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Original Article

Poor glymphatic function is associated with mild cognitive impairment and its progression to Alzheimer's disease: A DTI-ALPS study

Cuiping Bao[a], Hongbin Luo[b], Jiao Wang[c,d], Xuehuan Liu[a], Yiming Li[a], Jun Yang[a], Chong Chen[e], Rongrong Yang[f], Weili Ba[a], Xinying Lian[g], Michelle Dunk[d], Jun Liu[g,h,i,*], Weili Xu[d]

[a] Department of Radiology, Tianjin Union Medical Center, The First Affiliated Hospital of Nankai University, Tianjin 300121, China
[b] Tianjin Jinnan District Center for Disease Control and Prevention, 28 Highway Road, Jinnan District, Tianjin 300350, China
[c] Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, China; National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China
[d] Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Skockholm, Sweden
[e] Department of Clinical Laboratory, Tianjin Union Medical Center, The First Affiliated Hospital of Nankai University, Tianjin 300121, China.
[f] Public Health Science and Engineering College, Tianjin University of Traditional Chinese Medicine, Tianjin, China.
[g] Tianjin Fourth Central Hospital, The Affiliated Hospital of Tianjin Medical University, Zhongshan Rord 1st Tianjin 300140, China
[h] Tianjin Fourth Central Hospital, Tianjin University, Zhongshan Rord 1st, Tianjin 300140, China
[i] The Institute of Translational Medicine, Tianjin Union Medical Center, The First Affiliated Hospital of Nankai University, Tianjin, 300121, China

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ABSTRACT

Background: We aimed to explore the association between ALPS index and both risks of MCI from cognitively normal (CN) and incident AD progressed from MCI, as well as potential mediating factors.

Methods: This study included 519 adults including 253 (48.75 %) CN and 266 (51.25 %) MCI participants from Alzheimer's Disease Neuroimaging Initiative. Glymphatic function (assessed by along the perivascular space [ALPS] index) was measured by diffusion tensor image at baseline. Neurobiomarkers (Aβ and tau from CSF, plasma and PET) and cognitive functions were served as mediators. Data were analyzed using Cox and Laplace regression and mediation analysis.

Results: During follow-up (median 3.6 years, interquartile range [IQR]: 2.0–4.9 years), 30 (11.86 %) participants developed MCI in the CN cohort and 73 (27.4 %) participants progressed to AD in the MCI cohort. The hazard ratios (95 % confidence intervals [CIs]) of the higher ALPS index was 0.605 (0.386–0.948) for MCI and 0.501 (0.356–0.706) for AD. In addition, participants with high ALPS index had 3.837 and 3.466 years prolonged onset of MCI and AD, separately. Aβ in choroid plexus (17.1 %), tau in cortex [Inferiortemporal (21.1 %), Middletemporal (AV1451:17.0 %, FTP:15.5 %), Superiortemporal(7.7 %), Meta_temporal (AV1451:17.5 %, FTP:16.6 %)], and executive function (14.1 %) mediated the association between ALPS and MCI-AD progression.

Conclusion: High ALPS index decreases MCI risk and delays MCI progression to AD by approximately 3.5 years. Aβ in choroid plexus, tau in cortex, and executive function may partially mediate the MCI-AD progression in relation to ALPS index.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting millions of individuals worldwide. It is characterized by progressive cognitive decline, memory loss, and functional impairment, leading to significant challenges for patients, caregivers, and healthcare systems [1]. The pathophysiology of cognitive dysfunction and AD involves the accumulation of neurotoxic proteins, including amyloid-beta (Aβ) and neurofibrillary tangles of hyperphosphorylated tau, which disrupt neuronal function and contribute to neurodegeneration [2]. The glymphatic and meningeal lymphatic systems are crucial for clearing metabolic waste from cerebrospinal fluid (CSF) in the brain, and their dysfunction, particularly regarding the accumulation of Aβ and extracellular tau, may contribute to Alzheimer's disease (AD)[3–10].

Magnetic resonance imaging by infusion of gadolinium-based contrast agents is the gold standard for assessing glymphatic function [11,12]. However, the invasive nature of the contrast agent injection

* Corresponding author at: Tianjin Fourth Central Hospital, The Affiliated Hospital of Tianjin Medical University, Tianjin Fourth Central Hospital, Tianjin University, Zhongshan Rord 1st, Tianjin 300140, China. The Institute of Translational Medicine, Tianjin Union Medical Center, The First Affiliated Hospital of Nankai University, Tianjin, 300121, China.
E-mail address: cjr.liujun@vip.163.com (J. Liu).

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method has limited its applications in clinical settings. Recently, Taoka et al. developed a method to measure diffusivity along the perivascular space (ALPS) based on diffusion tensor images, which allows for non-invasive and efficient assessment of glymphatic function [13]. This approach quantifies the diffusion of water within the perivascular space along deep medullary veins and has been correlated with glymphatic clearance by dynamic contrast-enhanced imaging [14]. Recent studies have shown that the ALPS index is associated with cognitive decline, AD, and multiple neurological disorders, and might serve as a biomarker for neurodegenerative diseases [15–23]. However, no studies have been conducted on the association of ALPS index with MCI and its progression to AD.

Studies have shown that ALPS index is negatively associated with AD-related Aβ and tau deposition [22,23]. A recent study reported that the association between the ALPS index and cognitive decline was mediated by Aβ PET and brain atrophy [23]. hHowever, limited studies are currently available on the role of Aβ and tau deposition in the association between the ALPS index and the progression from MCI to AD.

In the present study, to clarify the relationship between the glymphatic function and MCI-AD progression using data from ADNI, we sought to: 1) analyze the association between glymphatic function, assessed by ALPS index and risk of MCI and its progression to AD; 2) examine the mediating role of cognitive biomarkers in the progression from MCI to AD in relation to ALPS index.

2. Methods

2.1. Study population

The participants included in this study were from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/). The ADNI was launched in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. ADNI is a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD). We included all cognitively normal control participants (CN) and MCI participants with diffusion tensor imaging (DTI) from ADNI and then selected a second subset of participants with follow-up diagnostic information for longitudinal analysis. The inclusion criteria were as follows: [1] complete clear diffusion tensor imaging (DTI); [2] multiple DTI examinations, and only the first DTI examination were included in the study; [3] DTI was acquired using the same diffusion sensitivity factor (b = 0 s/mm2 and b = 1000 s/mm2); [4] The participants with follow up and data whose follow-up time was longer than 6 months. The exclusion criteria were as follows: [1] Participants with a history of stroke; [2] Baseline diagnosis of AD; [3] The diagnosis was inversed during follow-up.

In the present study, we finally selected 266 participants with MCI and 253 cognitively normal participants (CN). Written informed consent was obtained from all participants, authorized representatives, and study partners before any protocol-specific procedures in the ADNI study.

2.2. Data collection

The ADNI database collected information on demographic data (age, sex, education, weight, and height) and medical history (apolipoprotein E [APOE] ε4 genotype, stroke history, and hypertension) of the participants. APOE ε4 carrier status was categorized as negative and positive. Stroke history was defined as a self-reported history of stroke. Hypertension was defined as a self-reported history of hypertension. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2).

2.3. Assessments of MCI and AD

The assessments of MCI and AD were previously reported [24]. Briefly, the inclusion criteria of MCI were the following:[1] one or more cognitive domain (memory, language or speed, executive function) scores were below the standard deviation of the age/education corrected normative mean and the cognitive domains were found to be impaired; [2] The Functional Activities Questionnaire (FAQ) scores ≥ 9. The assessments AD was according to diagnostic criteria by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) working group.

During the follow-up period, participants who were initially cognitively normal and subsequently experienced cognitive decline, leading to a diagnosis of MCI, were defined to have reached the endpoint event of disease progression; Participants with MCI experienced disease progression and were diagnosed with AD were considered to have reached the endpoint event.

2.4. Neuropsychological assessment

Four domains of cognitive function were assessed in ADNI: memory function (ADNI_MEM), executive function (ADNI_EXF), language function (ADNI_LAN), and visual function (ADNI_VSP). The details of their measurement were from Cognitive Composite Scores as follows:

ADNI_MEM was evaluated using several assessments, including Rey Auditory Verbal Learning Test (AVLT), Alzheimer's Disease Assessment Scale (ADAS)-Cognitive Behavior, Logical Memory and Mini-Mental State Examination (MMSE). ADNI_EXF included Category Fluency-animals, Category Fluency-vegetables, Trails A and B, Digit span backward, WAIS-R Digit Symbol Substitution, and 5 Clock Drawing items (circle, symbol, numbers, hands, time). ADNI_LAN comprised the Neuropsychological Battery, ADAS-Cognitive Behavior, MMSE and MoCA. ADNI_VSP was assessed using the Neuropsychological Battery, ADAS-Cognitive Behavior and MMSE.

2.5. MRI acquisition and preprocessing

In the present study, DTI data were acquired for all participants using 3-T scanners, and the imaging protocol can be found in the open-source document (https://adni.loni.usc.edu/methods/documents/mriprotocols/).

2.6. ALPS index calculated by DTI

We first performed DTI image preprocessing, which included top-up correction, eddy-current correction, head motion correction and bias field correction. Preprocessing was performed using DSI Studio (version 2022), which has high reliability and repeatability [25]. We then generated diffusivity maps. Diffusivity maps in the x-axis (Dxx), y-axis (Dyy) and z-axis (Dzz) directions and color-coded fractional anisotropy (FA) maps were generated in DSI Studio. ITK-SNAP (version 3.8, www.itk-snap.org) was used to generate circular ROIs (diameter, 3 voxels) in the projection and association areas at the level of the lateral ventricle body, and diffusivity in the x, y, and z directions was measured.

DTI ALPS index was calculated according to the method proposed by Taoka et al [13]. The calculation formula is a ratio of the mean diffusivity in the projection fibers (Dxx_proj) and association fibers (Dxx_assoc) on the x-axis to the diffusivity in the projection fibers (Dyy_proj) on the y-axis and the association fibers (Dzz_assoc) on the z-axis (Supplementary Figure 1). We calculated the left- and right-side ALPS index using the formula:

$$ALPS\ index\ = mean(\mathrm{Dxx\_proj},\ \mathrm{Dxx\_assoc})/\mathrm{mean}(\mathrm{Dyy\_proj}, \mathrm{Dzz\_assoc})$$

Then we calculated the average bilateral ALPS index for analysis. The ALPS index was operationalized as both a continuous (lower ALPS index indicating poor lymphatic function) and a categorical variable (low,

moderate, and high tertiles; reference: low), with the low ALPS index tertile representing poor lymphatic function. The ALPS index were converted to z-scores before regression analysis.

2.7. CSF, plasma, and PET biomarkers

The CSF biomarkers contained Aβ42, t-tau, and p-tau181. The CSF concentrations were measured following a Roche Study Protocol at the UPenn/ADNI Biomarker Laboratory [26–28]. Plasma axonal protein neurofilament light (NFL) was analyzed by the Single Molecule array (Simoa) technique. The assay uses a combination of monoclonal antibodies and purified bovine NFL as a calibrator. All samples were above the limit of detection and measured as duplicate, analytical sensitivity was <1 pg/mL [29].

A subset of participants provided eligible positron emission tomography (PET) data, consisting of Aβ ([18F] florbetaben (FBB), [18F] florbetapir (FBP)) and tau ([18F] flortaucipir (FTP, image smoothing with 6 mm resolution), and [18F] AV1451 (image smoothing with 8 mm resolution)) measurements. PET data were preprocessed using a native-space structural MRI scan that is closest in time to each amyloid PET scan. The MRI is first segmented and parcellated with Freesurfer and then coregistered to the amyloid PET image with SPM. The mean standard uptake value ratio (SUVR) of targeted ROIs was calculated by dividing the tracer uptake in these regions by the value in a predefined reference region. For Aβ, we analyzed the cortical SUVR (Choroid_Plexus, CSF, Caudalmiddlefrontal, Frontalpole, Inferiortemporal, Lateralorbitofrontal, Medialorbitofrontal, Middletemporal, Rostralmiddlefrontal, Superiorfrontal, Temporalpole, Transversetemporal, Superiortemporal, Summary). The cortical summary region is made up of frontal, anterior/posterior, cingulate, lateral parietal, and lateral temporal regions). For tau, we analyzed the cortical SUVR (Choroid_plexus, CSF, Inferiorparietal, Inferior temporal, Lateraloccipital, Lateralorbitofrontal, Medialorbitofrontal, Middletemporal, Rostralmiddlefrontal, Superiorfrontal, Superiorparietal, Superior temporal, Temporalpole, Transversetemporal, Meta_temporal).

2.8. Statistical analysis

Student's t-test was used to compare means of continuous variables with a normal distribution. The Mann-Whitney test was used for continuous variables that were not normally distributed. Chi-square test was used to compare composition ratio for categorical variables.

Hazard ratios (HRs) and 95 % confidence intervals (CIs) for the incidence of MCI in CN cohort and AD in MCI cohort in relation to ALPS index (as continuous and tertiled variables) were estimated using Cox regressions. Follow-up time was defined as the time from study entry to the first occurrence of MCI/AD or the last follow-up. Restricted cubic spline curves with 4 knots at the 5th, 35th, 65th, and 95th percentiles were used to analyze the non-linear association between ALPS index and risk of MCI/AD. The 50th percentile differences and 95 % CIs for the onset of MCI/AD between different ALPS index levels were estimated using Laplace regression. All analyses were adjusted for age, sex, education, BMI, hypertension, and APOE ε4 carrier status.

Correlation analyses were used to analyze the association between ALPS index and neurobiomarkers and cognitive functions. Mediation analysis for the association of ALPS index (exposure) with AD (outcome) through the neurobiomarkers and cognitive functions (mediator) was evaluated by the 2-stage regression method for survival data proposed by VanderWeele [30]. Generally, two regression models are established for the mediation analysis, one was a linear regression model for the mediator variable, and the other was a Cox regression model for the outcome variable. The estimates for the effect size of mediation were obtained according to parameter estimates and standard errors.

We performed sensitivity analyses by repeating the main analyses after 1) excluding follow-up time below 1 year; 2) excluding age over 85 years old; 3) stratified by sex, age, and APOE ε4 carrier status. All analyses were performed with R 3.6.2 and Stata SE 15.0 for Windows (StataCorp). The level of statistical significance for the two-tailed test of each hypothesis was set at $P<0.05$.

3. Results

3.1. Baseline characteristics

At baseline, a total of 519 participants fulfilled the initial inclusion criteria (Supplementary Figure 2). During follow-up, 30 participants in the CN cohort developed MCI, and 73 participants in the MCI cohort developed AD.

Among them, 266 (51.25 %) were in the MCI cohort and 253 (48.75 %) were in the CN cohort. Among the CN participants, 112 (44.5 %) were male, and the mean (SD) age was 72.85 (6.8) years. Among the MCI participants, 151 (56.8 %) were male, and the mean (SD) age was 74.01 (7.5) years. In the CN cohort, the ALPS index was lower in participants who developed MCI; In the MCI cohort, the ALPS index was lower in participants who developed AD. Baseline characteristics of the participants by disease progression in the CN cohort and MCI cohort are presented in Supplementary Tables 1,2 and Supplementary Figure 3.

3.2. Association between ALPS index and risk of MCI

During follow-up (median 4.08 years, interquartile range [IQR]: 2.17–5.54 years), 30 (11.86 %) participants in the CN cohort developed MCI. Among those who were CN at baseline, a higher ALPS index (assessed as a continuous variable) was associated with a lower risk of MCI (HR=0.605, 95 % CI 0.386–0.948) in multi-adjusted Cox regression (Table 1). We used restricted cubic splines to construct a flexible multiple adjustment model and visualize the relationship between the ALPS index and the risk of MCI. The results showed a linear relationship (P for nonlinearity=0.482), and the risk of MCI decreased as the ALPS index increased (P=0.034) (Fig. 1A). Further categorical analysis of the ALPS index revealed that, moderate and high ALPS index were associated with a decreased risk of MCI (HR=0.375, 95 % CI:0.143–0.984; HR=0.271, 95 % CI: 0.105–0.698, respectively) compared to low ALPS index, with a significant trend (HR=0.529, 95 % CI: 0.324–0.864, $P<0.001$) (Table 1). Laplace regression analysis revealed moderate and high ALPS index delayed MCI onset by 2.032 (95 % CI: -0.090–4.155) and 3.837 (95 % CI: 0.877–6.798) years, respectively, compared to low ALPS index (Table 1, Fig. 2A).

3.3. Association between ALPS index and progression from MCI to AD

During follow-up (median 2.92 years, IQR: 1.98–4.27 years),73 (27.4 %) participants in the MCI cohort developed AD.

In the MCI cohort, we similarly found that the risk of AD in relation to a lower ALPS index increase (HR=0.501, 95 % CI: 0.356–0.706) in multi-adjusted Cox regression models (Table 1). We used restricted cubic splines to construct a flexible multiple adjustment model and visualize the relationship between the ALPS index and the risk of MCI. The results showed a linear relationship (P for nonlinearity=0.838), and the risk of MCI decreased as the ALPS index increased ($P<0.001$) (Fig. 1B). When we treated ALPS index as a categorical variable, moderate and high ALPS index were also associated with a decreased risk of AD (HR=0.445, 95 % CI: 0.251–0.792; HR=0.359, 95 % CI:0.137–0.942, respectively) compared to low ALPS index, with a significant trend (HR=0.526, 95 % CI: 0.345–0.801, P=0.003). Laplace regression analysis showed that moderate or high ALPS index delayed AD onset by 3.348 (95 % CI: 1.857–4.839) and 3.466 (95 % CI: 0.339–6.594) years, respectively, compared to low ALPS index (Table 1, Fig. 2B).

Table 1
Multi-adjusted hazard ratios (HRs), 50th percentile diferences (PDs, years), and 95 % confdence intervals (95 % CIs) for the association between ALPS index and disease progression analyzed in CN cohort and MCI cohort.

ALPS index	CN cohort			MCI cohort		
	No. of cases	Basic-adjusted HR (95 %CI)[a]	Multi-adjusted HR (95 %CI)[b]	No. of cases	Basic-adjusted HR (95 %CI)[a]	Multi-adjusted HR (95 %CI)[b]
Hazard ratios						
Continuous (per 1 SD increase)	30	0.625 (0.399–0.980)	0.605 (0.386–0.948)	73	0.474 (0.339–0.662)	0.501 (0.356–0.706)
Categorical variable						
Low	10	1.000	1.000	51	1.000	1.000
Moderate	9	0.355 (0.140–0.900)	0.375 (0.143–0.984)	17	0.404 (0.230–0.708)	0.445 (0.251–0.792)
High	11	0.280 (0.108–0.723)	0.271 (0.105–0.698)	5	0.315 (0.123–0.803)	0.359 (0.137–0.942)
P for trend	30	0.534 (0.324–0.879)	0.529 (0.324–0.864)	73	0.484 (0.321–0.730)	0.526 (0.345–0.801)
50th percentile differences						
Continuous (per 1 SD increase)	30	1.330 (0.053–2.607)	1.378 (0.023–2.734)	73	2.378 (1.350–3.407)	2.099 (0.857–3.341)
Categorical variable						
Low	10	1.000	1.000	51	1.000	1.000
Moderate	9	2.125 (0.178–4.073)	2.032 (-0.090–4.155)	17	3.973 (1.555–6.390)	3.348 (1.857–4.839)
High	11	3.902 (1.049–6.755)	3.837 (0.877–6.798)	5	3.183 (-0.063–6.430)	3.466 (0.339–6.594)

HR, Hazard Ratio; CI, confidence interval.
[a] Basic adjustment model, adjusted for age and sex,
[b] multivariate adjustment model, adjusted for age and sex, APOE ε4 carrier status, BMI, hypertension, education.

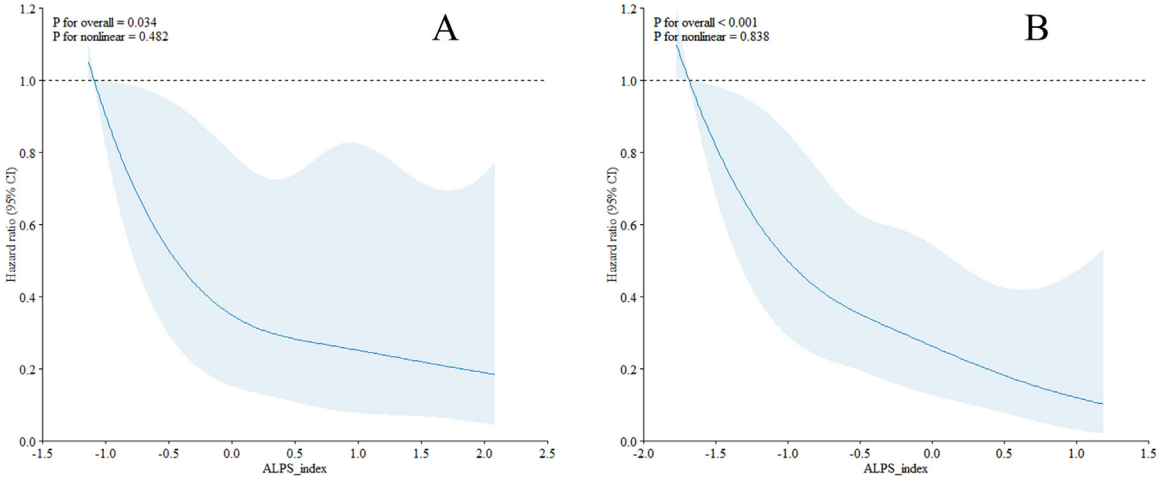

Fig. 1. Association Between ALPS index and MCI and AD using a restricted cubic spline regression.
HRs for MCI and AD according to ALPS index in CN cohort (A) and MCI cohort (B), adjusted for age and sex, APOE ε4 carrier status, hypertension, BMI, education. Data were fitted by a cox regression model, and the model was conducted with 4 knots at the 5th, 35th, 65th, 95th percentiles of ALPS index (reference is the 5th percentile). Solid lines indicate HRs, and shadow shape indicate 95 % CIs. HR, hazard ratio; CI, confidence interval.

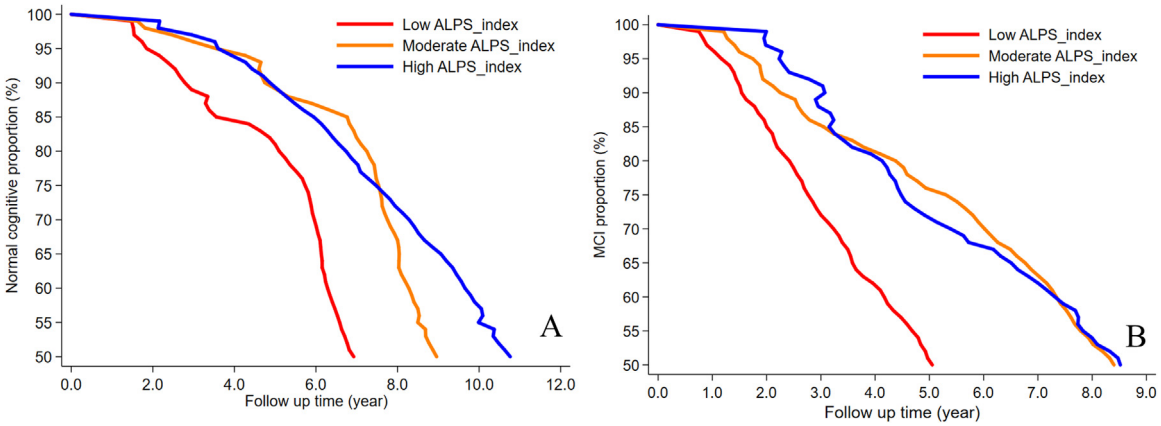

Fig. 2. Laplace regression analysis for 50th percentile differences in years until disease progression in CN cohort (A) and MCI cohort (B).
The model was adjusted for age and sex, APOE ε4 carrier status, hypertension, BMI, education.

Table 2
Hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) for mediating effects of PET SUVR and executive function on the association between ALPS index and incident AD in MCI cohort during follow-up.

Mediating factors	No. of subjects	No. of cases	Total effect HR (95 % CI)[a]	Indirect effect HR (95 % CI)[a]	Direct effect HR (95 % CI)[a]	Percent mediation (%)
Aβ PET in choroid plexus	170	43	0.531 (0.335–0.843)	0.898 (0.773–0.995)	0.557 (0.350–0.885)	17.1
AV1451 PET SUVR						
Middletemporal	168	35	0.366 (0.227–0.592)	0.843 (0.728–0.951)	0.405 (0.248–0.660)	17.0
Superiortemporal	168	35	0.366 (0.227–0.592)	0.926 (0.845–0.994)	0.381 (0.233–0.622)	7.7
Meta_temporal	168	35	0.366 (0.227–0.592)	0.838 (0.709–0.956)	0.403 (0.249–0.652)	17.5
FTP PET SUVR						
Inferiortemporal	162	35	0.369 (0.231–0.590)	0.853 (0.721–0.982)	0.416 (0.262–0.660)	21.1
Middletemporal	162	35	0.369 (0.231–0.590)	0.857 (0.739–0.969)	0.410 (0.255–0.661)	15.5
Meta_temporal	162	35	0.369 (0.231–0.590)	0.847 (0.713–0.982)	0.420 (0.264–0.667)	16.6
Executive function	246	67	0.471 (0.327–0.674)	0.899 (0.796–0.998)	0.543 (0.383–0.772)	14.1

[a] Adjusted for age and sex, APOE ε4 carrier status, BMI, hypertension, education.

3.4. Exploration mediating role of cognitive biomarkers in ALPS-AD associations in MCI cohort

In the correlation analysis, we observed significant associations between the ALPS index and cognitive domain scores (Supplementary Figure 4). In the CN cohort, a higher ALPS index was associated with better memory function (r=0.184). In the MCI cohort, a higher ALPS index was associated with better memory function (r=0.135), executive function (r=0.142), and vision function (r=0.151).

We also found significant associations between ALPS index and multiple pathological markers (Supplementary Figures 5-9). In both the CN cohort and MCI cohort, the ALPS index was related to Aβ and tau in CSF/PET and with NFL in plasma. In the MCI cohort, the ALPS index was positively related to Aβ and tau in CSF and choroid plexus, however, the ALPS index was negatively related with Aβ and tau in part of the cortex (Temporal, inferior temporal, lateral orbitofrontal, middle temporal, superior frontal, inferior parietal, superior temporal, transverse temporal).

In the MCI cohort, we further assessed the mediation analysis for the association of the ALPS index with AD through cognitive biomarkers related to ALPS index during the follow-up period. The mediation analyses revealed that a lower ALPS index was associated with a greater decrease Aβ in choroid plexus evaluated by FBB and FBP PET, a greater increase tau in part of the cortex [tau evaluated by AV1451 PET SUVR (Middle temporal, Superior temporal, and temporal) and FTP PET SUVR (Inferior temporal, Superior temporal, and temporal)] and a greater decrease executive function, both of which were in turn related to a high risk of AD. After controlling for a range of potential confounders, 17.1 % of ALPS-AD association was mediated by decrease Aβ in choroid plexus. Whereas increase tau in part of the cortex mediated ALPS-AD association, and the proportion of mediating effects was above 15 % in both middle temporal and temporal. 14.1 % ALPS-AD association was also mediated by a decrease of executive function. The detailed estimates of the mediation parameters are presented in Table 2 and Fig. 3.

3.5. Sensitivity and subgroup analysis

In the CN cohort and MCI cohort, we performed the sensitivity analysis of ALPS-MCI /AD associations after excluding participants with follow-up time below 1 year or age over 85 years old, and the results were not very different than those from initial analyses (Supplementary Tables 3-4). In the MCI cohort, we further performed stratified analyses, and the associations between ALPS index and AD risk did not vary by sex, age, and APOE ε4 carrier status (Supplementary Tables 5-6). We also assessed the mediating role of baseline cognitive biomarkers in the association between ALPS index and AD risk, and the results were similar to initial analyses (Supplementary Table 7, Supplementary Figure 10).

4. Discussion

In this study, we used the ALPS index to reflect glymphatic function and explore the role of glymphatic dysfunction in the risk of MCI and AD onset. Overall, we found that: [1] Low ALPS index was significantly associated with high risk of MCI, and the risk of MCI decreased linearly with a higher ALPS index; [2] High ALPS index was dose-dependently associated with a decreased progression from MCI to AD [3]. High ALPS index may delay the MCI onset approximately 3.8 years among CN participants and delay MCI progression to AD by approximately 3.5 years in MCI cohort [4]; Aβ in choroid plexus, tau in part of the cortex and executive function partially mediated ALPS-AD association.

At present, there is a lack of research on the relationship between ALPS index and MCI onset and transition from MCI to AD. A few recent studies have reported that a reduction in the ALPS index is associated with an increased risk of MCI and AD [21–23,31], which is in agreement with our findings. Our study showed that a higher ALPS index is associated with a 40 % decreased risk of developing MCI and may delay the MCI onset about 1.4 years among CN participants.We also found that a lower ALPS index was associated with a linear increase in MCI risk. When we performed further tertiled analysis of the ALPS index, the risk of MCI gradually decreased in the second and third tertiles. These results suggested that the glymphatic system in the brain may already be dysfunctional in the early stages of cognitive impairment. Similarly, a case-control study showed that MCI exhibited decreased glymphatic activity compared to control participants [32]. Consistent with our findings, an elderly cohort study reported a significant decrease in the ALPS index among patients with MCI compared to control participants [33]. A study also reported a decrease in the ALPS index among individuals experiencing normal aging-related cognitive decline [34]. However, in contrast to our results, one recent case-control study reported that no significant difference was found between patients with MCI and control participants [21]. This discrepancy may be attributed to the small sample size and the weaker causal relationships in the case-control study. Our results and those of a previous study showed that the risk of progression from MCI to AD gradually increases as the ALPS index decreases. However, there is lack of research on the glymphatic system in the brain

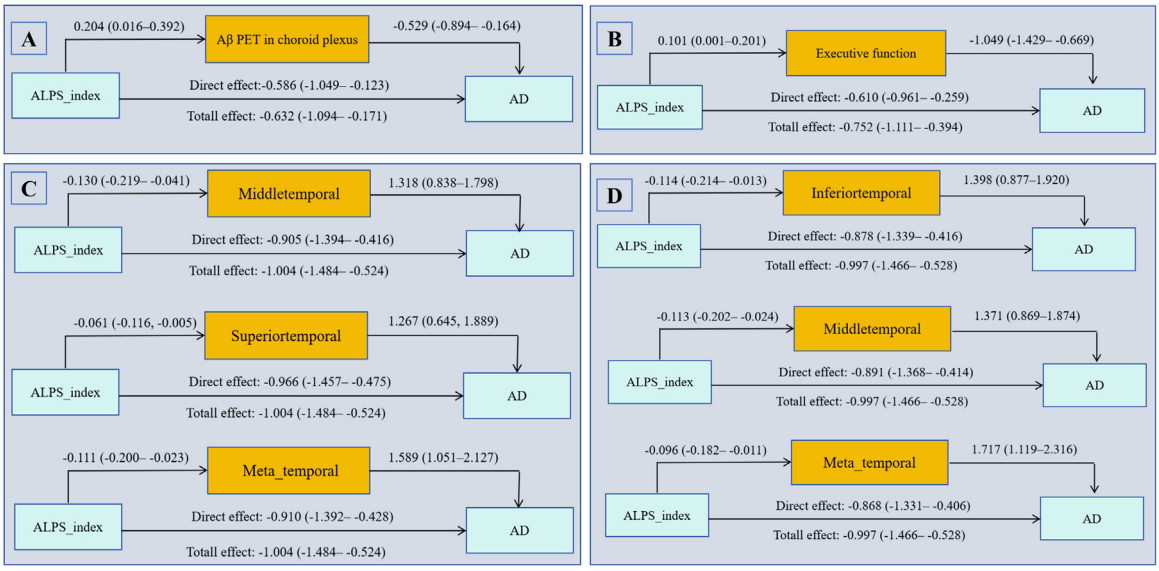

Fig. 3. Mediating effects of PET SUVR and executive function on the association between ALPS index and incident AD in MCI cohort during follow-up. A: Mediator factor is Aβ PET in choroid plexus. B: Mediator factor is Executive function. C: Mediator factor is AV1451 PET SUVR. D: Mediator factor is FTP PET SUVR.

during the stages from MCI to AD. Our study showed that a high ALPS index is associated with a 50 % decreased risk of progression from MCI to AD, and the risk exhibits a negative linear relationship with the ALPS index. A recent study reported that the ALPS index was lower in the preclinical and prodromal stages of AD and significantly lower in AD dementia patients than in MCI patients, even though abnormalities in the ALPS index gradually increased during the late stages of AD [23]. Consistent with this, another study reported a lower ALPS index among young-onset AD patients compared to control [35]. As far as we can ascertain, there was limited study to demonstrate that high ALPS index may delay the progression from MCI to AD. Our study showed that high ALPS index may delay MCI progression to AD by 2 years in MCI cohort.

We further found a significant relationship between the ALPS index and cognitive performance in domain-specific cognitive scales, including significant correlations between the ALPS index and memory function, executive function, and visual function. Notably, the ALPS index was more strongly correlated with the memory domain, which is consistent with findings from a previous study [36,37]. Another recent study also reported that a lower ALPS index was correlated with worse cognitive performance in certain cognitive domains [38]. Our results also showed that ALPS index was associated with multiple pathological markers, including a positive correlation with Aβ in choroid plexus and negative correlation with tau in the cortex. In the mediation analysis we found that the association between ALPS index and risk of AD was partial mediated by Aβ in choroid plexus, tau in brain cortex and executive function. A recent study reported that the ALPS index was significantly correlated with Aβ and tau protein deposition in the bilateral temporal lobe cortex, left and right parietal lobe cortex and posterior cingulate gyrus [39]. Another study reported that the ALPS index functions as a significant mediator of cognitive dysfunction in multiple brain regions (anterior/posterior cingulate cortex, precuneus, and frontal region) that are responsible for attention, memory, and executive function [22]. These findings indicate that the relationship between the glymphatic system and Aβ and tau clearance might play an important role in cognitive dysfunction.

A study of behavioral-variant frontotemporal dementia patients showed that the anterior and middle ALPS indices were related to global cognition and disease severity [40]. The reduction in the ALPS index in individuals with a high risk of AD may be due to the following possible mechanisms. On the one hand, a recent study revealed negative associations between ALPS index and whole-brain Aβ aggregation [37]. Similarly, our study, along with previous research, confirmed that poor glymphatic activity may influence the progression of Aβ deposition in the preclinical stage of AD [41]. The results of an animal study revealed that the glymphatic system is very important for the clearance of tau proteins [42]. In the brains of AD mouse model showed that there was a significant reduction in glymphatic transport prior to extensive Aβ deposition [43]. Another AD mice model reported that increased glymphatic function can decrease Aβ accumulation and enhance memory in the early period of AD [44]. On the other hand, extracellular tau accumulation may be responsible for the glymphatic functional burden. The ALPS index showed negative correlations with the deposition of tau on PET images [22,39]. The results of one animal study showed that long-term exposure to Aβ can further damage the glymphatic system [43]. Therefore, glymphatic dysfunction may be deteriorates due to Aβ and tau protein accumulation in patients with cognitive decline. In summary, the ALPS index leads to the occurrence of Alzheimer's disease through the deposition of Aβ and tau proteins.

Our study has several strengths. Firstly, this population-based, prospective cohort study provides a clearer understanding of causal relationships compared to previous research. Secondly, To the best of our knowledge, this is the first study to demonstrate that high ALPS index may delay MCI progression to AD by 2 years. Thirdly, this study explores the mediating role of AD pathological changes in the relationship between ALPS index and risk of AD. Our study has several limitations. First, participants' DTI images were obtained from different MR scanners and varying scan parameters, which could introduce variability in the ALPS index. Second, although we included a relatively large sample compared with previous studies, the sample sizes for our longitudinal analysis was limited. Third, in the mediation analysis model, due to the limited number of MCI cases,we did not conduct a mediation analysis on the relationship between the ALPS index and the risk of developing MCI. Fourth, the ALPS index was measured manually, which comes with both benefits and drawbacks. While manual assessment of the ALPS index can minimize inaccuracies from automated measurement, it also comes with a risk of inaccuracy due to human error. Fifth, the relatively short follow-up period for some participants may introduce certain biases into the results. Finally, since the study participants may come from different regions or countries, there may be selection bias.

In conclusion, our findings filled a knowledge gap by showing that the ALPS index decreased in MCI and the risk of MCI decreased linearly as the ALPS index increased. The ALPS index could affect transition from

MCI to AD, and delayed the MCI and AD onset. Consequently, our findings add to the growing literature on the important role of glymphatic function in AD development, and posit the ALPS index as a promising novel biomarker for the prevention and treatment of neurodegenerative diseases, warranting further exploration in clinical applications.

Author Contributions

Cuiping Bao, Jun Liu and Weili Xu contributed to the conception and design of the study. Cuiping Bao, Xuehuan Liu, Yiming Li, Jun Yang, Rongrong Yang, Weili Ba and Xinying Lian contributed to the acquisition and analysis of data. Cuiping Bao and Hongbin Luo contributed to drafting the text and preparing the figures. Jiao Wang and Michelle Dunk contributed to the methodology, Writing-review & editing. Jun Liu, Yiming Li and Chong Chen contributed to the Writing-review & editing.

Ethics approval and consent

All procedures conducted in studies involving human participants adhered to the ethical standards set by the Institutional and National Research Committee, as well as the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical guidelines. Written informed consent was obtained from all participants, their authorized representatives, and study partners prior to the implementation of any protocol-specific procedures in the ADNI study. For more information, please visit http://www.adni-info.org.

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.

CRediT authorship contribution statement

Cuiping Bao: Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Hongbin Luo:** Writing – original draft, Methodology. **Jiao Wang:** Writing – review & editing, Methodology. **Xuehuan Liu:** Data curation. **Yiming Li:** Writing – review & editing. **Jun Yang:** Data curation. **Chong Chen:** Writing – review & editing. **Rongrong Yang:** Methodology. **Weili Ba:** Data curation. **Xinying Lian:** Methodology. **Michelle Dunk:** Methodology. **Jun Liu:** Writing – review & editing, Validation, Supervision, Formal analysis, Conceptualization. **Weili Xu:** Formal analysis, Conceptualization.

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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.2025.100156.

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