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Longitudinal study of Alzheimer's disease biomarkers, allostatic load, and cognition among memory clinic patients

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ABSTRACT

Background: Allostatic load (AL) is defined as the cumulative dysregulation of neuroendocrine, immunological, metabolic, and cardiovascular systems that increases the susceptibility to stress-related health problems. Several dementia and Alzheimer's disease (AD) risk factors have been identified, yet little is known about the role of AL and its associations with AD biomarkers (e.g., beta-amyloid (Aβ) or tau) and cognitive function among memory clinic patients. Hence, this study aims to assess the association between AL and AD biomarkers, cognitive performance, and cognitive decline after 3-years of follow-up.

Methods: Data from 188 memory clinic patients were derived from the Cortisol and Stress in AD (Co-STAR) study in Sweden. Participants underwent baseline assessments including blood tests for AL measures (including cortisol, thyroid stimulating hormone, cobalamin, homocysteine, leukocytes, glycated hemoglobin, albumin, high-density and low-density lipoprotein cholesterol, triglycerides, and creatinine), cerebrospinal fluid (CSF) sampling for AD biomarkers and neuropsychological tests including five cognitive domains. Linear regressions were conducted, adjusting for age, sex, and education.

Results: Higher AL was associated with lower CSF Aβ1-42 levels ($\beta = -0.175$, $p = 0.025$), reflecting higher brain levels of Aβ1-42. Stratified analyses suggested a significant association among women but not men, although the AL-sex interaction was not statistically significant. AL was not significantly associated with T-tau level ($\beta = -0.030$, $p = 0.682$) and P-tau level ($\beta = 0.091$, $p = 0.980$). There were no significant associations between AL and cognition or cognitive decline after 3 years.

Conclusion: This study showed that higher AL was associated with increased brain amyloid accumulation. This suggests that AL may play a role in AD/dementia pathophysiology. Potential sex-related differences should be assessed in further larger studies.

1. Introduction

The number of older people, including those living with dementia, is rising, as younger age mortality declines (Livingston et al., 2020). Worldwide around 50 million people live with dementia, and this number is projected to increase to 152 million by 2050, rising

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particularly in low-income and middle-income countries (LMIC) where around two-thirds of people with dementia live (Patterson, 2018). Dementia affects individuals, their families, and the economy, with global costs estimated at about US$1 trillion annually (Patterson, 2018).

Various concepts have been used to study the aging process and its association with neurodegenerative conditions and cognitive impairment. Allostatic load (AL) is defined as the frequent activation and cumulative dysregulation of the neuroendocrine, immunological, metabolic, and cardiovascular systems that increases one's susceptibility to stress-related health problems and diseases (McEwen and Stellar, 1993). As a marker of accelerated aging, AL has been the focus of many gerontological studies due to similarities between the biological mechanisms involved in chronic stress and AD pathophysiology (Matos and Souza-Talarico, 2019).

Different studies reported that high AL scores were associated with older age (Doamekpor and Dinwiddie, 2015) and identified AL as an antecedent to the development of significant health consequences including cognitive impairment, with potential predictive value for cognitive decline (Booth et al., 2015; Juster et al., 2010; Juster et al., 2011b; Karlamangla et al., 2014; Maloney et al., 2009; Narbutas et al., 2019; Seeman et al., 2001). Another study revealed that higher cognitive reserve and lower AL were related to better cognitive efficiency, suggesting that previous lifestyle characteristics and current physiological status may simultaneously explain the variability in cognitive ability (Narbutas et al., 2019). A meta-analysis demonstrated cross-sectional associations between higher AL and poor global cognition and executive function, but not memory (D'Amico et al., 2020). Longitudinal studies have shown that AL was associated with cognitive decline after three years (Seeman et al., 2001) and was inversely associated with processing speed, general cognitive ability, knowledge and performance (Booth et al., 2015; Narbutas et al., 2019).

Studies on AL and cognitive performance to date have been conducted among populations of healthy older adults (Beckie, 2012; Russell and Lightman, 2019). It is therefore currently unknown whether AL has a similar association with cognition among memory clinic patients who already have subjective or objective cognitive impairment. The importance of incorporating an AL index is demonstrated by good prediction of morbidity and mortality in numerous studies among middle aged and older adults (Beckie, 2012; Russell and Lightman, 2019).

According to the AL model, physiological dysregulations start to emerge decades before diseases manifest, and they may assist in identifying individuals at increased risk for cognitive impairment (Juster et al., 2010; Karlamangla et al., 2014; Matos and Souza-Talarico, 2019). Changes in cognitive performance occur 3–7 years prior to mild cognitive impairment (MCI) diagnosis, and up to 10 years before dementia diagnosis (Bateman et al., 2012). Such changes represent a preclinical AD stage when AD brain pathology is already present but clinical symptoms are not evident (Jaewon Jang, 2019). Abnormal Aβ production and deposition is a pathological hallmark of AD and precedes the onset of dementia due to AD by 20–30 years (Bateman et al., 2012; Sperling et al., 2011). Amyloid plaque accumulations are associated with cognitive symptoms due to impairment of synapses that are essential to memory, learning, and decision-making (Fripp et al., 2008). The interplay between AL and AD biomarkers is currently unknown.

Recent discussion has called for sex-based investigation of the etiology of dementia (Nebel et al., 2018). Two thirds of persons diagnosed with AD dementia are women (Association, 2016). In Europe the prevalence of AD in men was 3.31%, and 7.13% in women (Niu et al., 2017). In a systematic review of 62 studies, men appeared to have higher AL than women, and women showed sex-specific variation for numerous factors such as age, race/ethnicity, adversities, social support, and health behaviors that influence the associations between AL and mental health (Kerr et al., 2020).

To the best of our knowledge, little is known about the association between AL, AD biomarkers and cognition among memory clinic patients. The aim of this study was to assess the associations between AL, AD biomarkers, cognitive function, and decline, as well as the potential sex differences in these associations among memory clinic patients.

2. Methods

2.1. Study design and participants

This study is based on the Cortisol and Stress in Alzheimer's disease (Co-STAR) study, a longitudinal observational study investigating the role of stress and lifestyle factors among patients referred to the Memory Clinic at the Karolinska University Hospital, Huddinge (Sweden).

Patients aged 45 years and above attending their first visit at the Karolinska University Hospital Memory Clinic (between 2014 and 2017) were invited to participate in the study. Exclusion criteria were severe sensory impairments (e.g., cognitive, visual, or auditory) or other conditions that would compromise their ability to participate, or conditions affecting hypothalamic-pituitary-adrenal (HPA)-axis activity (e.g. Cushing's disease). A total of 233 participants agreed to participate, and 188 participants provided sufficient data for inclusion in this study. For the follow-up assessments, the goal was to investigate potential cognitive decline among participants with SCI and MCI. Therefore, 123 participants who did not have dementia or AD were invited between February 2018 and May 2019, and 68 participated in the follow-up assessments, after 32 months on average. The follow-up assessment included an abbreviated neuropsychological test battery with a focus on tests that are sensitive to cognitive decline in this population.

3. Standard protocol approvals, registrations and patient consents

The Co-STAR study received ethical approval by the Regional Ethical Review Board (Stockholm) (reference number: (2014/524-31/1). Participants were only included in the data collection if they provided written informed consent.

3.1. Procedures

At the baseline assessment, eligible patients had undergone routine clinical assessments at the memory clinic. This included the collection of information on demographic factors, medical exams, blood samples, measures of cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), genetics, and a comprehensive neuropsychological test battery.

Dementia diagnosis was based on criteria of the International Classification of Diseases 10 revision (World Health Organization, 1992), diagnosis for mild cognitive impairment (MCI) was given according to criteria by Winblad and colleagues (Winblad et al., 2004), which include subjective cognitive complaints, impairment on cognitive tests, no major impairments in daily life activities, and no dementia. Subjective Cognitive Impairment (SCI) was diagnosed when neither dementia nor MCI criteria were fulfilled, but the participant reported perceived cognitive impairment.

Co-STAR participants were additionally provided with a kit for salivary cortisol sampling at home. Participants were instructed to provide saliva samples at six time points on two non-consecutive weekdays. Sampling time points were upon awakening (t1), 30 min (t2) and 60 min (t3) after awakening, at 2:00 p.m. (t4), at 4:00 p.m. (t5), and before going to bed (t6). To avoid contamination, participants were asked not to eat or brush their teeth before sampling. Participants were also provided with journals to document the exact sampling time.

3.2. Cognitive performance

The cognitive performance domains processing speed, memory, working memory, perceptual reasoning and general cognitive functioning were measured using a comprehensive battery of neuropsychological tests. The memory score was based on four tests related to

memory performance: the Rey Auditory Verbal Learning Test (delayed recall) (Bowler, 2013), the Rey Complex Figure test (delayed recall) (McKinlay, 2011), the letter-symbol pairings test (Bettcher et al., 2011), and the Hagman test immediate recall which was developed and is used at the Karolinska University Hospital memory clinic, Huddinge for the assessment of visual memory.

A composite working memory score was calculated from Wechsler's Adult Intelligence Scale Digit Span and Arithmetic, processing speed was assessed with the Wechsler's Adult Intelligence Scale Digit Symbol Substitution Test (Erdodi et al., 2017). Perceptual reasoning was assessed with the perceptual reasoning index from the Wechsler's Adult Intelligence Scale (Block Design and Matrix Reasoning) (Erdodi et al., 2017). The general cognitive functioning score was obtained using four Wechsler Abbreviated Scale of Intelligence (WASI) tests (Block Design, Similarities, Matrix Reasoning, and Information) (Irby and Floyd, 2013). Two of these tests are related to verbal cognition (Similarities and Information), while the other two are related to non-verbal cognition (Ryan et al., 2003). Follow-up data on memory and perceptual reasoning was collected.

3.3. Allostatic load index

The AL index was constructed using 16 biomarkers derived from patients' electronic health records collected within one year prior to the memory clinic visit based on the cut-off points summarized in Supplement Table 1. Variables which were included in the calculation of AL were: systolic blood pressure (SBP), diastolic blood pressure (DBP), cortisol awakening response (CAR; calculated using t1 and t2), cortisol afternoon level (calculated by averaging t5 & t6), cortisol bedtime level (t6), total cortisol output (area under the curve with respect to ground (AUCg), constructed using t1, t2, t4, t5, t6), thyroid stimulating hormone (TSH), cobalamin, homocysteine, leukocytes, glycated hemoglobin (HbA1C), albumin, high-density lipoprotein (HDL) cholesterol, Low-density lipoprotein (LDL) cholesterol, triglycerides, and creatinine.

The AL index score was calculated based on the count of AL biomarkers falling into the high-risk zone and can range from 0 (lowest risk) to 16 (highest risk). The definition of high-risk zones is based on previous research conducted with the count-based AL index (Juster et al., 2010). Participants received a score of one for values above the 75th percentile (high levels) on seven biomarkers (HbA1c, LDL cholesterol, Creatinine, Triglycerides, Homocysteine, SBP, and DBP), values below the 25th percentile (low levels) on three biomarkers (Albumin, HDL, and Cobalamin), values below the 12.5th percentile for Leukocytes and values below the 12.5th or above the 87.5th percentile (high and low levels) on five biomarkers (CAR, cortisol afternoon level, cortisol bedtime level, AUCg cortisol, and TSH) considering that both hypo and hyper states may have negative health effects (Juster et al., 2010).

For all values that fall within normal ranges, the number zero was assigned. Subsequently, all biomarker scores were added to provide the AL index (ranging from 0 to 16) with higher scores representing greater physiological dysregulation.

3.4. AD-related biomarkers

Three CSF biomarkers (Aβ1-42, T-tau, and P-Tau) within the standard assessment protocol at the Karolinska University Hospital memory clinic were included. CSF was obtained by lumbar puncture and Aβ1-42, t-tau and p-tau were measured using procedures previously described for Aβ1-42 (Andreasen et al., 1999) and for t-tau and p-tau (Blennow et al., 1995).

3.5. Data analyses

Before conducting the statistical analyses, diagnostic analyses with the Shapiro-Wilk test were performed to ascertain whether the scores were normally distributed. Additionally, each regression model was tested for multicollinearity using the Variance Inflation Factor statistic, homoscedasticity generating a scatter plot with standardized residuals versus standardized predictors, and independence of errors by applying the Durbin- Watson statistic. Zero-skewness log-transformations were performed for T-tau and P-tau due to non-normal distribution.

The AL index can range between 0 and 16. The mean AL of the study sample was 5.1 (SD = 1.8), with scores ranging from 1 to 9. In this sample, the AL scores were not normally distributed. However, the kurtosis and skewness were in the acceptable range (skewness = −0.164, kurtosis = −0.673).

Linear regression analyses were performed to assess the associations between AL, cognition, cognitive decline, and AD biomarkers. Analyses were adjusted for age, sex, and education (the standard covariates in the AL and cognitive impairment literature (Juster et al., 2010)). Little's test was performed for all continuous and categorical variables included in the analyses and showed that the type of missingness was missing completely at random. Sensitivity analysis which aimed to determine whether the model results were influenced by inclusion of all participants was undertaken and results were similar when restricting analysis to participants with 13 or more AL biomarkers. The statistical analyses were performed using the IBM SPSS Statistics for Mac (Version 27.0) program, except for zero skewness log transformations that were performed with STATA 15.

4. Results

4.1. Baseline characteristics of the study population

A total of 188 participants aged from 46 to 85 years at recruitment (Mean ± SD = 62.69 ± 8.12) were included in this analysis. Education ranged between 7 and 26 years of studies (Mean ± SD = 14 ± 3.27), and a slight majority of participants were women (59.6%). In addition, 68 (36.2%) were diagnosed with SCI, 78 (41.5%) were diagnosed with MCI, and 38 (20.3%) were diagnosed with AD (Table 1).

4.2. Associations between AL and AD biomarkers (at baseline)

Multiple regression analyses showed that there was a significant association between AL and $A\beta_{1\text{-}42\ level}$ ($\beta = -0.175$, p = 0.025); the higher individuals scored on the AL index, the lower their CSF Aβ1-42

Table 1
Baseline characteristics of participants.

Baseline Variables (continuous)	n	(Mean ± SD)
Age (range 46–85 Years)	188	62.7 ± 8.1
Education (years) (range 7–26 Years)	188	14 ± 3.3
Follow up time (range 456–1556 days)	64	978.5 ± 263.8
AD Biomarkers		
$A\beta_{1\text{-}42}$ (ng/L) (range 256–1450)	163	718 ± 250.0
T-tau (ng/L) (range 4.57–7.33)	163	5.75 ± 0.6
P-tau (ng/L) (range 2.83–5.14)	163	3.79 ± 0.4
Cognition		
General cognition (range −2.93-1.0)	146	−0.8 ± 1.3
Processing speed (range −3.79-2.56)	146	−0.8 ± 1.3
Working memory (range −2.96-4.14)	128	−0.7 ± 1.0
Memory (range −4.17-1.29)	156	−1.1 ± 1.4
Perceptual reasoning (range −2.88-1.34)	149	−0.5 ± 1.0
Baseline Variables (categorical)	n	%
Sex	188	
Men	76	40.4
Women	112	59.6
Diagnosis	187	
SCI	68	36.4
MCI	78	41.7
AD	38	20.3
Other Dementia	3	1.6

Note: $A\beta_{1\text{-}42}$ = amyloid-beta peptide; AD = Alzheimer's disease; P-tau = Phosphorylated-tau; MCI = mild cognitive impairment; T-tau = total tau.

level, which indicates higher brain Aβ1-42 level. However, there was no significant associations between AL and T-tau levels (β = −0.030, p = 0.682) or P-tau levels (β = 0.091, p = 0.980) (Table 2). To assess whether the associations were sex-specific, we performed additional linear regressions separately for women and men and found significant association between AL and Aβ1-42 (β = −0.260, p = 0.010) among women. We also assessed the potential interaction between AL and sex in the associations with the AD biomarkers and found no significant interactions (Aβ1-42 (β = −0.051, p = 0.837), T-tau levels (β = 0.238, p = 0.299) or P-tau levels (β = 0.268, p = 0.258)).

4.3. Associations between AL and cognitive function (at baseline)

Results from multiple linear regression analyses showed no significant associations between AL and general cognitive functioning (β = 0.09, p = 0.180), processing speed (β = 0.03, p = 0.683), working memory (β = 0.027, p = 0.759), memory (β = −0.014, p = 0.842), and perceptual reasoning (β = 0.03, p = 0.645).

4.4. Associations between AL and cognitive decline (at follow-up)

There were no significant associations between baseline AL and change in memory (β = −0.159, p = 0.266) or processing speed (β = 0.176, p = 0.228) in the longitudinal analyses (Table 3). Additional stratified linear regressions for women and men showed similar results (p-values >0.05). Other cognitive domains were not measured at the follow-up assessment.

To assess whether there were interactions between AL and AD biomarkers in the associations with cognition, interaction terms were added to the linear regression models (results not presented in a table). In the first model (with no interaction terms), results showed significant associations between CSF Aβ1-42 and general cognition (β = 0.243, p = 0.001), working memory (β = 0.241, p = 0.014) and memory (β = 0.475, p < 0.001) as expected. Similarly, significant associations were observed for T-tau; higher CSF T-tau levels were associated with lower memory scores (β = −0.20, p = 0.016). No significant associations were observed for P-Tau levels. There were no statistically significant interactions between AL and AD biomarkers in relation to any cognitive measures. Furthermore, analyses were re-run separately for women and men, and results were similar.

5. Discussion

This study investigated the associations between AL, CSF AD biomarkers and cognitive function cross-sectionally, the associations between AL and cognitive decline, and potential sex differences. Results showed that higher AL was associated with lower CSF Aβ1-42 levels, which reflect higher brain levels of Aβ1-42. Stratified analyses showed that AL was significantly associated with Aβ1-42 levels among women, but not among men. AL was not significantly associated with T-tau or P-tau levels or cognition. There were no interaction effects between AL and sex in relation to CSF AD biomarkers, or between AL and CSF biomarkers in relation to cognition.

Table 2
Associations between AL and AD biomarkers.

	$A\beta_{1-42}$		T-tau		P-tau	
Variables	β	P-value	β	P-value	β	P-value
AL (total sample) (n = 163)[a]	−0.175*	0.025	−0.030	0.682	−0.002	0.980
AL (women) (n = 97)	−0.260*	0.010	0.185	0.070	0.195	0.056
AL (men) (n = 66)	−0.183	0.141	−0.065	0.605	−0.055	0.660
AL × sex interaction (n = 163)	−0.051	0.837	0.238	0.299	0.268	0.258

β = standardized beta, *$p < 0.05$.
[a] Adjusted for age, sex, and education.

To the best of our knowledge, studies that identify an association between AL and the AD biomarker Aβ1-42 are rare, and this study provides an important contribution to the current literature on AL and AD. There are several possible reasons explaining this association, based on available evidence on the role of individual AL components in AD/dementia risk. For example, HPA-axis biomarkers, which were given a higher representation in our AL formulation, have been associated with AD pathology markers in human and animal studies (Sami Ouanes, 2019). Diabetes has been previously linked to increased dementia risk (Xue et al., 2019) although there are conflicting findings on whether elevated HbA1c and insulin resistance are related to brain amyloid accumulation and AD pathology (Kellar et al., 2022). There are similar patterns for studies linking hypercholesterolemia or hypertension to increased risk of AD/dementia, but their associations with AD pathophysiology are not yet fully clarified (Kivipelto et al., 2018). Elevated homocysteine has also been shown to contribute to increased AD pathology (Hooshmand et al., 2013).

Given that the current evidence on associations of individual AL components and AD pathology is often inconsistent, it is possible that, as a combined index accounting for multiple biomarkers with potential relevance for both AD pathophysiology and aging, AL may be a better reflection of the overall role of all these biomarkers taken together. Compared with individual biomarkers, AL may be a more accurate indicator of ongoing complex disease processes such as Aβ accumulation in the brain, a central feature of AD. Since CSF biomarker data were only available at baseline, and this is a memory clinic sample, it was not possible to assess whether a dysregulated AL profile increases the risk of future AD pathology development, or if it merely reflects already ongoing disease processes.

Interestingly, the association between higher AL and lower CSF Aβ1-42 reflecting increased brain amyloid accumulation was significant among women, but not among men. Although the corresponding AL-sex interaction was not significant, the small sample size may have reduced the statistical power to detect significant differences between men and women. Considering that two-thirds of individuals living with AD are women, these findings warrant further investigation (Alzheimer's disease facts and figures, 2020). Women may have different vascular, metabolic, lifestyle, psychiatric and psychosocial risk factors throughout the life course (Ferretti et al., 2020). Further research is needed on the underlying mechanisms to identify potential sex-related differences with particular relevance for early identification of AD pathology, and prevention of cognitive decline/dementia.

While higher AL was related to lower CSF Aβ1-42, and lower Aβ1-42 was related to poor cognition, AL was surprisingly not associated with global or domain-specific cognition at baseline or change in cognition during the 3-year follow-up. This is in contrast to results from previous studies, where higher AL was cross-sectionally associated with poorer global and domain-specific cognitive performance, and longitudinally associated with cognitive decline during follow-up of up to 12 years (Booth et al., 2015; D'Amico et al., 2020; Karlamangla et al., 2014; Narbutas et al., 2019; Oi and Haas, 2019; Seeman et al., 2001; Seeman et al., 1997). Our results may be due to several reasons: the cognitive status among participants in the current memory clinic sample was not comparable to the primarily high-functioning general population cohorts included in previous studies; the small sample size may have limited the statistical power to detect associations with cognition; the use of different cognitive measures, i.e. cognitive domains in this study were assessed using multiple (not single) tests, as composite measures are considered more reliable to measure cognition; and follow-up time was relatively short (up to 3 years).

It is noteworthy that in the AL research field, there is vast heterogeneity in its operationalization (Beckie, 2012), including the types and number of parameters, which may lead to diverse findings. After the first

Table 3
Association between allostatic load and cognitive function.

Variables	General cognition n = 146		Perceptual Reasoning n = 149		Working Memory n = 128		Memory				Processing Speed			
							Baseline (n = 156)		At follow-up (n = 57)		Baseline (n = 146)		At follow-up (n = 53)	
	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
AL	0.090	0.180	0.033	0.645	0.027	0.759	−0.014	0.842	−0.159	0.266	0.030	0.683	0.176	0.228

β = standardized beta.
Adjusted for age, sex, and education.

AL algorithm was developed with 10 biomarkers (Seeman et al., 1997), it has been modified on the basis of available data to encompass different number of biomarkers (Crimmins et al., 2007; Doamekpor and Dinwiddie, 2015). Although this flexibility has allowed for its measurement in a wider range of datasets, more standardization would allow for better comparisons of results across studies.

The scoring of AL may need further adaptations and tailoring to memory clinic patients, and more detailed delineation of the time course of AL and AD/dementia biomarkers (Juster et al., 2011a). For instance, it is unlikely that each biomarker contributes equally to AL. Our AL formulation considered a higher representation of HPA-axis biomarkers, which is consistent with theoretical AL literature (Juster et al., 2011). With the traditional count-based AL approach, each score is derived using a threshold demarcating the high-risk end of the distribution for each biomarker (75th or 25th percentile) based on the given sample. Moving forward, further exploration of these parameters and their weighting is warranted.

The limitations of our study include the small sample size, which limited statistical power. The analyses on AD biomarkers were cross-sectional, which limited our ability to infer causality within the associations. In addition, due to the lower statistical power, we did not adjust our analysis for comorbidities, such as physical and mental conditions. Finally, as the interest of the study was to assess cognitive decline at follow-up, and due to the availability of resources, participants performed an abbreviated neuropsychological test battery and did not undergo a full diagnostic assessment including MRI and CSF sampling, which prevented us from identifying those who may have developed AD at the follow-up. Nevertheless, the main strengths of our study were that it was the first study to investigate the association between AL and CSF AD biomarkers, based on a representative sample of memory clinic patients covering the entire cognitive continuum from SCI to AD. Our AL measure included various important AL biomarkers, including salivary cortisol. Cognition included measures from several cognitive domains, cerebrospinal measures were available for the measurement of AD biomarkers.

6. Conclusion

This study showed that higher AL was associated with increased brain amyloid accumulation, with potential sex-related differences. AL was not associated with cognition or CSF T-Tau and P-Tau, which suggests potentially distinct pathophysiological correlates. Early identification of individuals with altered AL biomarkers may help identify ongoing AD-related disease processes that increase the risk for cognitive decline and may be important when designing preventive interventions. Our results need to be replicated in large longitudinal studies, with a longer follow-up duration and different populations. Further research should also explore adaptations in the weighting of AL biomarkers, and how they affect relationships between AL, AD biomarkers and cognition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data access (data dictionary and de-identified data) is subject to the GEDOC legal framework. Requests with study plan will be assessed on a case-by-case basis. An access agreement will be required.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bbih.2023.100592.

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