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Original Article

Amyloid pathology and modifiable risk factors in cognitive decline among cognitively unimpaired older adults

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ABSTRACT

Background: Alzheimer's disease (AD) pathology, particularly amyloid-β (Aβ) deposition, occurs years before clinical symptoms. Modifiable risk factors may influence cognitive trajectories during this preclinical stage, but whether amyloid status alters their effects remains unclear.
Objectives: To investigate interactions between amyloid pathology and modifiable risk factors in predicting longitudinal cognitive decline among cognitively unimpaired older adults.
Design and Setting: This study was a secondary analysis of data derived from two large multicenter longitudinal cohort studies, the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) Study and the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) Study.
Participants: A total of 1707 cognitively unimpaired adults aged 65–85 years were included, comprising 1169 amyloid-positive participants from the A4 Study (Aβ+) and 538 amyloid-negative participants from the LEARN Study (Aβ–).
Measurements: Cognitive function was assessed every six months using the Preclinical Alzheimer's Cognitive Composite (PACC) over a mean follow-up of 4.9 years. Eight established modifiable risk factors—low education, alcohol use, diabetes, high cholesterol, high blood pressure, obesity, depressive symptoms, and physical inactivity—were evaluated. Linear mixed-effects models were applied to examine associations between each risk factor and longitudinal PACC decline, and to test interactions with amyloid status, adjusting for demographic and genetic covariates.
Results: Significant interactions between amyloid status and modifiable risk factors were observed for diabetes (adjusted $\beta = -0.206$, $p = 0.032$), high cholesterol (adjusted $\beta = -0.155$, $p < 0.001$), and physical inactivity (adjusted $\beta = -0.161$, $p = 0.046$), indicating combined effects rather than additive effects on cognitive decline among Aβ+ individuals. In the A4 study (Aβ+), low education, diabetes, high cholesterol, and physical inactivity were independently associated with accelerated cognitive decline, whereas obesity was linked to slower decline. In contrast, in the LEARN study (Aβ-), these associations were not statistically significant.
Conclusions: In conclusion, the significant interactions with amyloid status were observed for diabetes, high cholesterol, and physical inactivity, indicating that these risk factors were associated with faster cognitive decline specifically in Aβ+ individuals. The results suggest that consideration of amyloid status may be important when evaluating the potential role of metabolic and lifestyle risk factors in preclinical cognitive decline. In Aβ+ individuals, obesity was associated with slower cognitive decline, while low education was linked to lower

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baseline cognition or a reduced symptom threshold, without a significant interaction with amyloid status. Future studies should incorporate amyloid status and longitudinal biomarkers to assess whether modifying these factors can slow preclinical cognitive decline.

1. Introduction

Alzheimer's disease (AD), a leading cause of dementia worldwide, represents an increasing public health challenge as populations age [1]. Pathological changes, particularly amyloid-β (Aβ) deposition, occur years before the onset of clinical symptoms and define the preclinical stage of AD [2]. This stage, characterized by preserved cognitive function despite the presence of Aβ pathology [3], offers a critical window for identifying factors that influence cognitive trajectories. Recent large prevention trials and observational studies have focused on identifying early determinants of cognitive decline in cognitively unimpaired older adults [1,4].

In addition to Aβ pathology, numerous epidemiological studies have identified modifiable risk factors for cognitive decline and progression to dementia, such as low education, physical inactivity, obesity, hypertension, diabetes, dyslipidemia, smoking, excessive alcohol use, and depressive symptoms [5–7]. Importantly, over 40% of dementia risk is attributable to factors that are potentially preventable or manageable through targeted interventions [1]. High education has been associated with lower Aβ burden in AD, indicating that certain protective factors may be particularly relevant for individuals at elevated risk of Aβ pathology [8]. Large population-based neuroimaging studies have shown that diabetes triples the likelihood of amyloid deposition, with greater burden over time. They also found that hypertension is linked to increased amyloid burden among APOE ε4 carriers, suggesting that genetically susceptible individuals are at increased vascular risk [9]. Additionally, elevated LDL-C appears to amplify the impact of Aβ deposition on tau pathology, underscoring the potential role of lipid management in modifying AD progression [10].

However, due to differences in study populations and methodologies, findings on the association between modifiable risk factors and cognition stratified by amyloid status remain inconsistent. Findings from the Korean Brain Aging Study suggest that vascular risk control may provide cognitive benefits in amyloid-negative (Aβ–) individuals, whereas the benefits in amyloid-positive (Aβ+) individuals remain uncertain [11]. Similarly, a study in mixed small vessel disease and AD pathology populations found that vascular burden primarily affected cognition via amyloid-independent pathways, through localized neurodegeneration, suggesting that vascular risk may influence cognition independently of amyloid pathology [12] Therefore, further research is warranted to determine whether modifiable risk factors influence cognitive trajectories differently in Aβ+ and Aβ– individuals, and to clarify whether they exert additive effects among cognitively unimpaired older adults.

The present study aimed to examine the association between amyloid pathology and modifiable risk factors with longitudinal cognitive changes, as measured by the Preclinical Alzheimer's Cognitive Composite (PACC). We hypothesized that the combined effects of amyloid pathology and modifiable risk factors on cognitive decline exceed additive expectations. Modifiable risk factors were selected based on evidence synthesized in the 2024 Lancet Dementia Commission [1], including low education, diabetes, high cholesterol, blood pressure, obesity, depressive symptoms, and physical inactivity. These findings may contribute to risk stratification and guide prevention strategies in preclinical cognitive decline.

2. Methods

2.1. Study population

We conducted a secondary analysis of data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study (ClinicalTrials.gov Identifier: NCT02008357) and the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) Study (ClinicalTrials.gov Identifier: NCT02488720). The screening procedures and outcome measures for both studies have been described previously [13,14], and the relevant sections are briefly summarized below. Both studies enrolled cognitively unimpaired individuals aged 65–85 years with Clinical Dementia Rating (CDR) Global Scores of 0 (range 0–3), Mini-Mental State Examination (MMSE) scores of 25–30 (range 0–30) and a Weschler Memory Scale-Revised Logical Memory Delayed Recall score of 6–18 (range 0–25), consistent with the eligibility criteria used in the original A4 and LEARN prevention trials [13,14]. Participants with stable chronic conditions including hypertension, diabetes, hypercholesterolemia, and mild-to-moderate small vessel ischemic disease were permitted.

Participants underwent 18F-Florbetapir PET imaging, with mean cortical SUVRs calculated using a cerebellar reference [15]. Amyloid status was determined at a central laboratory using an algorithm that combined quantitative SUVR values, which were converted to the Centiloid (CL) scale, with qualitative visual assessments [16]. Participants with elevated amyloid who met all inclusion and exclusion criteria [17] were randomized 1:1 to receive intravenous solanezumab or placebo. This randomization was part of the original A4 trial and was not considered in the present secondary analysis, which does not evaluate treatment effects. Participants who were otherwise eligible for the A4 study but did not show elevated amyloid were enrolled in the LEARN study, which was launched a year later at a subset of A4 sites. LEARN participants completed the same cognitive and functional assessments and served as the non-amyloid comparator group. All participants from the A4 and LEARN studies who had available baseline amyloid PET and longitudinal PACC data were included in this secondary analysis. Baseline demographic variables including age, sex, ethnicity, marital status and APOE ε4 carrier status were collected and included as covariates in the statistical analyses.

2.2. Assessment of modifiable risk factors

Modifiable risk factors were selected based on the 2024 Lancet Commission report on dementia prevention [1]. Variables were limited to those documented in both the A4 and LEARN studies, resulting in eight factors: low education, alcohol use, diabetes, high cholesterol, high blood pressure, obesity, depressive symptoms, and physical inactivity. Smoking status was excluded from the analyses due to the very low prevalence in the study population (A4: N = 20, 1.7%; LEARN: N = 3, 0.6%). Educational level was dichotomized as ≤12 years versus >12 years. Alcohol use was incorporated as binary variables. Participants were classified as non-drinkers (0 drinks/day) or drinkers (≥1 drink/-day), with one drink defined as 4 ounces of wine, 12 ounces of beer, or 1 ounce of liquor. Elevated HbA1c was defined as ≥6.5%, consistent with the diagnostic threshold for diabetes [18]. Total cholesterol levels ≥200 mg/dl were classified as high [19]. High blood pressure was defined at baseline as a single measurement with systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg [20]. Body mass index (BMI) was classified as obesity (≥30 kg/m^2) or no obesity (<30 kg/m^2) [21,22]. Depressive symptoms were defined using the 15-item Geriatric

Depression Scale (GDS-15) [23], with a cutoff score of ≥5. Self-reported walking time was categorized as physical active (>10 min/day) or physical inactive (≤10 min/day) to distinguish individuals with very low levels of daily walking from those reporting some walking activity [24]. Other risk factors identified by the Lancet Commission (e.g., hearing loss, traumatic brain injury, social isolation, and air pollution) were not included because relevant variables were not available or could not be harmonized across the A4 and LEARN datasets.

2.3. Evaluation of cognitive performance

The primary outcome was longitudinal cognitive performance, evaluated using the Preclinical Alzheimer's Cognitive Composite (PACC) [25] and assessed at 6-month intervals throughout the study period. The participants were followed for a mean duration of 4.92 years (standard deviation [SD] = 2.28), with an average of 12.5 visits (SD = 4.7) over the study period. The PACC represents the sum of normalized scores on four cognitive assessments: the Free and Cued Selective Reminding Test [26], assessing semantic memory and learning; the Logical Memory Delayed Recall test [27], measuring episodic memory; the Digit Symbol Substitution Test [28], capturing attention and processing speed; and the MMSE [29], reflecting global cognitive function. Raw scores from each component were transformed into z-scores based on baseline means and standard deviations, and the total PACC score was calculated as the unweighted sum of these four z-scores. Lower PACC scores over time indicated greater cognitive decline.

2.4. Statistical analysis

Continuous variables are expressed as means ± standard deviations, and categorical data are expressed as numbers (percentages). Continuous variables were compared using the independent Student's *t*-test. Categorical data were compared using the chi square test or Fisher's exact test, as appropriate. Linear mixed-effects models were used to examine associations between each modifiable risk factor and longitudinal PACC decline, including its interaction with amyloid status (A4 [Aβ+] vs. LEARN [Aβ–]), adjusted for baseline age, sex, marital status, education, APOE ε4 carrier status, and ethnicity. When education itself was analyzed as the exposure variable, it was not included as a covariate to avoid overadjustment. Linear mixed-effects models with random intercepts and random slopes for participants were used to account for between-subject variability in baseline PACC scores and individual differences in longitudinal rates of cognitive change. The primary focus of the analysis was on differences in the slopes of cognitive change over time. Group-specific slopes were compared using Tukey-adjusted post hoc tests, and contrast analyses were used to evaluate whether the combined effects of amyloid status and modifiable risk factors exceeded additive expectations by comparing the observed slope in the joint exposure group (Aβ+ with the risk factor present) with the expected slope under an additive model, defined as the slope in the Aβ+ group without the risk factor plus the slope in the Aβ− group with the risk factor minus the slope in the Aβ− group without the risk factor. P values were adjusted for multiple comparisons using the Bonferroni correction [30]. In addition, a sensitivity analysis using false discovery rate (FDR) control based on the Benjamini–Hochberg method was performed [31]. Adjusted p-value < 0.05 (two-tailed) was considered statistically significant for all tests. Analyses were conducted using R, version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

A total of 1707 cognitively unimpaired participants aged 65–85 years were included: 1169 individuals with elevated amyloid from the A4 study (Aβ+) and 538 individuals without elevated amyloid from the LEARN study (Aβ-) (Fig. 1). All participants completed baseline amyloid PET imaging and were followed longitudinally with cognitive assessments using the PACC.

3.2. Baseline characteristics

Table 1 summarizes the baseline demographic and clinical characteristics of participants in the A4 and LEARN study. Compared with participants in the LEARN study, those in the A4 study were older (71.9 ± 4.8 vs. 70.5 ± 4.3 years; p < 0.001), had lower educational years (9.8% vs. 6.3%; p = 0.02), and were more frequently APOE ε4 carriers (58.9% vs. 22.9%; p < 0.001). The prevalence of high cholesterol was also higher in A4 than in LEARN (49.1% vs. 42.5%; p = 0.01). Other baseline demographic and clinical characteristics did not differ significantly between the two studies.

3.3. Interaction between amyloid status and modifiable risk factors

In Table 2, significant interactions between Aβ status and risk factors were identified for diabetes (β = −0.206, SE = 0.072; adjusted P = 0.032), high cholesterol (β = −0.155, SE = 0.037; adjusted P < 0.001), and physical inactivity (β = −0.161, SE = 0.058; adjusted P = 0.046), indicating combined effects rather than additive effects on cognitive decline among Aβ+ individuals.

In the A4 study (Aβ+), linear mixed-effects models revealed that low education (β = –0.129, SE=0.030; adjusted p < 0.001), diabetes (β = –0.350, SE=0.039; adjusted p < 0.001), high cholesterol (β = –0.068, SE=0.018; adjusted p = 0.007), and physical inactivity (β = –0.121, SE=0.029; adjusted p = 0.002) were each independently associated with accelerated cognitive decline, as measured by PACC scores. Sensitivity analyses using FDR correction yielded similar results, with diabetes, high cholesterol, and physical inactivity remaining statistically significant (Supplementary Table). These patterns are illustrated in Supplementary Figure 1A–1H, which display the estimated group-specific PACC slopes across the four amyloid–risk factor groups, with selected Tukey-adjusted pairwise comparisons. Pairwise comparisons showed that Aβ+ groups with low education, diabetes, high cholesterol, and physical inactivity exhibited significantly more negative slopes than the other groups (all P < 0.05). In contrast, obesity showed an opposite

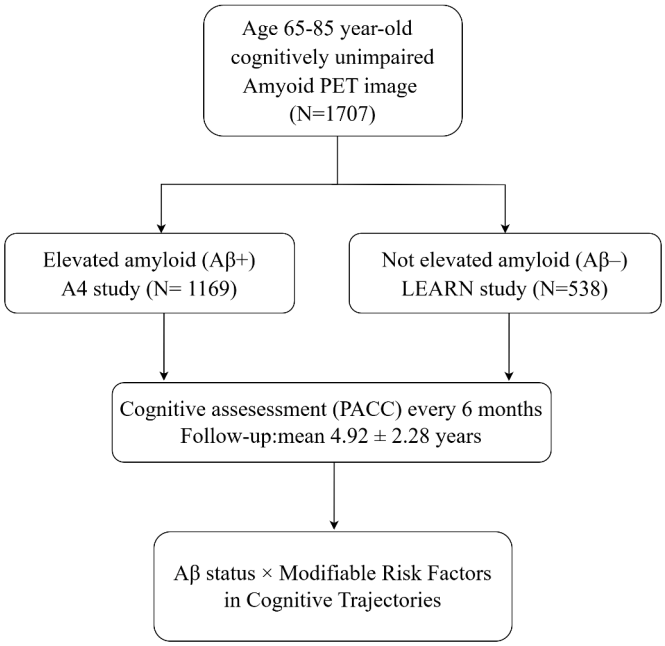


Fig. 1. Study design flowchart.

Table 1
Baseline characteristics of A4 (Aβ+) and LEARN (Aβ–) study participants.

Category	A4 (Aβ+) (N = 1169)	LEARN (Aβ-) (N = 538)	p-value
Age (mean ± SD*)	71.9 ± 4.8	70.5 ± 4.3	<0.001
Male	475 (40.6%)	208 (38.7%)	0.47
Marital status			0.22
Married	836 (71.5%)	386 (72.3%)	
Divorced/ Widowed	272 (23.7%)	119 (22.3%)	
Never married	42 (3.7%)	29 (5.4%)	
Ethnicity			0.74
Hispanic or Latino	34 (2.9%)	18 (3.4%)	
Not Hispanic or Latino	1124 (97.1%)	516 (96.6%)	
Education ≤ 12 years	114 (9.8%)	34 (6.3%)	0.02
APOE Carrier†	689 (58.9%)	123 (22.9%)	<0.001
Smoker	20 (1.7%)	3 (0.6%)	0.09
Alcohol use	599 (51.3%)	289 (53.7%)	0.38
Diabetes (HbA1C ≥ 6.5%)	71 (6.1%)	42 (7.8%)	0.22
High total cholesterol (≥ 200 mg/dl)	572 (49.1%)	228(42.5%)	0.01
High blood pressure	519 (44.4%)	249 (46.3%)	0.51
Obesity (BMI ≥30 kg/m²)	285 (24.4%)	143 (26.6%)	0.37
Depressive mood‡	26 (2.2%)	15 (2.8%)	0.59
Physical activity (Walking time>10 mins)	1028 (88.2%)	475 (88.5%)	0.93

* SD: standard deviation.
† APOE carrier status was defined as the presence of at least one ε4 allele.
‡ Depressive mood: using the 15-item Geriatric Depression Scale with a cutoff score of ≥5.

pattern, with the Aβ+ obesity group exhibiting a less negative slope than the Aβ+ non-obesity group. However, only diabetes, high cholesterol, and physical inactivity demonstrated patterns consistent with combined effects exceeding additive expectations in the Aβ+ group, as confirmed by contrast analyses comparing the estimated longitudinal PACC slopes across the four amyloid–risk factor groups. These findings were not observed in the LEARN study (Aβ−). Additional trajectory analyses are provided in Supplementary Figures 2A–2H

Within the A4 (Aβ+) group, obesity demonstrated a positive association with PACC scores ($\beta = 0.094$, SE = 0.021; $p < 0.001$), indicating a slower rate of cognitive decline among obese participants compared to those without obesity. We further examined whether this association differed by sex. A significant three-way interaction between time, obesity, and sex was observed ($\beta = -0.095$, $p = 0.01$, data not shown), indicating that the association between obesity and longitudinal PACC decline differed between men and women, with a stronger protective association observed in women. In contrast, none of the modifiable risk factors showed significant associations with cognitive decline in the LEARN study (Aβ−) (Table 2).

4. Discussion

In this longitudinal analysis of cognitively unimpaired older adults from the A4 and LEARN studies, we found that diabetes, high cholesterol, and physical inactivity exhibited significant interactions with amyloid status, indicating that the combined effects of amyloid status and these risk factors exceeded additive expectations, resulting in greater cognitive decline among Aβ+ individuals. In the A4 study (Aβ+), low education, diabetes, high cholesterol, and physical inactivity were associated with accelerated cognitive decline in PACC scores, underscoring the potential vulnerability of Aβ+ individuals to these risk factors. Obesity was linked to a slower rate of cognitive decline compared to non-obese participants. In contrast, these associations were absent in the LEARN study (Aβ -). Cognitive change in the LEARN cohort was generally modest over the follow-up period, and longer follow-up may be required to detect potential effects of these risk factors in amyloid-negative individuals. Together, these findings highlight the importance of considering both amyloid pathology and modifiable risk factors in predicting cognitive trajectory.

The combined effects of amyloid positivity and three major modifiable risk factors, including diabetes, high cholesterol, and physical inactivity may inform potential intervention strategies in cognitively unimpaired older adults. Consistent with our findings, previous literature suggests that diabetes is associated with an increased risk of cognitive decline and dementia [32,33]. Furthermore, diabetes has been shown to promote Aβ aggregation and tau hyperphosphorylation via mechanisms involving insulin resistance and chronic hyperglycemia, and may further exacerbate neurodegeneration through cerebrovascular damage, chronic inflammation, oxidative stress, and impaired central insulin signaling, thereby contributing to synaptic dysfunction and cognitive decline [34–36].

An observational study from the Alzheimer's Disease Neuroimaging Initiative cohort reported that dyslipidemia has been associated with increased amyloid burden and accelerated cognitive decline [37]. These associations may be explained by several underlying biological mechanisms. High cholesterol, aligned with our results, is linked to Aβ accumulation through cholesterol-rich lipid rafts that facilitate Aβ binding and aggregation at neuronal membranes, leading to membrane toxicity [38]. It may also impair Aβ clearance across the blood–brain barrier, while dyslipidemia-induced inflammation can further exacerbate amyloid related pathology [39,40].

In addition, a prospective longitudinal cohort study demonstrated that greater physical activity and lower vascular risk independently attenuated the negative association of Aβ burden with cognitive decline and neurodegeneration in asymptomatic individuals [41]. Regular physical activity can enhance neurotrophic support, improve perfusion, and promote synaptic plasticity, potentially reducing amyloid-related neurodegeneration [42]. Conversely, Physical inactivity may

Table 2
Interaction between amyloid status and modifiable risk factors in cognitive decline.

Variables	Aβ status × modifiable risk factors interaction			Strata specific results A4 (Aβ+)			LEARN (Aβ−)		
	β (SE†)	95% CI‡	Adjusted P	β (SE†)	95% CI‡	Adjusted P	β (SE†)	95% CI‡	Adjusted P
Low education	−0.147 (0.073)	−0.29 to −0.004	0.34	−0.129 (0.030)	−0.21 to −0.05	<0.001	0.018 (0.066)	−0.15 to 0.19	>0.99
Alcohol use	−0.006 (0.037)	−0.08 to 0.07	>0.99	0.005 (0.018)	−0.04 to 0.05	>0.99	0.011 (0.033)	−0.07 to 0.09	>0.99
Diabetes	−0.206 (0.072)	−0.35 to −0.07	0.032	−0.350 (0.039)	−0.45 to −0.25	<0.001	−0.144 (0.060)	−0.30 to 0.01	0.58
High cholesterol	−0.155 (0.037)	−0.23 to −0.08	<0.001	−0.068 (0.018)	−0.11 to −0.02	0.007	0.088 (0.033)	0.004 to 0.17	0.30
High BP*	0.053 (0.037)	−0.02 to 0.13	>0.99	0.024 (0.018)	−0.02 to 0.07	>0.99	−0.029 (0.033)	−0.11 to 0.05	>0.99
Obesity	0.070 (0.042)	−0.01 to 0.15	0.75	0.094 (0.021)	0.04 to 0.15	<0.001	0.024 (0.036)	−0.07 to 0.12	>0.99
Depressive mood	0.161 (0.133)	−0.10 to 0.42	>0.99	−0.051 (0.070)	−0.23 to 0.13	>0.99	−0.212 (0.113)	−0.50 to 0.08	>0.99
Physical inactivity	−0.161 (0.058)	−0.28 to −0.05	0.046	−0.121 (0.029)	−0.20 to −0.05	0.002	0.039 (0.051)	−0.09 to 0.17	>0.99

* BP: Blood pressure.
† SE: Standard error.
‡ 95% CI:95% Confidence Interval
P values were adjusted using the Bonferroni correction; values exceeding 1 are presented as >0.99.

aggravate amyloid-related cognitive decline by reducing cerebral blood flow, impairing neurotrophic signaling, and increasing systemic inflammation [43]. However, reverse causation should also be considered. Previous literature has shown that declines in physical activity may occur several years prior to the onset of dementia, suggesting that reduced activity may represent an early behavioral manifestation of neurodegenerative processes [44]. Therefore, lower levels of physical activity observed among cognitively unimpaired individuals with elevated amyloid may partly reflect preclinical disease rather than a direct causal effect. Nevertheless, these observations and mechanistic pathways suggest that Aβ+ individuals may be particularly susceptible to the combined effects of metabolic and lifestyle risk factors, highlighting the potential value of targeted preventive interventions in this high-risk group.

These findings may also have implications for precision prevention strategies in preclinical Alzheimer's disease. With the increasing availability of amyloid PET and blood-based biomarkers (e.g., plasma p-tau217 and Aβ42/40), cognitively unimpaired individuals with elevated amyloid may be identified earlier in clinical settings [45]. Our results suggest that metabolic and lifestyle risk factors such as diabetes, dyslipidemia, and physical inactivity may accelerate cognitive decline specifically in Aβ+ individuals. These results raise the possibility that Aβ+ cognitively unimpaired individuals may represent a subgroup who could particularly benefit from early and targeted management of metabolic and lifestyle risk factors. Such interventions may potentially serve as an adjunct strategy alongside emerging anti-amyloid therapies by reducing co-pathological burden. Future studies are needed to determine whether optimizing metabolic and lifestyle factors may enhance the effectiveness of anti-amyloid treatments or improve the cost-effectiveness of amyloid-stratified prevention approaches.

In contrast, although low education was significantly associated with faster cognitive decline in the A4 study (Aβ+), this association was not observed in the LEARN study (Aβ−), and the interaction between low education and amyloid status did not reach statistical significance. One possible explanation is that the proportion of low education was higher in the Aβ+ group than in the Aβ− group (9.8% vs. 6.3%, $p = 0.02$), despite small absolute numbers. Although the mean years of education also differed significantly between groups (16.58 ± 2.73 vs. 16.80 ± 2.58, $p = 0.02$), the absolute difference was small, suggesting limited clinical significance.. This pattern may suggest that education level modifies the cognitive effects of amyloid pathology, with lower education linked to greater vulnerability. Higher education, consistent with the cognitive reserve hypothesis, reduces the impact of elevated amyloid burden, with no benefit when amyloid levels are low [46]. In the preclinical stage, education affects baseline performance or symptom threshold [47], rather than accelerating cognitive decline, which may explain the lack of a significant interaction between education and amyloid status.

Another finding was that the A4 study (mean age = 71.92 years) showed that obesity was positively associated with PACC scores, suggesting slower cognitive decline, consistent with evidence that higher late-life BMI may reduce dementia risk [48,49]. However, this finding should be interpreted cautiously because the relationship between adiposity and cognition in older adults may differ substantially from that observed in midlife populations [50]. A potential mechanism involves improved nutritional status and hormonal pathways, such as leptin, which regulates hippocampal synaptic plasticity and may help reduce the risk of Alzheimer's dementia [48,51]. This pattern is also consistent with the so-called obesity paradox [52,53], in which higher body mass index in late life appears to be associated with a lower risk of dementia. One possible explanation for this paradox is reverse causation, whereby individuals in the early stages of neurodegenerative disease may experience unintentional weight loss prior to the onset of clinically detectable cognitive decline [50,54]. In this context, lower BMI in late life may reflect underlying preclinical disease processes rather than a direct protective effect of adiposity. Sex differences may also influence the relationship between adiposity and cognitive outcomes in preclinical Alzheimer's disease. A cross-sectional analysis of the A4 cohort reported that overweight and obesity were associated with better verbal memory in women but worse global cognition in men [22]. Consistent with these findings, our longitudinal analysis suggests that the association between obesity and cognitive trajectories differs by sex, with a stronger inverse association observed among women. Potential explanations may include sex-related differences in adipose tissue distribution, estrogen metabolism, and inflammatory pathways, although these mechanisms require further investigation. Although obesity was significantly associated with slower cognitive decline in Aβ+ individuals, the interaction between Aβ status and obesity was not significant. This is likely because the Aβ− group showed a similar but smaller, non-significant association, possibly reflecting that the potential protective effects of late-life obesity occur independently of amyloid pathology. Therefore, future studies incorporating longitudinal weight trajectories and metabolic biomarkers are needed to clarify whether the observed association reflects biological protection or prodromal weight loss associated with neurodegeneration.

In contrast, depressive mood and alcohol use were not significantly associated with cognitive decline and amyloid status in our analysis. Several explanations may account for these negative findings. The prevalence of depressive symptoms in this cohort was very low (approximately 2–3%), and depressive symptoms were assessed using a screening tool at a single time point, which may not capture chronic or clinically significant depression that has been linked to cognitive decline in prior studies [55]. Similarly, alcohol use was defined as a binary variable without accounting for dose or long-term exposure, potentially obscuring nonlinear or threshold effects. In addition, blood pressure was assessed using a single baseline measurement without longitudinal variability or treatment status, which may have led to misclassification. Therefore, the absence of significant associations should be interpreted with caution and does not exclude a potential role of these factors in cognitive decline.

This study analyzed two large, well-characterized cohorts with longitudinal cognitive assessments and amyloid PET imaging, enabling direct comparison between Aβ+ and Aβ- individuals. However, this study has several limitations. First, as an observational secondary analysis, causal inference cannot be established and residual confounding may remain. In addition, the Aβ+ and Aβ− groups were derived from two related but separate cohorts (A4 and LEARN) rather than a single cohort stratified by amyloid status. Although both cohorts were derived from a unified screening process, with amyloid-negative individuals from A4 screening enrolled into LEARN, and used standardized cognitive assessments, residual between-cohort differences may still exist. Furthermore, the LEARN study was conducted at a subset of A4 sites and initiated approximately one year later, raising the possibility of secular trends in clinical practice over time. For example, A4 participants were slightly older and had higher APOE ε4 carrier rates than LEARN participants. Although age and APOE ε4 status were included as covariates in the statistical models, such adjustments may not fully capture the complex and potentially nonlinear biological effects of APOE ε4 on amyloid accumulation and cognitive trajectories. Therefore, the observed interactions between amyloid status and modifiable risk factors should be interpreted with caution, as they may partially reflect residual between-cohort confounding. Moreover, detailed site-level information was not available in the publicly released dataset, preventing site-restricted analyses or propensity-score matching. Second, modifiable risk factors were assessed only at baseline. Because longitudinal laboratory measurements were not consistently available across both cohorts, risk factors were defined at baseline to maintain comparability between groups. In addition, detailed information on pharmacological treatments was not consistently available in the publicly released dataset used for this analysis. Moreover, metabolic conditions such as diabetes, hypercholesterolemia, and hypertension are dynamic; incorporating time-varying or cumulative exposure measures

may provide a more accurate characterization of metabolic burden. Third, obesity was defined using a single BMI threshold ($\geq$30 kg/m^2) and modeled as a binary variable, which may obscure potential non-linear or J-shaped associations between adiposity and cognitive decline across obesity classes. Because of limited numbers in higher BMI categories, we used a binary classification consistent with prior A4 analyses. Fourth, the low prevalence of certain risk factors, such as low education, diabetes, and depressive mood, in this study may have limited the statistical power to detect meaningful associations; nevertheless, the positive interaction observed for diabetes is consistent with prior evidence but should be interpreted with care. In addition, the very low prevalence of smoking in this cohort prevented evaluation of this important modifiable risk factor. Fifth, the A4 and LEARN cohorts comprised highly selected participants who were predominantly non-Hispanic White, highly educated, and cognitively intact at baseline. These characteristics, along with the likelihood that participants were more health-conscious, may limit the generalizability of our findings to more diverse populations. Future studies incorporating longitudinal biomarkers, treatment data, and broader populations are needed to clarify how modifiable risk factors interact with amyloid pathology and influence trajectories of preclinical cognitive decline.

5. Conclusion

In conclusion, the significant interactions with amyloid status were observed for diabetes, high cholesterol, and physical inactivity, indicating that these risk factors were associated with faster cognitive decline specifically in Aβ+ individuals. The results suggest that consideration of amyloid status may be important when evaluating the potential role of metabolic and lifestyle risk factors in preclinical cognitive decline. In the A4 study (Aβ+), obesity was associated with a slower rate of cognitive decline and low education appeared to influence baseline cognition or the symptom threshold; however, we did not observe a significant interaction between these factors and amyloid status. Future studies should incorporate amyloid status and longitudinal biomarkers to clarify causal pathways and assess whether modifying these factors can slow preclinical cognitive decline.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT for limited technical assistance in reviewing R scripts. All outputs were reviewed and verified by the authors, who take full responsibility for the content of this publication.

Ethical standards

All procedures performed in the original A4 and LEARN studies were approved by the institutional review boards at each participating site, and all participants provided written informed consent. The present study is a secondary analysis of de-identified data obtained through the A4/LEARN data sharing platform. Therefore, additional institutional review board approval and informed consent were not required for this analysis. The A4 study is registered at ClinicalTrials.gov (Identifier: NCT02008357), and the LEARN study is registered at ClinicalTrials.gov (Identifier: NCT02488720).

CRediT authorship contribution statement

Ying-Hsin Hsu: Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation. **Chih-Kuang Liang:** Validation, Data curation. **Ming-Yueh Chou:** Software, Methodology. **Jaysón Davidson:** Methodology, Data curation. **Yu-Chun Wang:** Data curation. **Mike A. Nalls:** Supervision. **Luigi Ferrucci:** Methodology. **Mark Cookson:** Methodology. **Hirotaka Iwaki:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hirotaka Iwaki reports a relationship with DataTecnica LLC that includes: employment and funding grants. Mike A. Nalls reports a relationship with DataTecnica LLC that includes: employment and funding grants. Mike A. Nalls reports a relationship with Character Bio Inc. that includes: equity or stocks. Mike A. Nalls reports a relationship with Neuron23 Inc. that includes: equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100574.

References

[1] Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet 2024;404(10452):572–628.
[2] Hampel H, Hardy J, Blennow K, et al. The amyloid-β pathway in Alzheimer's disease. Mol Psychiatry 2021;26(10):5481–503.

[3] Jack Jr CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: alzheimer's Association Workgroup. Alzheimers Dement 2024;20(8):5143–69.
[4] Alzheimer's Association. 2025 Alzheimer's disease facts and figures. Alzheimer's & Dementia 2025;21(4). https://doi.org/10.1002/alz.70235.
[5] Pacholko A, Iadecola C. Hypertension, neurodegeneration, and cognitive decline. Hypertension 2024;81(5):991–1007.
[6] Wee J, Sukudom S, Bhat S, et al. The relationship between midlife dyslipidemia and lifetime incidence of dementia: a systematic review and meta-analysis of cohort studies. Alzheimers Dement (Amst) 2023;15(1):e12395.
[7] Sebastian MJ, Khan SK, Pappachan JM, Jeeyavudeen MS. Diabetes and cognitive function: an evidence-based current perspective. World J Diabetes 2023;14(2):92.
[8] Gonneaud J, Bedetti C, Pichet Binette A, et al. Association of education with Aβ burden in preclinical familial and sporadic Alzheimer disease. Neurology 2020;95 (11):e1554–64.
[9] van Arendonk J, Neitzel J, Steketee RM, et al. Diabetes and hypertension are related to amyloid-beta burden in the population-based Rotterdam Study. Brain 2023;146(1):337–48.
[10] Han SM, Byun MS, Yi D, et al. Modulatory effect of blood LDL cholesterol on the association between cerebral Aβ and tau deposition in older adults. J Prev Alzheimers Dis 2024;11(6):1767–74.
[11] Chaudhuri S, Dempsey DA, Huang YN, et al. Association of amyloid and cardiovascular risk with cognition: findings from KBASE. Alzheimers Dement 2024;20(12):8527–40.
[12] Ottoy J, Ozzoude M, Zukotynski K, et al. Vascular burden and cognition: mediating roles of neurodegeneration and amyloid PET. Alzheimers Dement 2023;19(4): 1503–17.
[13] Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in preclinical Alzheimer's disease. N Engl J Med 2023;389(12):1096–107. https://doi.org/ 10.1056/NEJMoa2305032.
[14] Sperling RA, Donohue MC, Rissman RA, et al. Amyloid and tau prediction of cognitive and functional decline in unimpaired older individuals: longitudinal data from the A4 and LEARN studies. J Prev Alzheimers Dis 2024;11(4):802–13. https://doi.org/10.14283/jpad.2024.122.
[15] Royse SK, Minhas DS, Lopresti BJ, et al. Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. Alzheimers Res Ther 2021;13(1):99. https://doi.org/10.1186/s13195-021-00836-1.
[16] Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement 2015;11(1): 1–15. https://doi.org/10.1016/j.jalz.2014.07.003.
[17] ClinicalTrials.gov. Clinical trial of Solanezumab for older individuals who may be at risk for memory loss (A4) (NCT02008357). Updated December 28, 2023. Accessed March 30, 2026. https://clinicaltrials.gov/study/NCT02008357.
[18] American Diabetes Association Professional Practice Committee. Diagnosis and classification of diabetes: standards of care in diabetes-2025. Diabetes Care 2025; 48(Suppl 1):S27–49. https://doi.org/10.2337/dc25-S002.
[19] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73 (24):e285–350.
[20] Vidal-Petiot E. Thresholds for hypertension definition, treatment initiation, and treatment targets: recent guidelines at a glance. Circulation 2022;146(11):805–7.
[21] Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. Nutr Today 2015;50(3):117–28.
[22] Wang X, Sundermann EE, Buckley RF, et al. Sex differences in the associations of obesity with tau, amyloid PET, and cognitive outcomes in preclinical Alzheimer's disease: cross-sectional A4 study. J Alzheimers Dis 2023;95(2):615–24.
[23] Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clinical Gerontology. Routledge; 2014. p. 165–73.
[24] Saint-Maurice PF, Graubard BI, Troiano RP, et al. Estimated number of deaths prevented through increased physical activity among US adults. JAMA Intern Med 2022;182(3):349–52.
[25] Papp KV, Rofael H, Veroff A, et al. Sensitivity of the preclinical Alzheimer's cognitive composite (PACC), PACC5, and repeatable battery for neuropsychological status (RBANS) to amyloid status in preclinical Alzheimer's disease-atabecestat phase 2b/3 EARLY clinical trial. J Prev Alzheimers Dis 2022;9 (2):255–61.
[26] Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Int Neuropsychol Soc 2008;14(2):266–78.
[27] Morris J, Swier-Vosnos A, Woodworth C, Umfleet LG, Czipri S, Kopald B. Development of alternate paragraphs for the Logical Memory subtest of the Wechsler Memory Scale-IV. Appl Neuropsychol: Adult 2014;21(2):143–7.
[28] Rosano C, Perera S, Inzitari M, Newman AB, Longstreth WT, Studenski S. Digit symbol substitution test and future clinical and subclinical disorders of cognition, mobility and mood in older adults. Age Ageing 2016;45(5):688–95.
[29] Folstein MF, Folstein SE, McHugh PR. Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3): 189–98.
[30] Hooper R. To adjust, or not to adjust, for multiple comparisons. J Clin Epidemiol 2025;180:111688.
[31] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc: B (Methodol) 1995;57(1): 289–300.
[32] Dove A, Shang Y, Xu W, et al. The impact of diabetes on cognitive impairment and its progression to dementia. Alzheimers Dement 2021;17(11):1769–78.
[33] Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and cognitive impairment. Curr Diab Rep 2016;16(9):87.
[34] Yoon JH, Hwang J, Son SU, et al. How can insulin resistance cause Alzheimer's disease? Int J Mol Sci 2023;24(4):3506.
[35] Vargas-Soria M, Ramos-Rodriguez JJ, Del Marco A, et al. Accelerated amyloid angiopathy and related vascular alterations in a mixed murine model of Alzheimer s disease and type two diabetes. Fluids Barriers CNS 2022;19(1):88.
[36] Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol 2018;14(3):168–81.
[37] Wang Q, Zang F, He C, Zhang Z, Xie C. Dyslipidemia-induced large-scale network connectivity abnormality facilitates cognitive decline in Alzheimer's disease. J Transl Med 2022;20:567. https://doi.org/10.1186/s12967-022-03786-w.
[38] Rudajev V, Novotny J. Cholesterol as a key player in amyloid β-mediated toxicity in Alzheimer's disease. Front Mol Neurosci 2022;15:937056.
[39] Wang Z, Zhang L, Qin C. Alzheimer's disease pathogenesis: standing at the crossroad of lipid metabolism and immune response. Mol Neurodegener 2025;20 (1):67.
[40] de Lima Oliveira BC, Bellozi PMQ, Reis HJ, de Oliveira ACP. Inflammation as a possible link between dyslipidemia and Alzheimer's disease. Neuroscience 2018; 376:127–41.
[41] Rabin JS, Klein H, Kirn DR, et al. Associations of physical activity and β-amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. JAMA Neurol 2019;76(10):1203–10.
[42] Rashid MH, Zahid MF, Zain S, Kabir A, Hassan SU. The neuroprotective effects of exercise on cognitive decline: a preventive approach to Alzheimer disease. Cureus 2020;12(2):e6958. https://doi.org/10.7759/cureus.6958.
[43] Singh B, Bennett H, Miatke A, et al. Effectiveness of exercise for improving cognition, memory and executive function: a systematic umbrella review and meta-meta-analysis. Br J Sports Med 2025;59(12):866–76.
[44] Sabia S, Dugravot A, Dartigues JF, et al. Physical activity, cognitive decline, and risk of dementia: 28-year follow-up of Whitehall II cohort study. BMJ 2017;357: j2709. https://doi.org/10.1136/bmj.j2709.
[45] Janelidze S, Barthélemy NR, Salvadó G, et al. Plasma phosphorylated tau 217 and Aβ42/40 to predict early brain aβ accumulation in people without cognitive impairment. JAMA Neurol 2024;81(9):947–57.
[46] Roe CM, Mintun MA, D'Angelo G, Xiong C, Grant EA, Morris JC. Alzheimer disease and cognitive reserve: variation of education effect with carbon 11–labeled Pittsburgh Compound B uptake. Arch Neurol 2008;65(11):1467–71.
[47] Sedghi F, Foroughi E, Sheikhzadeh F, et al. Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: a meta-analysis. IBRO Neurosci Rep 2025;19:133–42. https://doi.org/ 10.1016/j.ibneur.2025.05.010.
[48] Sun Z, Wang Z-T, Sun F-R, et al. Late-life obesity is a protective factor for prodromal Alzheimer's disease: a longitudinal study. Aging (Albany NY) 2020;12 (2):2005.
[49] Arvanitakis Z, Capuano AW, Bennett DA, Barnes LL. Body mass index and decline in cognitive function in older black and white persons. J Gerontol: A 2018;73(2): 198–203.
[50] Singh-Manoux A, Dugravot A, Shipley M, et al. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. Alzheimers Dement 2018;14(2):178–86.
[51] Malekizadeh Y, Holiday A, Redfearn D, Ainge JA, Doherty G, Harvey J. A leptin fragment mirrors the cognitive enhancing and neuroprotective actions of leptin. Cereb Cortex 2017;27(10):4769–82.
[52] Zhai W, Zhang G, Wei C, Zhao M, Sun L. The obesity paradox in cognitive decline: impact of BMI dynamics and APOE genotypes across various cognitive status. Diabetes Obes Metab 2025;27(7):3967–83.
[53] Pegueroles J, Jiménez A, Vilaplana E, et al. Obesity and Alzheimer's disease, does the obesity paradox really exist? A magnetic resonance imaging study. Oncotarget 2018;9(78):34691.
[54] Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol 2009;66(3):336–42.
[55] Gatchel JR, Rabin JS, Buckley RF, et al. Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. JAMA Netw Open 2019;2(8):e198964.