outcomes. Finally, replication of these results in cohorts with alternate outcomes will be key to understanding whether these effects generalize to volumetric loss and its cognitive expression in brain regions and domains other than the hippocampus and episodic memory.

Dementia risk scores are used to identify individuals at risk of developing dementia.[10] However, their application in clinicopathologic models of AD can be confounding, as they mask differential associations between modifiable and nonmodifiable dementia risk factors. The results of this study have important implications for clinicopathologic models of AD and support the hypothesis that interventions to reduce modifiable AD risk by targeting vascular risk factors should occur in midlife, or even earlier, before Aβ accumulates to abnormal levels. In addition, as plasma biomarkers become more commonplace and increase the accessibility/feasibility of large-scale biomarker assessment, clinically relevant AD biomarkers (e.g., Aβ) should be included in dementia risk scores,[50] as relationships between risk factors and clinical outcomes may differ according to Aβ classifications.

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Yen Ying Lim, PhD	Monash University, Victoria, Australia	Study concept or design; analysed the data; interpretation of the data; drafted and revised the manuscript for content

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Differential Effects of *APOE* and Modifiable Risk Factors on Hippocampal Volume Loss and Memory Decline in A β– and Aβ+ Older Adults

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