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Liver function and Alzheimer's brain pathologies: A longitudinal study Liver and Alzheimer's pathologies

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Authors' contributions

JWK and DYL conceived and designed the study. JWK, MSB, DY, JHJ, NK, YYJ, GJ, HA, J-YL, KMK, C-HS, Y-SL, YKK, and DYL were involved in acquisition, or analysis and interpretation of the data and helped to draft the manuscript. JWK, MSB, DY, and DYL were major contributors in writing the manuscript and critically revising the manuscript for intellectual content. DYL served as principal investigator and supervised the study. All authors read and approved the final manuscript.

Declaration of competing interest

No disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2024.100012.

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Abstract

Importance: The neuropathological links underlying the association between changes in liver function and AD have not yet been clearly elucidated.

Objective: We aimed to examine the relationship between liver function markers and longitudinal changes in Alzheimer's disease (AD) core pathologies.

Design: Data from the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease, a longitudinal cohort study initiated in 2014, were utilized.

Setting: Community and memory clinic setting.

Participants: Three hundred forty-seven older adults.

Main Outcome and Measures: Participants underwent baseline and 2-year follow-up evaluations, including liver function assessments and various brain imaging techniques, such as amyloid and tau PET, FDG-PET, and MRI). Liver function indicators [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin] were examined as exposure variables.

Results: Higher baseline ALT levels were associated with a greater increase in beta-amyloid deposition over 2 years [$\beta = 0.166$, Bonferroni-corrected $P\ (P_B) = 0.012$], while lower total bilirubin levels were associated with a greater increase in tau deposition over the same period ($\beta = -0.570$, $P_B < 0.001$). In contrast, AST alone showed no significant association with changes of AD pathologies.

Conclusions and Relevance: The findings suggest a possible link between lower liver function and the accumulation of core AD pathologies in the brain. These results also support the possibility that the liver-brain axis could be a potential target for therapeutic or preventive strategies against AD.

Keywords

alanine aminotransferase; total bilirubin; Alzheimer's disease; Aβ; tau

Introduction

Growing evidence indicates that metabolic disturbances may contribute to Alzheimer's disease (AD) [1]. The liver and its related signaling pathway, as a major metabolic hub [2,3], also has been proposed as a new window to understand the pathogenesis of AD [4–8]. Many human studies have shown association of altered liver function with AD or related dementia [7,9–12]. A cross-sectional study demonstrated that AD dementia was significantly

associated with decreased alanine aminotransferase (ALT) levels [7]. Other cross-sectional studies reported lower [9,10] or higher [13] serum bilirubin in AD dementia patients. Liver cirrhosis was also reported as one of the most common comorbidities of dementia [11]. A longitudinal study showed that frail older adults with a high liver fibrosis score had an increased overall risk of dementia [12].

Nevertheless, the neuropathological links underlying the association between liver function change and AD have not yet been clearly elucidated. Although only one cross-sectional study reported that lower ALT levels were associated with reduced cerebrospinal fluid beta-amyloid protein (Aβ) level [7], little information is available for the relationship between liver function and longitudinal change of AD pathology.

Therefore, we aimed to test the hypothesis that baseline liver function markers are associated with longitudinal changes in in vivo AD core pathologies, such as brain Aβ and tau deposition, using [^{11}C] Pittsburgh compound B (PiB)-positron emission tomography (PET) and [^{18}F] AV-1451 PET scans, respectively, in older adults. As an exploratory analysis, we additionally investigated the association between baseline liver function markers and longitudinal changes in cerebral glucose metabolism (AD-CM) and white matter hyperintensities (WMHs), using [^{18}F] fluorodeoxyglucose (FDG)-PET imaging and MRI, respectively.

Methods

Participants

This study is a component of the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), a continuous prospective cohort study initiated in 2014 [14]. By March 2017, 758 individuals volunteered for the KBASE cohort assessment. Of these, 591 were included in the baseline cohort, while 167 were excluded. The exclusions were due to: meeting exclusion criteria, such as medical, psychiatric, or neurological conditions (63 individuals); not meeting inclusion criteria for any diagnostic group (46 individuals); and withdrawal of consent or loss of contact (58 individuals) [14]. The 591 individuals included in the baseline KBASE cohort consisted of 74 cognitively normal (CN)-young (age 20-54 years), 291 CN-old (age 55-90 years), 139 mild cognitive impairment (MCI), and 87 AD dementia individuals. As of March 2019, we had finally enrolled a total of 347 participants between 55 and 90 years of age who had completed a baseline and 2-year follow-up assessments, including comprehensive clinical assessment, and multimodal neuroimaging scans such as [^{11}C] Pittsburg compound B (PiB)-positron emission tomography (PET), [^{18}F] fluorodeoxyglucose (FDG)-PET, and MRI for the current study. Among them, 73 participants had completed additional [^{18}F] AV-1451 PET scans at baseline and 2-year follow-up visit. The inclusion criteria for the study required participants to be between 55 and 90 years old and to have completed baseline and 2-year follow-up assessments, including clinical evaluation and neuroimaging. Participants also had to meet one of the following cognitive criteria: cognitively normal individuals with a Clinical Dementia Rating (CDR) of 0, without mild cognitive impairment (MCI) or dementia; individuals with amnestic MCI with a CDR of 0.5, meeting the National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines [15]; or individuals with Alzheimer's

disease (AD) dementia with a CDR of 0.5 or 1, meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria [16] and probable AD dementia according to the NIA-AA guidelines [17]. The exclusion criteria were as follows: the presence of a major psychiatric illness; significant neurological or medical conditions that could affect mental function; contraindications for MRI; illiteracy; significant visual or hearing difficulties and/or severe communication or behavioral problems that would make clinical examinations or brain scans difficult; and taking an investigational drug. More detailed information on the recruitment of the KBASE cohort is presented in a previous report from the research group [14].

Standard protocol approvals, registrations, and participants consent

This study protocol was approved by the institutional review boards of the Seoul National University Hospital (C-1401-027-547) and the Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center (26-2015-60), in Seoul, South Korea; and we conducted it in accordance with the recommendations of the current version of the Declaration of Helsinki. All the participants provided written informed consent.

Clinical assessments

Participants underwent standardized clinical and neuropsychological assessments conducted by trained board-certified psychiatrists. The assessments were based on the Korean Brain Aging Study for the KBASE clinical assessment protocol, which incorporated the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) clinical assessment [14]. A clinical neuropsychologist or trained psychometrists also administered a comprehensive neuropsychological assessment battery to the participants, following a standardized protocol that incorporates the CERAD-K neuropsychological battery. Details on the full assessment battery have been previous described [14].

Measurement of liver function markers and blood tests for potential confounders

Blood samples were collected through venipuncture in the morning (between 8 to 9 a.m.) after an overnight fast, at the initial baseline assessment. Serum levels of ALT, aspartate aminotransferase (AST), and total bilirubin were determined using a colorimetric method on the ADVIA 1800 Auto Analyzer by Siemens, located in Washington, DC, USA. Genomic DNA was extracted from whole blood and apolipoprotein E (APOE) genotyping was performed as described [18]. APOE $\varepsilon 4$ (APOE4) positivity was defined as the presence of at least one $\varepsilon 4$ allele.

Assessment of dietary patterns

All participants underwent systematic interviews to identify their dietary patterns including food types, such as protein and fruit or vegetables, using the Mini Nutritional Assessment [19].

Assessment of other potential confounders

The association between liver function markers and AD pathology or cerebrovascular injury could be influenced by factors such as age, sex, APOE4, clinical diagnosis,

depression, vascular risks, body mass index (BMI), alcohol drinking, smoking, concomitant prescriptions, supplement use, hormone use, and medical conditions affecting liver enzymes. The extent of depressive symptoms was evaluated using the 30-item Geriatric Depression Scale (GDS) [20,21]. Additionally, the prevalence of vascular risk factors was assessed through interviews with participants and their reliable informants, leading to the calculation of a vascular risk score (VRS) [22]. This score, reflecting the number of vascular risk factors present, was expressed as a percentage. The Body Mass Index (BMI) was determined using the individual's weight in kilograms divided by their height in meters squared. We calculated each participant's lifetime alcohol intake per week (standard drink/week) according to the WHO guideline (http://www.who.int/topics/alcohol_drinking/en/) [23] as well as their lifetime smoking per day (pack/day). In addition, concomitant prescriptions—such as antihypertensive medications, coronary artery medications, diabetes medications, lipid-lowering medications, aspirin, antiplatelet medications, non-steroidal anti-inflammatory drugs, ginkgo biloba extract, cerebral blood flow enhancers, and acetylcholinesterase inhibitors or memantine—were assessed, along with supplement use (such as vitamins, ginseng, omega-3 fatty acids, and green tea extract), hormone use (such as hormone replacement therapy), and medical conditions affecting liver enzymes (such as liver diseases including cirrhosis, hepatitis, or fatty liver disease, as well as infectious, endocrine, and metabolic diseases). To obtain precise information, interviews were conducted with reliable informants, and medical records were thoroughly reviewed.

Measurement of cerebral Aβ deposition

Cerebral Aβ deposition was measured by conducting simultaneous three-dimensional (3D) [^{11}C] PiB-PET and 3D T1-weighted MRI scans with a 3.0 T Biograph mMR (PET-MR) scanner (Siemens; Washington DC, USA) at both the initial baseline and the 2-year follow-up visit. The specifics of PiB-PET acquisition and preprocessing have been detailed in our prior report [18] and the supplementary materials (eMethods).

Measurement of cerebral tau deposition

A subset of participants (n = 73) underwent [^{18}F] AV-1451 PET scans utilizing a Biograph TruePoint 40 PET/CT scanner (Siemens), following the manufacturer's instructions. While all other neuroimaging scans were carried out at baseline and subsequently at the 2-year follow-up visit, AV-1451 PET imaging was first performed on average 2.5 years (with a standard deviation of 0.3 years) following the baseline visit, and then once more 2 years after the initial AV-1451 scan. The specifics of AV-1451 PET imaging acquisition and preprocessing are outlined in our previous report [18] and the supplementary materials (eMethods).

Measurement of AD-signature cerebral glucose metabolism

All participants underwent [^{18}F] fluorodeoxyglucose (FDG)-PET imaging at baseline and the 2-year follow-up visit using the PET-MR scanner previously mentioned. The process of FDG-PET image acquisition and preprocessing is detailed in a previous report [24] and the supplementary materials (eMethods).

Measurement of WMHs

All participants underwent MRI scans utilizing fluid-attenuated inversion recovery (FLAIR) with the previously mentioned PET-MR scanner. The details of WMH image acquisition and preprocessing were described in the supplementary materials (eMethods).

Statistical analysis

To examine the association between liver function markers at baseline and longitudinal changes of AD core pathology, we performed multiple linear regression with liver function marker level as an independent variable and corresponding longitudinal changes in global Aβ retention and AD-signature tau deposition, as dependent variables. In the analyses, liver function markers were initially used as continuous variables after undergoing natural log-transformation to achieve a normal distribution in the model. Each liver function marker was also used as a categorical variable, divided into three levels based on tertile values: high, middle, and low strata were > 24, 19 to 24 and < 19 U/L for ALT, > 28, 24 to 28 and < 24 U/L for AST, and > 0.94, 0.69 to 0.94 and < 0.69 mg/dL for total bilirubin, respectively. Global Aβ retention were also used after undergoing natural log-transformation to achieve a normal distribution. The longitudinal change in neuroimaging markers for each participant was determined by calculating the difference between the values at follow-up and those at baseline, denoted as delta (Δ). Linear mixed effect model analyses were also conducted to examine time × liver marker group interaction effect or time effect (i.e., within-subject effect) as well as liver marker group effect (i.e., between-subject effect). For each type of analyses, a Bonferroni-corrected P (P_B = 0.05/number of analyses) was applied as the threshold for statistical significance; the P_B was < 0.0083 (= 0.05/6). All the models included age, sex, APOE4 positivity, VRS, BMI, clinical diagnosis, education, GDS, alcohol intake, smoking, and dietary nutritional markers (such as protein, fruit, and vegetable intake) as covariates. As sensitivity analyses, we additionally conducted the same analyses 1) including drug use (such as antihypertensive medications, diabetes medications, lipid-lowering agents, aspirin, antiplatelet medications, non-steroidal anti-inflammatory drugs, ginkgo biloba extract, cerebral blood flow enhancers, acetylcholinesterase inhibitors, and memantine), supplement use (such as vitamins, ginseng, and green tea extract), and hormone use (such as hormone replacement therapy) as additional covariates; and 2) excluding participants with medical conditions that may affect liver enzymes, including liver diseases, infectious diseases, endocrine diseases, and metabolic diseases.

In addition, we investigated the moderating effects of age, sex, APOE4, BMI status, Aβ positivity, and lifetime alcohol intake status on the relationships between liver function markers and the neuroimaging markers that showed significant results in above analyses: We included a two-way interaction term between liver function markers and each factor (age, sex, APOE4, BMI status, Aβ positivity, or lifetime alcohol intake status), along with liver function marker itself, as independent variables in the regression model. For significant interactions, subsequent subgroup analyses were conducted using an additional regression model for each subgroup divided based on the moderating variable.

As an exploratory analysis, we performed the same multiple linear regression analyses with liver function marker level as an independent variable and corresponding longitudinal

changes in AD-CM and WMHs, as dependent variables. All statistical analyses were conducted using SPSS Statistics software (version 28; IBM Corp., Armonk, NY, USA).

Results

Participant characteristics

Table 1 displays the demographics and characteristics of the individuals participating in the study. The mean age (standard deviation) of all 347 participants was 70.6 (7.9), and 199 (57.4%) were women. Among all participates, 209 (60.2%) were CN, 95 (27.4%) had MCI, and 43 (12.4%) had AD dementia individuals at baseline. During a follow-up period of two years, 17 out of the 209 CN individuals at baseline converted to MCI, and 25 out of the 95 MCI individuals at baseline progressed to AD dementia. No participants were malnourished (*i.e.,* serum albumin <3.5 g/dL [25]). Most of the liver function markers were within the normal range, indicating the participants rarely showed liver function abnormalities.

Longitudinal association between liver function markers and in vivo brain core AD pathologies

A higher ALT level at baseline was associated with a greater increase of Aβ retention over a 2-year period (i.e., greater ΔAβ retention), but not with changes in tau deposition (Table 2 and Fig. 1(A)). A lower total bilirubin level was associated with a greater increase of tau deposition over a 2-year period (i.e., smaller Δtau deposition), but not with the changes in Aβ retention (Table 2 and Fig. 1(B)). In contrast, AST was not associated with the change of any *in vivo* brain AD core pathologies (Table 2). When stratified categorical values of liver function biomarkers were entered into the model instead of continuous values, the results were similar. The high ALT group showed significantly greater ΔAβ retention compared to the low ALT group (reference group), while the middle ALT group did not (Table 2). The low total bilirubin group had significantly greater Δtau deposition compared to the high bilirubin group (reference), while the middle group did not (Table 2). The linear mixed effects model analyses revealed results similar to those from the multiple regression analyses: we found a significantly positive time × ALT group interaction on Aβ deposition and a negative time × total bilirubin group interaction on tau deposition (Table 3, Figure 1(C) and Figure 1(D)), but did not observe a time AST group interaction effect on any AD pathologies (Table 3). The sensitivity analyses, which controlled for the use of drugs, supplements, hormones as additional covariates, or excluded participants with medical conditions that may affect liver enzymes, including liver diseases, infectious diseases, endocrine diseases, and metabolic diseases, revealed similar results (eTables 1–4).

Moderation effects of potential confounders on the association between liver function markers and longitudinal change of in vivo brain Aβ or tau deposition

There were no significant interaction effects between ALT and each of age, sex, APOE4, BMI status, Aβ positivity, and lifetime alcohol intake status on ΔAβ retention. Similarly, there were no significant interactions between total bilirubin levels and any of the confounders on Δtau deposition (Table 4).

Longitudinal association between liver function markers and in vivo *AD-CM, or WMH volume*

No significant association was found between liver function markers and either AD-CM or WMH volume (Tables 2 and 3, eTables 1–4).

Discussion

The present study demonstrated that higher ALT levels were associated with greater amyloid deposition over a 2-year period, while the AST level was not associated with any changes in brain pathologies. Additionally, a lower total bilirubin level was associated with greater tau deposition over 2 years, but not with other brain pathologies.

While significantly high aminotransferase levels exceeding the normal range can serve as biomarkers of hepatic injury [26–28], even slightly elevated levels of aminotransferase within the normal range may indicate liver dysfunction [29]. Given this, the observed relationship between higher ALT levels and an increase in Aβ retention in this study may indicate an association between subtle liver dysfunction and Aβ pathology. The liver is a major peripheral organ for metabolic detoxification and plays an essential role in clearing circulating Aβ, which can shift the dynamic equilibrium from Aβ deposition in senile plaques toward soluble Aβ [5]. The liver's uptake of peripheral circulating Aβ may be facilitated by the low-density lipoprotein receptor-related protein 1 (LRP-1), which is abundantly expressed in hepatocytes [30–32]. One animal study using AD transgenic mice demonstrated that stimulation of LRP-1-mediated liver uptake decreased brain Aβ aggregation [31]. An in-vitro cell culture study demonstrated that enhancing the translocation of LRP-1 to the hepatic plasma membrane from the intracellular pool notably increased the liver's uptake of Aβ from circulating blood [32]. Another study also reported that Aβ levels in liver samples from AD dementia patients were lower than those from healthy controls, suggesting the potential that the liver might not be effectively clearing circulating Aβ [33]. In addition, a human study indicated that plasma Aβ levels had a positive correlation with the severity of liver cirrhosis, implying that liver function plays a role in regulating Aβ balance in the peripheral system [34]. A recent study using an AD mouse model also demonstrated that age-related alterations in hepatic soluble epoxide hydrolase activity increased brain Aβ deposition via plasma 14,15-epoxyeicosatrienoic acid, which rapidly crosses the blood-brain barrier [4].

Interestingly, in the present study, only higher ALT (and not AST) was related to Aβ in the present study. ALT is predominantly generated in the liver, whereas AST can be synthesized in the skeletal muscle, heart, brain, and other tissues as well as liver [28]. This discrepancy in production sites may explain the different relationships with Aβ between ALT and AST.

A cross-sectional study reported that lower ALT levels were associated with lower Aβ in CSF [7]. These results seem to contrast with our findings, which showed a relationship between higher ALT and greater increase of global Aβ deposition on PET. However, this discrepancy may be partly attributed to the differences in study methodology, including study design and population, and the measurement of brain Aβ deposition. First of all, compared to our longitudinal design, the study had a cross-sectional design. In addition,

we measured brain Aβ deposition with PET, their primary analysis used CSF Aβ data. Regarding the cross-sectional relationship between liver function markers and global Aβ deposition on PET, there were also no significant results in previous study, which is similar to our results from the cross-sectional analyses shown in the supplementary materials (eTable 5). Moreover, while our participants included 60.2 % CN individuals and 39.8 % of cognitively impaired participants (27.4 % MCI and 12.4 % AD dementia), the study compromised 25.7 % of CN and 73.0 % of cognitively impaired participants (53.3 % MCI and 19.7 % AD dementia) [7]. Given that a state of dementia can influence health seeking behavior and self-care, including nutritional intake [35], a larger proportion of cognitively impaired participants could potentially affect the liver function markers or confound the relationship between these markers and AD pathology in the study. Clinically defined AD dementia state, as well as CSF Aβ was associated with decreased ALT levels in the same report [7]. Additionally, the study did not measure alcohol consumption, despite the liver being a primary organ for metabolizing alcohol, which significantly impacts liver function [7].

The present study revealed that a lower total bilirubin level was associated with an increase of tau deposition over 2 years. Bilirubin, a lipophilic linear tetrapyrrole found abundantly in the blood, represents the end product of heme metabolism. The enzyme heme oxygenase breaks down the heme ring, producing water-soluble biliverdin, which is subsequently reduced by biliverdin reductase (BVR) to bilirubin [36]. Notably, bilirubin demonstrates significant antioxidant capabilities, excelling in neutralizing peroxyl radicals and offering superior protection against lipid peroxidation compared to α-tocopherol [36]. Biliverdin reductase-A (BVR-A), one of the isoforms, specifically converts biliverdin IXα into bilirubin IXα, establishing it as one of the most potent endogenous antioxidants [37]. A reduction of BVR-A, accompanied by metabolic and liver dysfunction and a subsequent decrease in bilirubin, impairs the neuroprotective Akt-mediated inhibition of glycogen synthase kinase (GSK)-3 β. This enzyme significantly influences the pathological alterations of tau protein in AD in reaction to oxidative stress, thereby playing a part in the hyper-phosphorylation of tau [38–40]. Therefore, a lower bilirubin level could be associated with higher tau deposition due to reduced GSK-3 β inhibition.

Unlike the association with Aβ or tau deposition, there were no associations between liver biomarkers and neurodegeneration or WMHs. Our findings using FDG-PET (cerebral glucose metabolism) and structural MRI (WMHs) indicate that liver biomarkers do not exert their effects directly through neurodegenerative or vascular mechanisms in the brain. ALT and total bilirubin reflect liver function and hepatocellular integrity rather than brain function or structure. Their lack of association with brain glucose metabolism and WMHs may be due to distinct metabolic processes in the brain and liver, brain compensatory mechanisms, and the blood-brain barrier limiting their direct impact on the brain [41,42]. Additionally, other mechanisms like inflammation or lipid metabolism might better link liver function to brain health [41,42]. Further research is needed to clarify these relationships.

Our study found no significant cross-sectional association between liver function measures and AD pathologies at baseline, as shown in the supplementary materials (eTable 5). However, over a two-year follow-up, lower liver function at baseline was linked to cognitive

decline and AD progression. This indicates that liver function may play a more critical role in the progression rather than the onset of cognitive impairment. These findings highlight the importance of longitudinal data to uncover dynamic and temporal relationships that are not apparent in cross-sectional analyses, providing a deeper understanding of the interplay between liver function and AD progression. It is important to clarify that the cross-sectional data, as shown in the supplementary materials (eTable 5), refers to the analysis performed at baseline. However, caution is needed when interpreting the data, since this study targets patients with early-stage AD dementia classified as CDR 0.5 or 1. Further research is required to determine whether liver function markers continue to impact AD pathology in the later stages of the disease.

Limitations

Our study had several limitations. First, the 2-year follow-up period for longitudinal analysis may not sufficient to detect all changes in AD pathologies or cerebrovascular injury. The relatively short observational period might contribute to some null findings regarding the association between liver function marker and brain pathology. Indeed, further investigations with a longer follow-up period are warranted. Second, the initial tau PET was performed on average of 2.5 years (standard deviation 0.3 years) after the baseline measurement, while the initial amyloid PET and MRI scans were performed at baseline. This temporal gap may have influenced our results. However, the outcomes remained consistent even after adjusting for the temporal gap as an additional covariate. Third, as previously mentioned, only a subset of study participants underwent tau PET scans, making it challenging to detect any potential association between liver function markers (other than total bilirubin) and tau deposition. Fourth, the present study did not explore whether participants in the lowest tertile of ALT (or highest tertile of bilirubin) have lower rates of progression to MCI or from MCI to AD. Although we observed pathological changes over two years, the small number of clinical conversions (17 out of 209 individuals with baseline CN converted to MCI, and 25 out of 95 individuals with baseline MCI progressed to AD dementia) prevented thorough analysis, especially when dividing samples into tertiles based on liver function markers. Future long-term studies with larger sample sizes should investigate both pathological and clinical cognitive changes to fully understand the impact of liver function on AD progression. Lastly, the homogeneity of the cohort, consisting entirely of Korean individuals, may limit the generalizability of our findings to other populations.

Conclusions

These longitudinal findings in older adults suggest a possible link between lower liver function and the accumulation of core AD pathologies in the brain. These results also support the possibility that the liver-brain axis could be a potential target for therapeutic or preventive strategies against AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

[1]. Toledo JB, Arnold M, Kastenmuller G, et al. Metabolic network failures in Alzheimer's disease: A biochemical road map. Alzheimers Dement 2017;13:965–84. [PubMed: 28341160]

[2]. Sookoian S, Castano GO, Scian R, et al. Serum aminotransferases in nonalcoholic fatty liver disease are a signature of liver metabolic perturbations at the amino acid and Krebs cycle level. Am J Clin Nutr 2016;103:422–34. [PubMed: 26791191]

[3]. Sookoian S, Pirola CJ. Alanine and aspartate aminotransferase and glutamine-cycling pathway: their roles in pathogenesis of metabolic syndrome. World J Gastroenterol 2012;18:3775–81. [PubMed: 22876026]

[4]. Wu Y, Dong JH, Dai YF, et al. Hepatic soluble epoxide hydrolase activity regulates cerebral Abeta metabolism and the pathogenesis of Alzheimer's disease in mice. Neuron 2023.

[5]. Huang Z, Lin HWK, Zhang Q, Zong X. Targeting Alzheimer's Disease: The Critical Crosstalk between the Liver and Brain. Nutrients 2022:14. [PubMed: 36615673]

[6]. Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimers Dement (Amst) 2017;7:69–87. [PubMed: 28275702]

[7]. Nho K, Kueider-Paisley A, Ahmad S, et al. Association of Altered Liver Enzymes With Alzheimer Disease Diagnosis, Cognition, Neuroimaging Measures, and Cerebrospinal Fluid Biomarkers. JAMA Netw Open 2019;2:e197978. [PubMed: 31365104]

[8]. Estrada LD, Ahumada P, Cabrera D, Arab JP. Liver Dysfunction as a Novel Player in Alzheimer's Progression: Looking Outside the Brain. Front Aging Neurosci 2019;11:174. [PubMed: 31379558]

[9]. Hatanaka H, Hanyu H, Fukasawa R, et al. Differences in peripheral oxidative stress markers in Alzheimer's disease, vascular dementia and mixed dementia patients. Geriatr Gerontol Int 2015;15(Suppl 1):53–8. [PubMed: 26671158]

[10]. Kim TS, Pae CU, Yoon SJ, et al. Decreased plasma antioxidants in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2006;21:344–8. [PubMed: 16534775]

[11]. Chen TB, Yiao SY, Sun Y, et al. Comorbidity and dementia: A nationwide survey in Taiwan. PLoS One 2017;12:e0175475. [PubMed: 28403222]

[12]. Solfrizzi V, Scafato E, Custodero C, et al. Liver fibrosis score, physical frailty, and the risk of dementia in older adults: The Italian Longitudinal Study on Aging. Alzheimers Dement (N Y) 2020;6:e12065. [PubMed: 32864415]

[13]. Zhong X, Liao Y, Chen X, et al. Abnormal Serum Bilirubin/Albumin Concentrations in Dementia Patients With Abeta Deposition and the Benefit of Intravenous Albumin Infusion for Alzheimer's Disease Treatment. Front Neurosci 2020;14:859. [PubMed: 33013289]

[14]. Byun MS, Yi D, Lee JH, et al. Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease: Methodology and Baseline Sample Characteristics. Psychiatry investigation 2017;14:851–63. [PubMed: 29209391]

[15]. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's

Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9. [PubMed: 21514249]

[16]. American Psychiatric Association, American Psychiatric Association Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association; 2000.

[17]. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9. [PubMed: 21514250]

[18]. Park JC, Han SH, Yi D, et al. Plasma tau/amyloid-beta1-42 ratio predicts brain tau deposition and neurodegeneration in Alzheimer's disease. Brain: a journal of neurology 2019;142:771–86. [PubMed: 30668647]

[19]. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15:116–22. [PubMed: 9990575]

[20]. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. Journal of psychiatric research 1982;17:37–49. [PubMed: 7183759]

[21]. Kim JY, Park JH, Lee JJ, et al. Standardization of the korean version of the geriatric depression scale: reliability, validity, and factor structure. Psychiatry investigation 2008;5:232–8. [PubMed: 20046343]

[22]. DeCarli C, Mungas D, Harvey D, et al. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. Neurology 2004;63:220–7. [PubMed: 15277612]

[23]. Kim JW, Byun MS, Yi D, et al. Association of moderate alcohol intake with in vivo amyloid-beta deposition in human brain: A cross-sectional study. PLoS Med 2020;17:e1003022. [PubMed: 32097439]

[24]. Park J-C, Han S-H, Yi D, et al. Plasma tau/amyloid-β1–42 ratio predicts brain tau deposition and neurodegeneration in Alzheimer's disease. Brain 2019;142:771–86. [PubMed: 30668647]

[25]. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marin-Ciancas F, Malafarina V. Serum albumin and health in older people: Review and meta analysis. Maturitas 2015;81:17–27. [PubMed: 25782627]

[26]. Hunt NJ, Wahl D, Westwood LJ, Lockwood GP, Le Couteur DG, Cogger VC. Targeting the liver in dementia and cognitive impairment: Dietary macronutrients and diabetic therapeutics. Adv Drug Deliv Rev 2022;190:114537. [PubMed: 36115494]

[27]. Bassendine MF, Taylor-Robinson SD, Fertleman M, Khan M, Neely D. Is Alzheimer's Disease a Liver Disease of the Brain? J Alzheimers Dis 2020;75:1–14. [PubMed: 32250293]

[28]. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. CMAJ 2005;172:367–79. [PubMed: 15684121]

[29]. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ 2004;328:983. [PubMed: 15028636]

[30]. Kanekiyo T, Bu G. The low-density lipoprotein receptor-related protein 1 and amyloid-beta clearance in Alzheimer's disease. Front Aging Neurosci 2014;6:93. [PubMed: 24904407]

[31]. Sehgal N, Gupta A, Valli RK, et al. Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. Proc Natl Acad Sci U S A 2012;109:3510–15. [PubMed: 22308347]

[32]. Tamaki C, Ohtsuki S, Terasaki T. Insulin facilitates the hepatic clearance of plasma amyloid beta-peptide (1 40) by intracellular translocation of low-density lipoprotein receptor-related protein 1 (LRP-1) to the plasma membrane in hepatocytes. Mol Pharmacol 2007;72:850–5. [PubMed: 17609417]

[33]. Roher AE, Esh CL, Kokjohn TA, et al. Amyloid beta peptides in human plasma and tissues and their significance for Alzheimer's disease. Alzheimers Dement 2009;5:18–29. [PubMed: 19118806]

[34]. Wang YR, Wang QH, Zhang T, et al. Associations Between Hepatic Functions and Plasma Amyloid-Beta Levels-Implications for the Capacity of Liver in Peripheral Amyloid-Beta Clearance. Mol Neurobiol 2017;54:2338–44. [PubMed: 26957302]

[35]. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413–46. [PubMed: 32738937]

[36]. Baranano DE, Rao M, Ferris CD, Snyder SH. Biliverdin reductase: a major physiologic cytoprotectant. Proc Natl Acad Sci U S A 2002;99:16093–8. [PubMed: 12456881]

[37]. O'Brien L, Hosick PA, John K, Stec DE, Hinds TD Jr. Biliverdin reductase isozymes in metabolism. Trends Endocrinol Metab 2015;26:212–20. [PubMed: 25726384]

[38]. Medina M, Garrido JJ, Wandosell FG. Modulation of GSK-3 as a Therapeutic Strategy on Tau Pathologies. Front Mol Neurosci 2011;4:24. [PubMed: 22007157]

[39]. Sharma N, Tramutola A, Lanzillotta C, et al. Loss of biliverdin reductase-A favors Tau hyper-phosphorylation in Alzheimer's disease. Neurobiol Dis 2019;125:176–89. [PubMed: 30738142]

[40]. Hinds TD, Burns KA Jr, Hosick PA, et al. Biliverdin Reductase A Attenuates Hepatic Steatosis by Inhibition of Glycogen Synthase Kinase (GSK) 3beta Phosphorylation of Serine 73 of Peroxisome Proliferator-activated Receptor (PPAR) alpha. J Biol Chem 2016;291:25179–91. [PubMed: 27738106]

[41]. Yan M, Man S, Sun B, et al. Gut liver brain axis in diseases: the implications for therapeutic interventions. Signal Transduct Target Ther 2023;8:443. [PubMed: 38057297]

[42]. Sarikaya I, Sarikaya A, Sharma P. Assessing the Effect of Various Blood Glucose Levels on (18)F-FDG Activity in the Brain, Liver, and Blood Pool. J Nucl Med Technol 2019;47:313–18. [PubMed: 31182660]

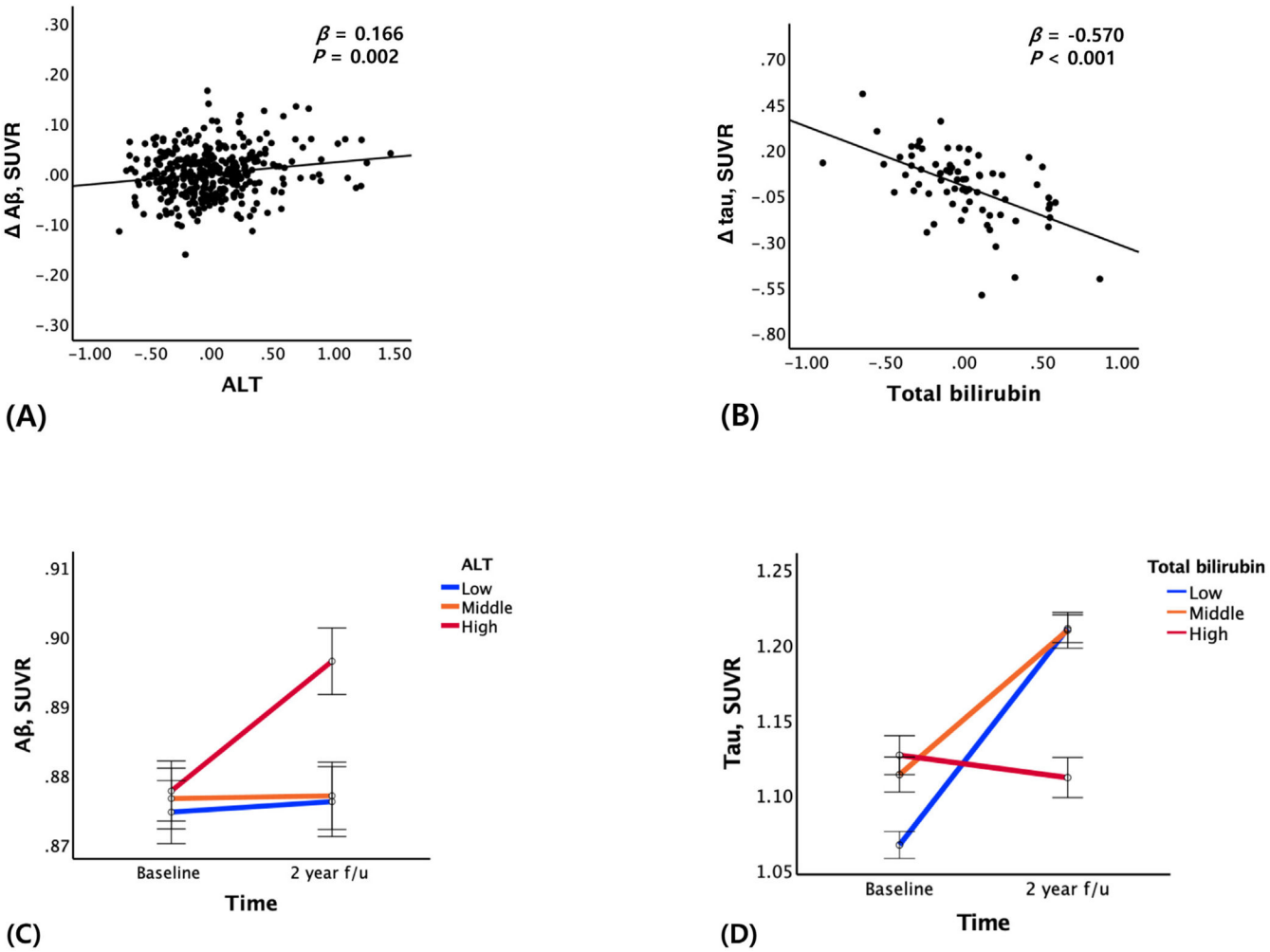

Figure 1.

Partial regression and profile plots illustrating the associations of ALT and total bilirubin levels with two-year changes of Aβ and tau deposition. *ALT=alanine aminotransferase, Aβ* = beta-amyloid, SUVR=standardized uptake value ratio.Partial regression plots depict the association of baseline ALT with two-year change in Aβ deposition (A), and baseline total bilirubin with two-year change in tau deposition (B), adjusted for factors including age, sex, apolipoprotein ε4, vascular risk score, body mass index, clinical diagnosis, education, geriatric depression scale, alcohol intake, smoking, and dietary nutritional markers. Profile plots illustrate two-year changes in Aβ (C) and tau (D) according to baseline ALT and total bilirubin strata, respectively.

Table 1

Baseline characteristics of study participants.

Characteristics	Overall	CN	MCI	AD	*p*
N	347	209	95	43	
Age, y	70.61 (7.94)	68.91 (7.98)	73.16 (6.74)	73.21 (8.17)	<0.001[a]
Female, n (%)	199 (57.35)	111 (53.11)	59 (62.11)	29 (67.44)	0.122 [b]
Education, y	11.21 (4.95)	11.88 (4.78)	10.26 (4.62)	10.07 (5.96)	0.008 [a]
MMSE	24.53 (4.32)	26.89 (2.41)	22.56 (3.18)	17.40 (3.65)	<0.001[a]
CDR	0 or 0.5 or 1	0	0.5	0.5 or 1	
APOE4 positivity, n (%)	95 (27.38)	39 (18.66)	32 (33.68)	24 (55.81)	<0.001[b]
Vascular risk score, %	18.49 (16.76)	17.78 (16.22)	21.05 (17.23)	16.28 (18.00)	0.188[a]
Geriatric depression scale	7.13 (6.47)	5.21 (5.24)	11.11 (7.37)	7.70 (5.77)	<0.001[a]
BMI, kg/m^2	24.36 (3.14)	24.21 (3.09)	25.01 (3.11)	23.67 (3.33)	0.036 [a]
Alcohol intake, lifetime, SD per week	5.80 (15.35)	5.95 (15.23)	7.01 (18.17)	2.43 (6.44)	0.263 [a]
Smoking, lifetime, pack per day	0.29 (0.52)	0.313 (0.53)	0.29 (0.57)	0.14 (0.31)	0.155 [a]
Liver function markers					
ALT, U/L	24.68 (13.02)	25.44 (13.40)	24.78 (13.82)	20.77 (7.88)	0.100 [a]
AST, U/L	28.04 (8.86)	28.36 (9.37)	28.25 (8.78)	25.98 (5.89)	0.264 [a]
Total bilirubin, mg/dL	0.87 (0.33)	0.87 (0.32)	0.87 (0.38)	0.84 (0.31)	0.799 [a]
Dietary nutritional markers					
Protein, No (%)					0.551[b]
High	41 (11.82)	21 (10.04)	12 (12.63)	6 (13.95)	
Moderate	141 (40.63)	80 (38.28)	43 (45.26)	18 (41.86)	
Low	165 (47.55)	107 (51.20)	39 (41.05)	19 (44.19)	
Fruit & Vegetables, No (%)					0.404 [b]
High	204 (58.79)	117 (55.98)	60 (63.16)	27 (62.79)	
Low	143 (38.61)	91 (43.54)	34 (35.79)	16 (37.21)	
Concomitant prescription					
Antihypertensive medications	172 (49.57)	96 (45.93)	56 (58.95)	20 (46.51)	0.100 [b]

Characteristics	Overall	CN	MCI	AD	*p*
Coronary artery medications	18 (5.19)	13 (6.22)	4 (4.21)	1 (2.33)	0.639 *c*
Diabetes medications	64 (18.44)	38 (18.18)	19 (20.00)	7 (16.28)	0.862 *b*
Lipid-lowering medications	103 (29.68)	61 (29.19)	31 (32.63)	11 (25.58)	0.681 *b*
Aspirin	74 (21.33)	46 (22.01)	21 (22.11)	7 (16.28)	0.739 *b*
Antiplatelet medications	12 (3.46)	3 (1.44)	7 (7.37)	2 (4.65)	0.024 *c*
Non-steroidal anti-inflammatory drugs	13 (3.75)	6 (2.87)	6 (6.32)	1 (2.33)	0.287 *c*
Ginkgo biloba extract	14 (4.03)	11 (5.26)	2 (2.11)	1 (2.33)	0.524 *c*
Cerebral blood flow enhancers	4 (1.15)	0 (0.00)	4 (4.21)	0 (0.00)	0.012 *c*
Acetylcholine esterase inhibitors or memantine	77 (22.19)	0 (0.00)	36 (37.89)	41 (95.35)	< 0.001 *b*
Supplement use					
Vitamins	135 (38.90)	89 (42.58)	30 (31.58)	16 (37.21)	0.207 *b*
Ginseng	37 (10.66)	23 (11.00)	10 (10.53)	4 (9.30)	0.947 *b*
Omega-3 fatty acids	96 (27.67)	49 (23.44)	35 (36.84)	12 (27.91)	0.046 *b*
Green tea extract	9 (2.59)	6 (2.87)	3 (3.16)	0 (0.00)	0.782 *c*
Hormone use					
Hormone replacement therapy	37 (10.66)	23 (11.00)	12 (12.63)	2 (4.65)	0.360 *b*
Medical conditions affecting liver enzymes					
Liver diseases (cirrhosis, hepatitis, and fatty liver disease)	64 (18.44)	44 (21.05)	16 (16.84)	4 (9.30)	0.174 *b*
Infectious diseases	5 (1.44)	2 (0.96)	3 (3.16)	0 (0.00)	0.243 *c*
Endocrine and metabolic diseases	84 (24.21)	45 (21.53)	25 (26.32)	14 (32.56)	0.262 *b*
Neuroimage markers					
Cerebral Aβ deposition					
Aβ retention, SUVR	0.88 (0.27)	0.78 (0.16)	0.96 (0.28)	1.22 (0.31)	<0.001 *a*
Δ Aβ retention, SUVR	0.01 (0.05)	−0.01 (0.05)	0.02 (0.05)	0.05 (0.06)	<0.001 *a*
Cerebral tau deposition					
AV-1451, SUVR (n = 73)	1.12 (0.26)	1.02 (0.13)	1.20 (0.28)	1.25 (0.38)	<0.001 *a*
Δ AV-1451, SUVR	0.09 (0.22)	0.07 (0.14)	0.04 (0.28)	0.31 (0.29)	0.006 *a*
Neurodegeneration					

Characteristics	Overall	CN	MCI	AD	*p*
AD-CM, SUVR	1.38 (0.14)	1.41 (0.15)	1.33 (0.12)	1.27 (0.13)	<0.001[a]
Δ AD-CM, SUVR	−0.13 (0.15)	−0.09 (0.15)	−0.18 (0.12)	−0.18 (0.14)	<0.001[a]
WMH volume, cm^3	13.49 (12.28)	13.79 (13.67)	13.07 (9.88)	12.85 (9.27)	0.849 [a]
Δ WMH volume, cm^3	0.78 (12.17)	0.43 (12.17)	1.32 (8.94)	1.44 (17.76)	0.803 [a]

Abbreviations: APOE4=apolipoprotein *ε*4, AD=Alzheimer's disease, MCI=mild cognitive impairment, CN=cognitively normal, CDR= clinical dementia rating, BMI=body mass index, SD=standard drink, ALT=alanine aminotransferase, AST=aspartate aminotransferase, A*β*=beta-amyloid, AD-CM=Alzheimer's disease signature cerebral glucose metabolism, SUVR standardized uptake value ratio, WMH white matter hyperintensities.

Unless otherwise indicated, data are expressed as means (standard deviations).

[a] by one-way analysis of variance.

[b] by chi-square test.

[c] by Fisher's exact test.

Table 2

Associations between liver function markers and two-year changes of Aβ, tau, AD-CM, and WMH volume: Results from multiple linear regression analyses (N = 347)*.

	Δ Aβ, SUVR		Δ tau, SUVR (n = 73)		Δ AD-CM, mm		Δ WMH volume, cm^3	
	β	*p*	β	*p*	β	*p*	β	*p*
Independent variable: ALT								
Continuous variable								
ALT	0.166	**0.002**	−0.010	0.939	−0.034	0.739	−0.027	0.650
Categorical variable								
ALT group								
High	0.167	**0.007**	0.073	0.633	−0.056	0.657	−0.068	0.327
Middle	−0.001	0.988	0.284	0.065	−0.021	0.865	−0.077	0.261
Low	Ref.		Ref.		Ref.		Ref.	
Independent variable: AST								
Continuous variable								
AST	0.080	0.110	−0.091	0.458	−0.079	0.426	0.049	0.390
Categorical variable								
AST group								
High	0.013	0.830	−0.049	0.767	−0.149	0.224	0.048	0.492
Middle	0.034	0.576	0.165	0.330	−0.046	0.706	0.054	0.443
Low	Ref.		Ref.		Ref.		Ref.	
Independent variable: total bilirubin								
Continuous variable								
Total bilirubin	−0.012	0.819	−0.570	**<0.001**	0.007	0.950	−0.042	0.464
Categorical variable								
Total bilirubin group								
High	Ref.		Ref.		Ref.		Ref.	
Middle	0.066	0.252	0.247	0.113	−0.128	0.290	0.038	0.564
Low	0.018	0.753	0.523	**0.002**	0.064	0.608	0.041	0.536

Abbreviations: Aβ=beta-amyloid protein, AD-CM=Alzheimer's disease signature cerebral glucose metabolism, WMH=white matter hyperintensities, SUVR=standardized uptake value ratio, ALT=alanine aminotransferase, AST=aspartate aminotransferase.

Liver function markers and global Aβ retention were used after natural log-transformation to achieve a normal distribution.

* Adjusted for age, sex, apolipoprotein *ε4*, vascular risk score, body mass index, clinical diagnosis, education, geriatric depression scale, alcohol intake, smoking, and dietary nutritional markers (such as protein intake and fruit or vegetable).

Table 3

Associations between liver function markers and two-year changes of Aβ, tau, AD-CM, and WMH volume: Results from linear mixed effect model analyses (N = 347)*.

	Aβ, SUVR				**tau, SUVR (n = 73)**				**AD-CM, mm**				**WMH volume, cm^3**			
	SS	**MS**	**F**	***p***	**SS**	**MS**	**F**	***p***	**SS**	**MS**	**F**	***p***	**SS**	**MS**	**F**	***p***
Independent variable: ALT group																
Between subjects																
ALT group	0.019	0.009	0.132	0.876	0.237	0.119	2.106	0.132	0.012	0.006	0.217	0.805	680.424	340.212	1.289	0.277
Error	22.880	0.072			3.042	0.056			9.088	0.028			77864.579	263.948		
Within subjects																
Time	0.001	0.001	0.499	0.481	0.020	0.020	1.000	0.322	0.055	0.055	5.548	0.019	227.034	227.034	3.078	0.080
Time × ALT group	0.011	0.006	4.967	**0.008**	0.054	0.027	1.336	0.272	0.031	0.016	1.563	0.211	137.720	68.860	0.933	0.394
Error	0.370	0.001			1.092	0.020			3.243	0.010			21761.650	73.768		
Independent variable: AST group																
Between subjects																
AST group	0.001	0.001	0.008	0.992	0.057	0.029	0.479	0.622	0.059	0.030	1.072	0.344	270.505	135.253	0.510	0.601
Error	22.898	0.072			3.223	0.060			9.040	0.028			78274.497	265.337		
Within subjects																
Time	0.001	0.001	0.775	0.379	0.008	0.008	0.398	0.531	0.049	0.049	4.908	0.027	165.797	165.797	2.289	0.136
Time × *AST group*	<0.001	<0.001	0.207	0.813	0.049	0.025	1.209	0.306	0.019	0.009	0.945	0.390	58.210	29.105	0.393	0.675
Error	0.381	0.001			1.097	0.020			3.255	0.010			21841.161	74.038		
Independent variable: total bilirubin group																
Between subjects																
total bilirubin group	0.273	0.136	1.936	0.146	0.092	0.046	0.797	0.456	0.004	0.002	0.073	0.930	627.700	313.850	1.166	0.313
Error	23.014	0.070			3.220	0.057			8.689	0.027			81255.238	269.057		
Within subjects																
Time	0.004	0.004	3.501	0.062	0.022	0.022	1.125	0.293	0.037	0.037	3.777	0.053	32.705	32.705	0.443	0.506
Time × *total bilirubin group*	0.001	0.001	0.565	0.569	0.208	0.104	5.241	**0.008**	0.055	0.028	2.776	0.064	44.289	22.144	0.300	0.741
Error	0.386	0.001			1.109	0.020			3.161	0.010			22297.801	73.834		

Abbreviations: Aβ=beta-amyloid protein, AD-CM=Alzheimer's disease signature cerebral glucose metabolism, WMH=white matter hyperintensities, SUVR=standardized uptake value ratio, SS=sum of squares, MS=mean square, ALT=alanine aminotransferase, AST=aspartate aminotransferase.

Liver function markers and global Aβ retention were used after natural log-transformation to achieve a normal distribution.

* Adjusted for age, sex, apolipoprotein *ε4*, vascular risk score, body mass index, clinical diagnosis, education, geriatric depression scale, alcohol intake, smoking, and dietary nutritional markers (such as protein intake and fruit or vegetable).

Table 4

Moderation effects of age, sex, APOE4, BMI, Aβ positivity, and alcohol intake on associations between liver function markers and two-year changes of Aβ or tau retention*.

	Δ Aβ, SUVR		Δ tau, SUVR	
	β	*p*	β	*p*
ALT	0.360	0.056	-	-
Age	0.622	0.095	-	-
ALT × Age	−0.448	0.250	-	-
ALT	0.165	0.016	-	-
Sex	0.083	0.831	-	-
ALT × Sex	−0.120	0.763	-	-
ALT	0.155	0.007	-	-
APOE4	0.288	0.495	-	-
ALT × APOE4	−0.061	0.885	-	-
ALT	0.092	0.820	-	-
BMI	−0.206	0.601	-	-
ALT × BMI	0.091	0.882	-	-
ALT	0.175	0.002	-	-
Aβ positivity	0.697	0.043	-	-
ALT × Aβ positivity	−0.173	0.614		
ALT	0.150	0.008		
Alcohol	0.020	0.975		
ALT × Alcohol	0.047	0.940		
Total bilirubin	-	-	0.453	0.542
Age	-	-	−0.140	0.433
Total bilirubin × Age	-	-	−0.905	0.226
Total bilirubin	-	-	−0.571	<0.001
Sex	-	-	0.027	0.817
Total bilirubin × Sex	-	-	0.183	0.197
Total bilirubin	-	-	−0.361	0.014
APOE4	-	-	−0.070	0.622
Total bilirubin × APOE4	-	-	−0.176	0.283
Total bilirubin	-	-	0.460	0.676
BMI	-	-	−0.211	0.146
Total bilirubin × BMI	-	-	−0.905	0.412
Total bilirubin	-	-	−0.007	0.904
Aβ positivity	-	-	0.518	<0.001
Total bilirubin × Aβ positivity	-	-	−0.024	0.696
Total bilirubin			−0.498	<0.001
Alcohol			0.138	0.331
Total bilirubin × Alcohol			0.186	0.176

Abbreviations: APOE4=apolipoprotein ε4, BMI=body mass index, Aβ=beta-amyloid, SUVR=standardized uptake value ratio, ALT=alanine aminotransferase, AST=aspartate aminotransferase.

[*] by multiple linear regression analyses including a two-way interaction term between liver function markers and each factor (age, sex, APOE4, BMI status, Aβ positivity, or lifetime alcohol intake status), along with liver function marker itself, as independent variables in the regression model.