Received: 9 June 2024 | Revised: 12 October 2024 | Accepted: 18 October 2024

DOI: 10.1111/jnc.16257

Journal of Neurochemistry JNC The Official Journal of the International Society for Neurochemistry WILEY

ORIGINAL ARTICLE

Elevated serum sodium is linked to increased amyloid-dependent tau pathology, neurodegeneration, and cognitive impairment in Alzheimer's disease

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Funding information
China Brain Project, Grant/Award Number: 2021ZD0200407

Abstract

Vascular dysfunction is implicated in the pathophysiology of Alzheimer's disease (AD). While sodium is essential for maintaining vascular function, its role in AD pathology remains unclear. We included 353 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI), assessing serum sodium levels, cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers, magnetic resonance imaging (MRI), and cognitive function. An independent sample ($N = 471$) with available CSF sodium-related proteins and AD biomarkers was also included. Associations between serum sodium levels and AD pathology, neurodegeneration, and cognition were evaluated using linear regression models. Spearman's correlation analyses assessed the relationships between CSF sodium-related proteins and AD biomarkers. Higher serum sodium levels were associated with increased AD pathology, reduced hippocampal volume, and greater cognitive decline (all $p < 0.05$). The relationship between serum sodium and amyloid PET was evident in several AD-susceptible brain regions, including the neocortex and limbic system. Individuals with high serum sodium exhibited higher tau pathology, lower hippocampal volume, and more severe cognitive decline per unit increase in amyloid PET compared to those with low serum sodium (all $p < 0.05$). Among the 14 CSF sodium-related proteins, which were inter-correlated, six were significantly correlated with CSF AD pathology and amyloid PET, while two were correlated with hippocampal volume and cognitive function, with sodium channel subunit beta-2 (SCN2B) and sodium channel subunit beta-3 (SCN3B)

Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; ADAS13, Alzheimer's Disease Assessment Scale 13-item cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; ADH, antidiuretic hormone; ANOVA, analysis of variance; ARIA-E, amyloid-related imaging abnormalities with edema; ATP1B1, sodium/potassium-transporting ATPase subunit beta-1; ATP1B2, sodium/potassium-transporting ATPase subunit beta-2; CDRSB, Clinical Dementia Rating-Sum of Boxes; CN, cognitive unimpaired; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; FDR, false discovery rate; FXYD2, Sodium/potassium-transporting ATPase gamma chain; GAM, generalized additive models; GLM, generalized linear models; HCN, potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1; ICVD, ischemic cerebrovascular disease; MCI, mild cognitive impairment; MLR, Multivariate linear regression; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; p-tau181, phosphorylated tau 181; QC, quality control; RFU, relative fluorescence units; SCN2B, sodium channel subunit beta-2; SCN3B, sodium channel subunit beta-3; SCN4B, sodium channel subunit beta-4; SLC4A8, electroneutral sodium bicarbonate exchanger 1; SLC5A5, sodium/iodide cotransporter; SLC5A8, sodium-coupled monocarboxylate transporter 1; SLC6A9, sodium- and chloride-dependent glycine transporter 1; SLC6A14, sodium- and chloride-dependent neutral and basic amino acid transporter B(0+); SLC6A16, orphan sodium- and chloride-dependent neurotransmitter transporter NTT5; SLC26A11, sodium-independent sulfate anion transporter; t-tau, total tau.

*Data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-ontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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showing the strongest correlations. These findings underscore the crucial role of serum sodium in AD progression, highlighting a potential network of sodium dysregulation involved in AD pathology. Targeting sodium may offer a novel therapeutic approach to slowing AD progression, particularly by impeding the progression of amyloid-related downstream events.

KEYWORDS
Alzheimer's disease, amyloid PET, anti-Aβ, CSF, sodium, therapy

1 | INTRODUCTION

Alzheimer's disease (AD) is a primary cause of dementia and is rapidly becoming one of the most expensive, deadliest, and most burdensome diseases of this century (Scheltens et al., 2021). AD is characterized by early impairments in learning and memory, followed by executive dysfunction, and its hallmark neuropathological features were extracellular β-amyloid (Aβ) deposits forming neuritic plaques and intracellular accumulation of hyperphosphorylated tau protein as neurofibrillary tangles (Jack Jr. et al., 2018; Long & Holtzman, 2019; Scheltens et al., 2021). Vascular dysfunction is recognized as a significant factor in the pathogenesis of AD (Sweeney et al., 2019; Vemuri et al., 2022; Yang et al., 2024), and a growing body of literature underscores the contributions of vascular risk factors and cerebrovascular injury to the biological and clinical manifestations of AD (Bos et al., 2019; Clark et al., 2019; Pettigrew et al., 2020; Rabin et al., 2018, 2022; Yang et al., 2024; Yau et al., 2022). In addition, cerebrovascular disease (CVD) was associated with worse brain and cognitive health (Vemuri et al., 2022), with ischemic cerebrovascular disease (ICVD) associated with elevated total tau (t-tau) levels and poorer cognitive functions (Han et al., 2024). Significantly, one recent study indicated that reducing vascular inflammation and restoring effective angiogenesis could mitigate vascular dysfunction in the onset or progression of early AD (Tsartsalis et al., 2024). Similarly, the observation of early vascular-Aβ synergy highlights vascular dysfunction as a promising therapeutic target, and when combined with emerging anti-Aβ therapies, this approach may alter the trajectory of AD progression (Yang et al., 2024). However, it remains unclear which vascular-related biological pathways are the most viable targets for intervention.

Sodium, a key extracellular electrolyte, is essential for maintaining extracellular fluid volume and transmembrane potential (Lee et al., 2021). Serum sodium significantly influences vascular function through its impact on plasma osmolarity. Elevated serum sodium levels have been associated with an increased risk of hypertension and heart failure, both of which are manifestations of vascular dysfunction (Dmitrieva et al., 2022; Hu et al., 2022). In addition, abnormalities in serum sodium—whether high or low—have been linked to an increased risk of stroke (Cook et al., 2020; Jayedi et al., 2019; Munoz 3rd et al., 2014; Wannamethee et al., 1994). These vascular-related diseases are recognized as independent risk factors for AD (Arega & Shao, 2022; Carey & Fossati, 2023; Vijayan & Reddy, 2016). Moreover, emerging evidence suggests a connection between serum sodium and dementia. For instance, hyponatremia has been associated with a 2.36-fold increased risk of dementia (Chung et al., 2017), while high serum sodium levels have been linked to a 3.7-fold increased risk of cognitive decline (Szalkai et al., 2017). Research in older men has further shown that serum sodium levels outside the normal range are independently associated with cognitive impairment (Nowak et al., 2018). Moreover, increased sodium signal intensities in CSF and brain tissue have been observed in AD patients compared to healthy controls (Haeger et al., 2022; Kerl et al., 2024). Collectively, these findings suggest a potential link between sodium and the risk of AD. However, research specifically examining the relationship between sodium and AD pathology is limited.

In this study, we aim to explore the association between serum and CSF sodium and AD pathology, neurodegeneration, and cognitive function within a large AD cohort. The ultimate goal of this study is to elucidate the role of sodium in the pathogenesis of AD, with the hope that sodium may emerge as a new therapeutical target for intervention.

2 | METHODS

2.1 | Study participants

All participants in this study were included in the Alzheimer's Disease Neuroimaging Initiative (ADNI) (ClinicalTrials.gov number, NCT00106899). As a public–private partnership, the ADNI project was established in 2003 to investigate whether imaging, clinical, biochemical, and genetic biomarkers can be integrated to validate and develop the early diagnosis of AD. This study included 353 participants who had available data for serum sodium, CSF biomarkers (Aβ42 and p-tau181), amyloid PET (18F-florbetapir or 18F-florbetaben), tau PET (18F-flortaucipir), MRI, and cognitive assessments within 1 year of serum sodium measurement. Given the established strong relationships between serum sodium levels and diseases such as heart disease, stroke, and hypertension (Cook et al., 2020; Dmitrieva et al., 2022; Hu et al., 2022; Wannamethee et al., 1994), medical history and records of these comorbidities were included in the analysis. Participants included in this study ranged from cognitively unimpaired (CN) to those with mild cognitive impairment (MCI) and dementia. Additionally, for exploring the role of CSF sodium in AD, we included an independent population with available CSF proteomics, amyloid PET, CSF AD

pathology, hippocampal volume, and cognitive assessments ($N=471$). Detailed information regarding clinical diagnoses is available at http://adni.loni.usc.edu. The ADNI study was approved by the institutional review boards of all participating centers, and all participants provided written informed consent in accordance with the Declaration of Helsinki. Ethics approval from our institution, the Chinese PLA General Hospital, was not required as this study exclusively utilized data from the ADNI cohort.

2.2 | Measurements of serum sodium

Serum sodium levels were measured using a Roche/Hitachi Cobas 8000 ISE analyzer (Roche Diagnostics, Indianapolis, IN, USA) with an ion-selective electrode at the Department of Clinical Chemistry, Erasmus Medical Center (van der Burgh et al., 2023). All sample measurements and quality control were processed promptly according to standardized protocols by the ADNI center. The ADNI3 URMC Lab provided screening laboratory kits, which included tubes specifically designed for chemistry panels. Samples were barcoded to prevent mix-ups and ensure accurate tracking throughout the analytical process. The quality control (QC) measures implemented included the use of internal controls and calibration standards. Each sample was analyzed in triplicate to ensure reproducibility and reliability of the results. The laboratory maintained rigorous standards for equipment calibration and sample handling to minimize the risk of contamination and measurement errors. For detailed procedures and protocols followed in this study, please refer to the ADNI3 Procedures Manual (https://adni.loni.usc.edu/wp-content/uploads/2012/10/ADNI3-Procedures-Manual_v3.0_20170627.pdf). In this study, we used the median serum sodium level of 141 mmol/L as the threshold to categorize participants into high and low serum sodium groups.

2.3 | Measurements of MRI and PET

Subjects underwent high-field 3 Tesla magnetic resonance imaging (3T MRI) using the 3D-MPRAGE sequence to obtain structural images. The structural MRI scans were processed using the automated brain segmentation software FreeSurfer, version 5.1. Detailed information regarding the analysis methods is available at http://adni.loni.usc.edu. We selected hippocampal volume as the neurodegenerative marker. Analyses using hippocampal volumes as the dependent variable were controlled for intracranial volume.

Amyloid PET imaging was conducted within 90–110 min post-injection of 18F-florbetapir or within 50–70 min following 18F-florbetaben administration, using a sequence of 4×5-min frames in each case. To ensure comparability between different amyloid PET tracers, we used centiloid as the unit of measurement. The ADNI cohort provided detailed methods for translating standardized uptake value ratios (SUVR) into Centiloids (http://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/pet/ADNI_Centiloids_Final.pdf). The amyloid PET-positive status was designated for subjects with >20 Centiloids, as previously reported (Royse et al., 2021).

Tau PET scans were acquired 75–105 min after administering 18F-flortaucipir, utilizing a 6×5-min frame sequence. For tau PET, we used a meta-temporal region composed of the bilateral entorhinal, amygdala, fusiform, inferior, and middle temporal cortices as defined by FreeSurfer. Tau PET positivity was defined as an SUVR threshold of >1.3, as previously described (Maass et al., 2017). Structural images were processed using FreeSurfer (version 5.1.0) and parcellated according to the Desikan–Killiany atlas (Cole & Seabrook, 2020).

2.4 | Measurements of CSF biomarkers

CSF AD core biomarkers (Aβ42 and phosphorylated tau 181 [p-tau181]) were measured using Roche Elecsys electrochemiluminescence immunoassays performed on a cobas 601 instrument. In addition, the thresholds for CSF Aβ42 and p-tau181 positivity were defined based on previous study: A ± (CSF Aβ42 ≥976.6 pg/mL or <976.6 pg/mL) and T ± (p-tau ≤21.8 pg/mL or >21.8 pg/mL) (Wang et al., 2022).

We selected 14 CSF sodium-related proteins from CSF proteomics, measured using the SomaScan 7K platform. The SomaScan 7K Platform utilizes aptamer-based technology with modified DNA aptamers (SOMAmers). Protein levels were reported as relative fluorescence units (RFU). All data normalization steps were performed by SomaLogic, with additional QC steps as previously described (Cruchaga et al., 2023; Wang et al., 2023). The 14 proteins include sodium- and chloride-dependent glycine transporter 1 (SLC6A9), potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1), electroneutral sodium bicarbonate exchanger 1 (SLC4A8), sodium/iodide cotransporter (SLC5A5), sodium- and chloride-dependent neutral and basic amino acid transporter B(0+) (SLC6A14), orphan sodium- and chloride-dependent neurotransmitter transporter NTT5 (SLC6A16), sodium/potassium-transporting ATPase subunit beta-1 (ATP1B1), sodium-independent sulfate anion transporter (SLC26A11), sodium-coupled monocarboxylate transporter 1 (SLC5A8), sodium channel subunit beta-3 (SCN3B), sodium/potassium-transporting ATPase gamma chain (FXYD2), sodium/potassium-transporting ATPase subunit beta-2 (ATP1B2), sodium channel subunit beta-4 (SCN4B), and sodium channel subunit beta-2 (SCN2B).

2.5 | Measurements of cognitive function

Cognitive function was assessed using the Alzheimer's Disease Assessment Scale 13-item cognitive subscale (ADAS13). This scale evaluates various aspects of cognitive function, including memory, language, praxis, orientation, and executive function. The ADAS13 has a scoring range of up to 85 points, with higher scores indicating poorer cognitive function. The Clinical Dementia Rating-Sum

of Boxes (CDRSB) and Mini-Mental State Examination (MMSE) were also included in this study. The CDRSB is used to measure the severity of dementia by assessing six cognitive and functional domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. The sum of these ratings provides a composite score ranging from 0 to 18, with higher scores indicating greater cognitive impairment. The MMSE is a widely used screening tool that assesses various cognitive domains, including arithmetic, memory, and orientation. It has a total score ranging from 0 to 30, where lower scores suggest more severe cognitive impairment.

2.6 | Statistical analysis

Statistical analyses were performed using R version 4.1.0 software, with significance set at a two-sided p value <0.05. Values outside four standard deviations were excluded from the analysis. The normality of each biomarker distribution was assessed using the Kolmogorov–Smirnov test, and log10 transformation was applied to continuous variables that are not following a normal distribution. Baseline characteristics of participants were compared using chi-square tests for categorical variables and one-way ANOVA for continuous variables.

Comparisons between two groups (low serum sodium group and high serum sodium group) or multiple groups (CSF A/T group and PET A/T group) also used the ANOVA model. Multivariate linear regression (MLR) was employed to investigate the relationship between serum sodium and AD pathology, including CSF and PET AD biomarkers (CSF Aβ42, CSF p-tau181, amyloid PET, and tau PET) as well as neurodegeneration and cognitive function. The MLR model was also used to test the association between serum sodium and amyloid PET and tau PET across 68 Desikan–Killiany atlas regions. Generalized linear models (GLMs) assessed the association between serum sodium levels and the positivity of amyloid PET and tau PET. MLR analyses were used to evaluate the interactive effect of serum sodium (high or low) and amyloid pathology (CSF Aβ42 or amyloid PET) on downstream events, including tau pathology, neurodegeneration, and cognitive decline. All above models were adjusted for age and sex, and for intracranial volume when hippocampal volume was the outcome, and further adjusted for years of education when cognition was the outcome. Spearman's correlation analyses tested the association between CSF sodium-related proteins and AD pathology, hippocampal volume, and cognitive function. The p values were adjusted for multiple hypothesis testing using the Benjamini–Hochberg method (false discovery rate [FDR] = 0.05).

Sensitivity analyses included: (1) further adjusting the history of cardiovascular diseases, including heart attack, stroke, and hypertension, in MLR models, and (2) excluding serum sodium values outside the laboratory reference range (serum sodium >145 or <135 mmol/L) to re-analyze the primary results, and (3) using generalized additive models (GAMs) to re-analyze the association between serum sodium and AD pathology, neurodegeneration, and cognition, adjusting for the same covariates described above in the MLR models.

This study did not involve a priori sample size calculation. The sample size was determined based on the availability of complete datasets within the ADNI cohort.

3 | RESULTS

3.1 | Characteristics of study participant

Table 1 details the demographic, clinical, and biomarker characteristics of the study population, including 195 CN, 121 MCI, and 37 dementia. The mean age of the participants was 70.6 years (SD 7.0), with 54.8% being female. Significant differences were observed among the three clinical groups (CN, MCI, and dementia) in terms of AD pathology (CSF Aβ42: $F_{2,351} = 17.17$, $p < 0.001$; CSF p-tau181: $F_{2,351} = 18.68$, $p < 0.001$; amyloid PET: $F_{2,351} = 47.89$, $p < 0.001$; tau PET: $F_{2,351} = 52.42$, $p < 0.001$), hippocampal volume ($F_{2,304} = 56.29$, $p < 0.001$), and ADAS13 scores ($F_{2,351} = 272.5$, $p < 0.001$). Additionally, *APOE* ε4 carrier status ($p = 0.003$) and demographic variables, including sex ($p < 0.001$) and years of education ($F_{2,351} = 3.848$, $p = 0.021$), showed significant differences across these groups. Among comorbidities, only the history of hypertension differed significantly between the groups ($p = 0.006$). The population characteristics of CSF sodium-related proteins are shown in Table S1.

3.2 | Serum sodium levels across different pathological stages

To investigate the association between serum sodium levels and the progression of AD pathology, we examined serum sodium fluctuations across distinct pathological stages defined by CSF A/T and PET A/T classifications. Our analysis revealed significant differences in serum sodium levels among PET-based A/T stages ($F_{3,348} = 4.062$, $p = 0.007$). Specifically, serum sodium levels showed a progressive increase along the AD continuum (A–T–, A+T–, and A+T+), with statistically significant differences observed between the A–T– and A+T+ groups following post-hoc analysis ($p = 0.003$; Figure S1A). A similar ascending pattern in serum sodium levels was observed within CSF-based A/T stages ($F_{3,348} = 1.202$, $p = 0.309$); however, no statistically significant differences were found after post-hoc comparisons (Figure S1B).

3.3 | Association between serum sodium and AD pathology

We examined the linear relationship between serum sodium and AD pathology. The analysis revealed that higher serum sodium

TABLE 1 Participant characteristics.

	CN	MCI	Dementia	*p* value
N	195	121	37	—
Age (mean (SD))	70.3 (6.2)	70.7 (7.4)	72.1 (9.1)	0.352
Sex, *n* (%) Female	127 (64.8)	54 (44.6)	14 (37.8)	<0.001
Education, mean (SD), years	16.8 (2.2)	16.3 (2.5)	15.8 (2.4)	0.021
APOE ε4 carriers, *n* (%)	67 (36.4)	44 (46.3)	21 (67.7)	0.003
Serum sodium (mean (SD)), mmol/L	140.2 (2.5)	140.7 (2.2)	140.9 (2.1)	0.105
ADAS13 (mean (SD))	8.0 (4.4)	14.8 (6.1)	30.5 (8.3)	<0.001
Hippocampus (mean (SD))[a]	7687.8 (815.3)	7196.3 (1021.6)	5841.9 (1130.6)	<0.001
History of Heart attack, *n* (%) Yes	1 (0.5)	2 (1.7)	2 (5.4)	0.067
History of Stroke, *n* (%) Yes	1 (0.5)	2 (1.7)	0 (0.0)	0.471
History of Hypertension, *n* (%) Yes	66 (33.8)	55 (45.5)	22 (59.5)	0.006
CSF Aβ42, mean (SD), pg/mL	1316.7 (661.6)	1119.6 (727.5)	631.7 (224.6)	<0.001
CSF Aβ42 positivity *n* (%)	69 (35.2)	66 (54.5)	34 (94.4)	<0.001
CSF p-tau181, mean (SD), pg/mL	20.5 (9.7)	26.2 (15.4)	32.0 (14.0)	<0.001
CSF p-tau181 positivity, *n* (%)	65 (33.7)	60 (50.0)	26 (72.2)	<0.001
Centiloid (mean (SD))	18.4 (32.3)	38.2 (47.0)	87.3 (48.2)	<0.001
Amyloid PET positivity, *n* (%)	57 (29.2)	61 (50.4)	30 (83.3)	<0.001
Tau PET SUVR mean (SD)	1.2 (0.1)	1.3 (0.3)	1.7 (0.5)	<0.001
Tau PET positivity, *n* (%)	17 (8.7)	47 (38.8)	24 (66.7)	<0.001

Note: *p* values were computed using the one-way analysis of covariance test for serum sodium, age, education, ADAS13, CSF Aβ42, CSF p-tau181, Centiloids, and Tau PET SUVR. The chi-squared test was used for sex, *APOE* ε4 status, CSF Aβ42 positivity, CSF p-tau181 positivity, amyloid PET positivity, tau PET positivity, and the history of heart attack, stroke, and hypertension.

Abbreviations: Aβ, β-amyloid; CN, cognitive normal; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; P-tau, phosphorylated tau.

[a]Data for the hippocampus are missing for 47 subjects.

was significantly associated with higher CSF p-tau181 ($\beta = 0.164$, $p = 0.002$; Figure 1b) but not CSF Aβ42 ($\beta = -0.052$, $p = 0.326$; Figure 1a). Additionally, serum sodium levels were positively correlated with PET-based AD biomarkers, showing associations with higher amyloid ($\beta = 0.146$, $p = 0.005$; Figure 1c) and tau PET ($\beta = 0.121$, $p = 0.024$; Figure 1d). Further investigation into specific brain regions indicated that the significant association between serum sodium and amyloid PET was present in multiple brain regions (58 out of 68 Desikan–Killiany atlas), including the bilateral frontal pole and the rostral and caudal middle frontal regions (FDR $p < 0.05$, Figure 2a). In contrast, the association between serum sodium and higher tau PET was confined to specific brain regions, such as the bilateral temporal pole and the right pars orbitalis (FDR $p < 0.05$, Figure 2b). In addition, we analyzed the association between serum sodium and biomarker positivity. The results showed that each 1 mmol/L increase in serum sodium levels was associated with a 2.9% increase in the risk of amyloid PET positivity and a 3.3% increase in the risk of tau PET positivity (Table 2).

Next, we explored the relationship between serum sodium, neurodegeneration, and cognitive function. The results demonstrated that higher levels of serum sodium were associated with lower hippocampal volume ($\beta = -0.13$, $p = 0.01$; Figure 3a). Similarly, higher serum sodium levels correlated with higher ADAS 13 scores ($\beta = 0.105$, $p = 0.04$; Figure 3b).

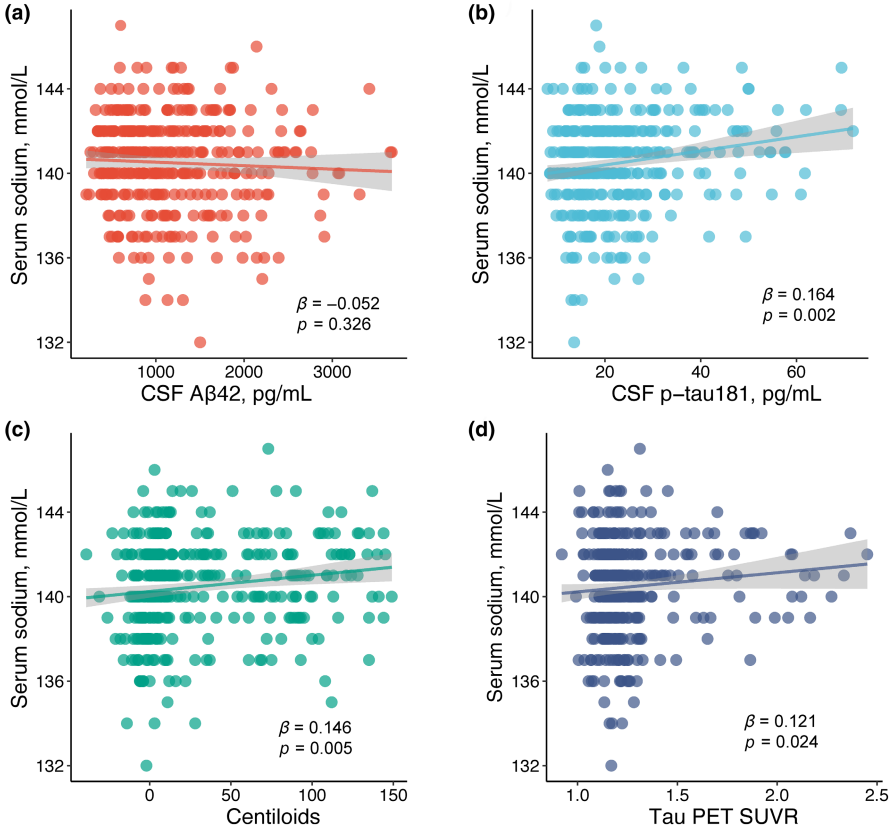


FIGURE 1 The association between serum sodium and AD pathology. Scatter plot illustrates the associations between serum sodium levels and CSF Aβ42 (a), CSF p-tau181 (b), amyloid PET (c), and tau PET (d). Standardized regression coefficients (β) and p values displayed in the scatter plot are derived from multiple linear regression analyses. The linear model fits are presented along with 95% confidence intervals. These models are adjusted for age and sex.

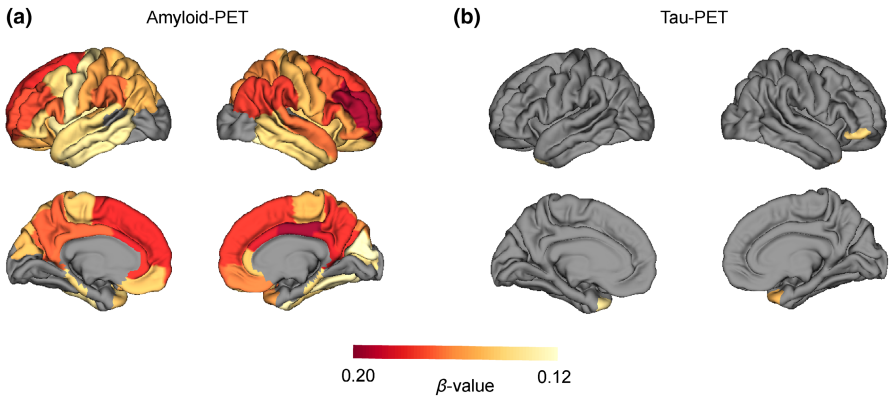


FIGURE 2 Spatial associations of serum sodium with amyloid PET and tau PET. Surface mapping of the association of serum sodium with amyloid PET (a) and tau PET (b) within 68 Desikan–Killiany atlas regions. Red colors indicate higher β-values reflective of a stronger correlation effect. Gray areas indicate no statistical significance. The β-values were derived from a multivariable linear model, adjusted for age and sex.

Predictors	Outcome variables	β value	Low 95% CI	Up 95% CI	p value
Serum sodium	Amyloid PET positivity	0.029	0.007	0.051	0.012
Serum sodium	Tau PET positivity	0.033	0.014	0.053	0.001

TABLE 2 The association of serum sodium with amyloid and tau PET positivity.

Note: Linear model fits are indicated together with 95% confidence intervals. The regression coefficients (β) and p values were derived from generalized linear model, controlling for age and sex.

3.4 | Interaction between serum sodium and amyloid pathology on downstream events

We investigated the interactive effects between serum sodium and amyloid pathology on downstream events, including tau pathology, neurodegeneration, and cognitive decline. Initially, we compared AD pathology between groups with high and low serum sodium levels (defined as ≥141 and <141 mmol/L). All modalities of AD pathology, except for CSF Aβ42, were higher in the high serum sodium group compared to the low serum sodium group (Table S2). Next, we examined the interaction between serum sodium levels and amyloid pathology (CSF Aβ42 or amyloid PET) on subsequent

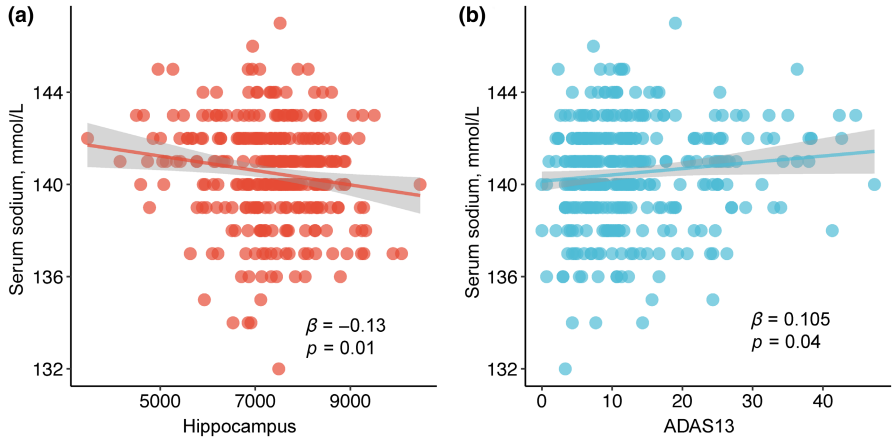
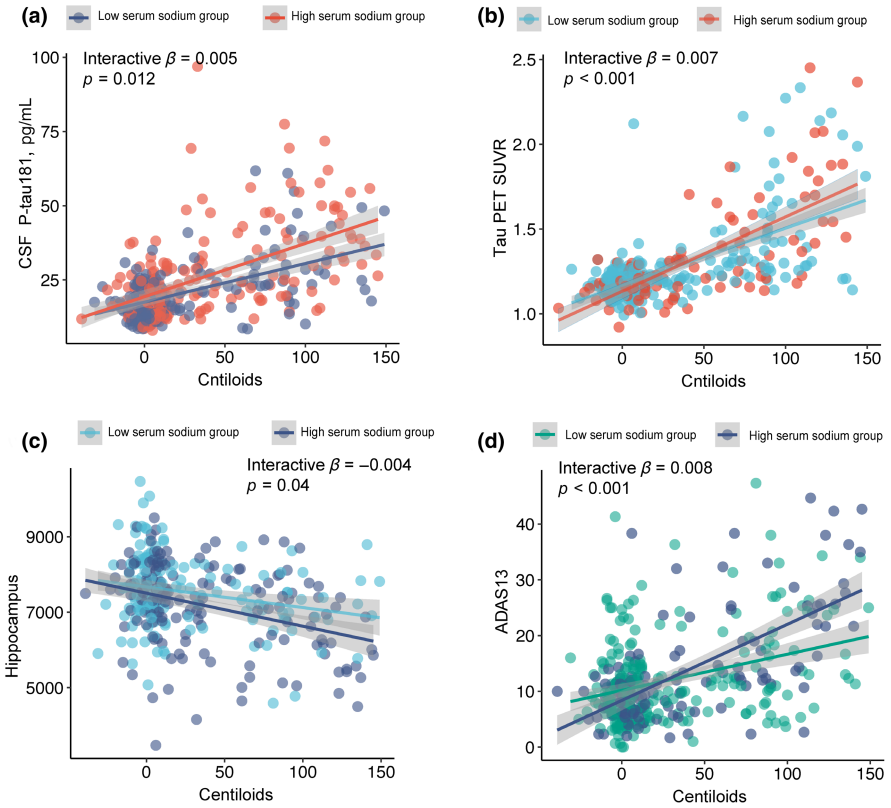


FIGURE 3 The association of serum sodium with neurodegeneration and cognition. Scatter plot illustrates the correlation of serum sodium levels with hippocampus (a) and ADAS13 (b). Standardized regression coefficients (β) and p values displayed in the scatter plot are derived from multiple linear regression analyses. The linear model fits are presented along with 95% confidence intervals. For hippocampus, the model was adjusted for age, sex, and intracranial volume. For ADAS13, the model was adjusted for age, sex, and years of education.

FIGURE 4 The interaction between serum sodium and amyloid PET on downstream events. Scatter plots show that in the high serum sodium group, the correlations between amyloid PET and CSF p-tau181 (a), tau PET (b), hippocampal volume (c), and ADAS13 scores (d) were more pronounced than in the low serum sodium group. Standardized regression coefficients (interactive β) and p values displayed in the scatter plot are derived from multiple linear regression analyses. All above models were adjusted for age and sex, and for intracranial volume when the hippocampus was the outcome, and further adjusted for years of education when ADAS13 was the outcome.



events. The results indicated that the interaction between serum sodium and amyloid PET significantly influenced tau pathology, neurodegeneration, and cognitive decline. Specifically, the correlations between amyloid PET and CSF p-tau181 (interactive $\beta = 0.005$, $p = 0.012$), tau PET (interactive $\beta = 0.007$, $p < 0.001$), hippocampal volume (interactive $\beta = -0.004$, $p = 0.04$), and ADAS13 scores (interactive $\beta = 0.008$, $p < 0.001$) were more pronounced in the high serum sodium group than in the low serum sodium group (Figure 4). However, the interaction between serum sodium and CSF Aβ42 did not significantly impact downstream events (Figure S2).

3.5 | Associations between CSF sodium-related proteins and AD biomarkers

Finally, we investigated whether CSF sodium-related proteins were associated with AD pathology, neurodegeneration, and cognition (Figure 5).

The 14 CSF sodium-related proteins were found to be inter-correlated. Among these, six proteins showed significant correlations with CSF AD biomarkers (Aβ42 and p-tau181) and amyloid PET. Additionally, two proteins were correlated with hippocampal volume and cognitive function. Notably, SCN2B and SCN3B exhibited the strongest correlation with AD pathology and neurodegeneration, respectively.

3.6 | Sensitivity analysis

To account for the potential confounding effects of comorbidities on serum sodium levels, we adjusted for a history of hypertension, heart attack, and stroke in our primary statistical analysis (Tables S3–S5). Additionally, considering the laboratory reference range for serum sodium (135–145 mmol/L), we restricted our analysis to participants within this range and reassessed the main findings (Tables S6–S8). The results of these sensitivity analyses were consistent with our primary findings.

We also employed a GAM to analyze the relationships between serum sodium levels and AD biomarkers. Our results indicated that the associations between serum sodium and AD pathology was consistent with the primary analysis, except for the association with tau PET, which became nonsignificant ($p = 0.069$) (Figures S3 and S4). Furthermore, the interaction effects between serum sodium and amyloid PET on downstream events remained consistent with our primary analysis (Figure S5).

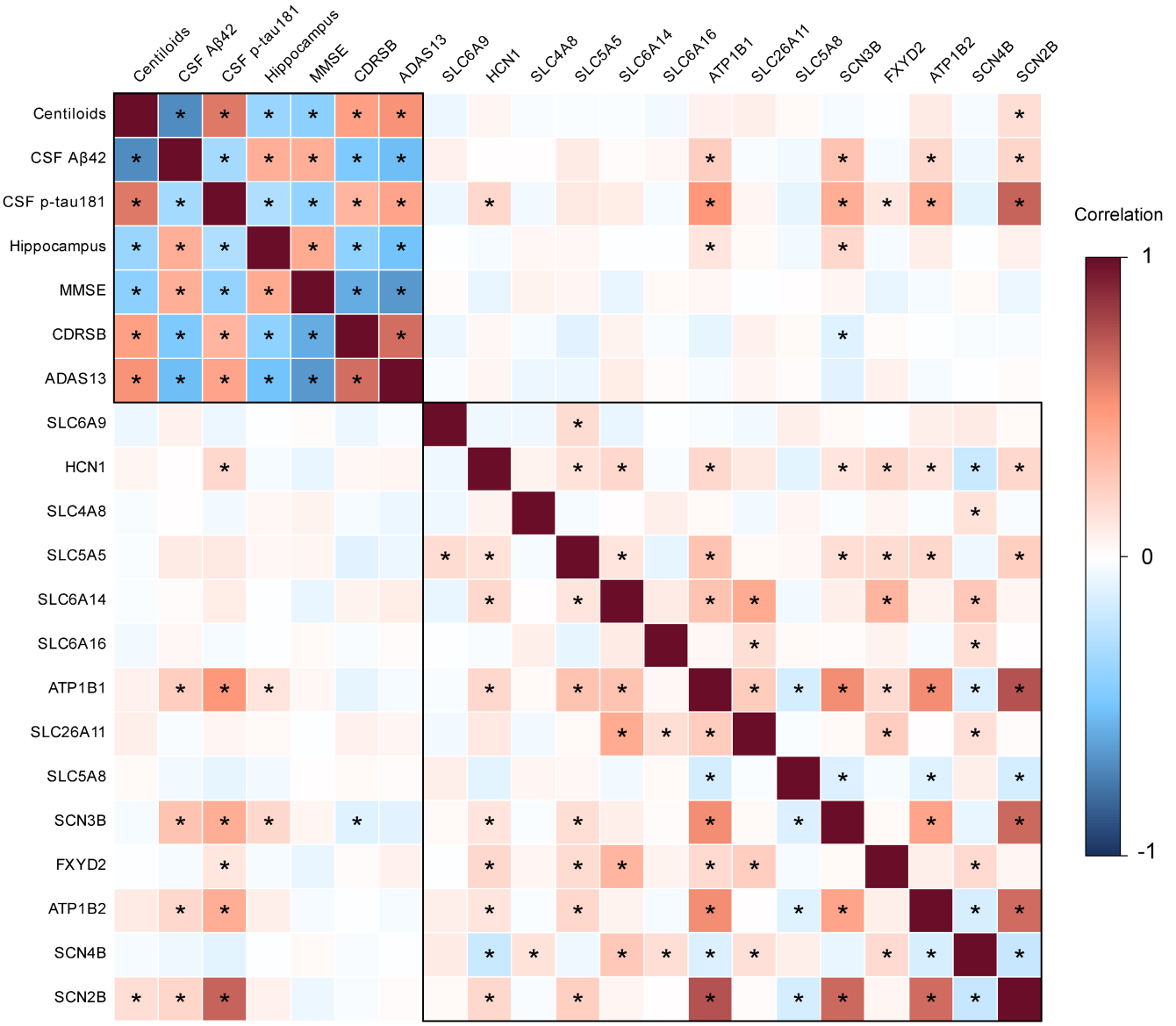


FIGURE 5 Associations between CSF sodium-related proteins and AD biomarkers. The heatmap illustrates the associations of 14 CSF sodium-related proteins with CSF AD pathology (Aβ42 and p-tau181), amyloid PET (Centiloids), hippocampal volume, and ADAS13 scores. Positive correlations are depicted in red, while negative correlations are shown in blue. Correlation coefficients and *p* values were derived from Spearman's correlation analyses. *p* values were adjusted for multiple hypothesis testing using the Benjamini–Hochberg method, with asterisks indicating statistical significance ($p < 0.05$).

4 | DISCUSSION

This study investigates the associations between serum and CSF sodium levels and AD pathology, neurodegeneration, and cognitive function. Our findings reveal that serum sodium levels fluctuate with PET-based pathological stages, showing significant correlations with both CSF- and PET-based AD biomarkers, as well as with hippocampal volume and cognitive decline. Notably, we identified interactive effects between serum sodium and amyloid PET on downstream events, including tau pathology, neurodegeneration, and cognitive impairment. Additionally, we found that CSF sodium-related proteins were correlated with AD biomarkers, further implicating sodium dysregulation in the pathogenesis of AD. These results provide critical evidence supporting the hypothesis that sodium may play a role in AD progression and could serve as a novel therapeutic target for slowing the progression of AD.

Our study identified a significant association between serum sodium levels and AD pathology, particularly with PET-based Aβ pathology. Elevated serum sodium has previously been linked to conditions such as cardiovascular diseases (Dmitrieva et al., 2022; Hu et al., 2022), diabetes-induced metabolic disorders (Cheng et al., 2022), and renal insufficiency (Lombardi et al., 2021; Tampe et al., 2023), all of which are implicated in the pathogenesis of AD (Etgen, 2015; Ezkurdia et al., 2023; Yang et al., 2024). These findings suggest that sodium-related vascular impairment may contribute to amyloid accumulation in the brain. Notably, we observed that the association between serum sodium and amyloid PET was most pronounced in AD-specific brain regions, particularly the neocortex (Braak & Braak, 1996) and limbic system (Hopper & Vogel, 1976), which are primary sites of Aβ deposition and are closely linked to cognitive and memory impairments in AD. Furthermore, our study revealed correlations between serum sodium and tau pathology, including CSF p-tau181 and tau PET, reinforcing the role of sodium dysregulation in AD pathophysiology.

Elevated serum sodium levels can also result from various factors, including dietary habits (Samadi et al., 2019), fluid loss (Anastasiou et al., 2009), endocrine disorders such as Cushing's disease and Conn's disease (which increase aldosterone secretion) (Berl et al., 1978), and abnormalities like reduced antidiuretic hormone (ADH) secretion (Nolph & Schrier, 1970). These factors have been increasingly associated with the progression of AD. For instance, diets high in sodium, saturated fats, and glycemic index have been shown to exacerbate AD pathology (Hoscheidt et al., 2022), while chronic hypercortisolemia, as seen in Cushing's disease, may accelerate cognitive decline (Starkman et al., 2001). Disturbances in ADH are also linked to neuronal dysfunction (Robertson, 2001), potentially impacting AD progression through disrupted electrolyte balance, particularly sodium homeostasis. Additionally, excessive fluid loss—whether due to dehydration, vomiting, or diuretics—can lead to elevated serum sodium levels, particularly in vulnerable populations such as the elderly (Begg, 2017). Aging is another critical factor influencing serum sodium levels, as it is often accompanied by a decline in kidney function, reducing the body's ability to excrete sodium and thereby affecting sodium balance (Shemin & Dworkin, 1997). In addition, the older population are more prone to dehydration due to a diminished sense of thirst, which can concentrate sodium levels in both plasma and CSF (Begg, 2017; Koch & Fulop, 2017). Previous studies have demonstrated that aging increases sodium accumulation in the CSF, plasma, and brain (Xia et al., 2024), which may contribute to conditions like hypertension and cognitive decline. Our results demonstrated that individuals with serum sodium levels exceeding 141 mmol/L exhibited greater amyloid-associated tau pathology and cognitive decline, indicating a potential interactive effect between elevated serum sodium and amyloid pathology in AD progression. These findings underscore the need to clarify whether changes in serum sodium mediate the causal relationships between sodium-affecting factors, such as aging and dietary habits, and AD progression or whether sodium is simply an independent risk factor reflecting disease progression. Future studies should explore these interactions to elucidate the specific mechanisms involved and inform potential clinical management strategies.

We further explored the association between serum sodium levels and downstream events of AD pathology, particularly focusing on hippocampal volume and cognitive function. Our findings revealed an inverse relationship between serum sodium and hippocampal volume, a region critically involved in memory and prominently impaired in AD (De Leon et al., 1989). Additionally, serum sodium levels were positively associated with ADAS13 scores, indicating a potential role for sodium in cognitive decline. This aligns with previous studies that have linked elevated serum sodium levels to worsened cognitive function in AD patients (Szalkai et al., 2017). However, the relationship between serum sodium and cognitive function is complex, as the literature presents conflicting evidence. Some studies have reported an association between lower serum sodium levels and cognitive decline (Chung et al., 2017; Lee et al., 2021; Nowak et al., 2018), while others have found no significant relationship between low serum sodium and cognitive function (Kerl et al., 2024). In our study, serum sodium levels predominantly fell within the normal range (135–145 mmol/L). Importantly, when we excluded values outside this range, our findings remained consistent, suggesting that the observed associations are robust and primarily driven by normal serum sodium levels. Furthermore, the cognitive scales used in our study, ADAS13, are commonly employed as a treatment endpoint in AD clinical trials (Sims et al., 2023), which may account for some of the discrepancies with other studies using different cognitive measures. These findings underscore the complexity of the relationship between serum sodium levels and AD pathology, emphasizing the need for further research to clarify these associations.

The relationship we identified between serum sodium levels and AD pathology, along with the subsequent progression of AD, holds significant clinical implications. Serum sodium is a routine laboratory test frequently employed in clinical practice due to its strong association with various adverse outcomes (Cecconi et al., 2016; Chewcharat et al., 2020; Grim et al., 2021; Kitai et al., 2017; Klein et al., 2005), like heart failure (Dmitrieva et al., 2022) and all-cause mortality (Chewcharat et al., 2020). Electrolyte disturbances, leading

to fluctuations in serum sodium levels, are particularly common in hospitalized patients with AD (Ito, 1996). Our findings observed an interactive effect between serum sodium and amyloid PET on the downstream events. This underscores the importance of closely monitoring serum sodium levels in amyloid PET-positive population. The clinical relevance of these findings is further supported by the well-established interventions available for managing serum sodium levels, including dietary modifications (Alvelos et al., 2004), oral medications (Cárdenas et al., 2012), and intravenous therapies (McNab et al., 2015). These established pathways for sodium management present an opportunity for these interventions to serve as a promising adjunctive therapy for AD patients, particularly those undergoing treatment with anti-Aβ drugs (Jaffe, 2021; Larkin, 2023). A critical issue with anti-Aβ drugs is their adverse effects, particularly amyloid-related imaging abnormalities with edema (ARIA-E) (Jeremic et al., 2023). In phase 3 clinical trials, symptomatic brain edema was reported in approximately 12.6% of participants treated with Lecanemab (van Dyck et al., 2023) and 24% of participants treated with Donanemab (Sims et al., 2023). Currently, no effective strategies exist to mitigate ARIA-E. Notably, sodium transport activity has been linked to brain edema in ischemic stroke (Betz et al., 1989), and sodium-related drugs have demonstrated efficacy in reducing brain edema (Kucharczyk et al., 1991). Based on our findings of the interactive association between serum sodium and amyloid PET, future studies are warranted to explore whether targeting sodium could reduce ARIA-E in AD patients treated with anti-Aβ drugs.

The precise mechanism linking sodium dysregulation to AD pathology remains incompletely understood. Our study identified significant correlations between CSF sodium-related proteins and AD pathology, suggesting a mechanistic connection between sodium imbalance and the progression of AD. The 14 inter-correlated sodium-related proteins indicate a network of sodium dysregulation that may collectively contribute to AD pathology. Notably, SCN2B and SCN3B, which showed the strongest associations with AD pathology and neurodegenerative processes, are key components of voltage-gated sodium channels that regulate neuronal excitability and signal transduction (Isom et al., 1992; Meadows et al., 2002). Disruptions in these subunits can impair sodium ion homeostasis, leading to neuronal hyperactivity and excitotoxicity—processes that are critical in the pathogenesis of AD (Meadows et al., 2002). Moreover, emerging research supports several mechanisms through which sodium dysregulation may influence AD pathology. For example, interactions between Aβ aggregates and sodium channels have been shown to cause pre-synaptic calcium overload, contributing to neurodegeneration (Ohnishi et al., 2015). Sodium MRI studies have also demonstrated that increased sodium signal intensity in the medial temporal lobes of AD patients was correlated with hippocampal atrophy and cognitive decline (Mellon et al., 2009). Another study found that sodium signal intensities in CSF were correlated with CSF tau pathology (p-tau and t-tau) but not CSF Aβ42 (Kerl et al., 2024). These findings suggest that sodium dysregulation may reflect or even contribute to the neuropathological changes observed in AD. Animal studies further support this link, showing that high dietary sodium intake is associated with increased amyloid aggregates and impacts both systemic and cerebral blood vessels (Cheng et al., 2015; Faraco et al., 2018), exacerbating neurodegeneration and cognitive impairment (Apátiga-Pérez et al., 2022; Nelson, 2022). Conversely, reducing sodium intake has been linked to improved cognitive outcomes (Tangney et al., 2014). These observations underscore the critical role of sodium regulation in AD pathology and highlight the potential of therapeutic strategies targeting sodium homeostasis. Further research is essential to fully elucidate these mechanisms and their implications for AD progression and treatment.

Similarly, other electrolytes such as chloride and potassium play pivotal roles in neuronal function and may be implicated in AD pathology. Chloride ions are essential for regulating osmolality and acid–base balance (Doyon et al., 2016) and are central to the inhibitory function of gamma-aminobutyric acid (GABA)ergic neurons (Bakouh et al., 2024). The efficacy of GABAergic inhibition relies on the maintenance of low intracellular chloride concentrations ($[Cl^-]_i$), primarily regulated by chloride transporters such as the sodium-potassium-chloride cotransporter 1 (NKCC1) and the potassium-chloride cotransporter 2 (KCC2) (Talifu et al., 2022). Disruption of chloride homeostasis can lead to depolarizing GABA responses, neuronal hyperexcitability, and excitotoxicity (Bakouh et al., 2024; Talifu et al., 2022), which are processes implicated in neurodegeneration. Studies have suggested that altered expression of chloride transporters and disrupted chloride gradients may contribute to the pathophysiology of AD by affecting synaptic inhibition and network excitability (Chen et al., 2017). Potassium ions (K^+) are fundamental in maintaining neuronal resting membrane potential, action potentials, and regulating neuronal excitability (Magura et al., 2015). Although potassium levels were not directly explored in this study, literature suggests that an imbalance of potassium ions may lead to neuronal dysfunction, which in turn affects cognitive function (Kapogiannis & Mattson, 2011). The interplay between potassium and sodium is critical for maintaining electrochemical gradients across neuronal membranes; disturbances in either can disrupt neuronal excitability and synaptic transmission (Hodeify et al., 2024; Pivovarov et al., 2018). Overall, electrolyte homeostasis is essential for maintaining normal neurotransmission, synaptic plasticity, and cellular function in the brain. Our findings, along with existing literature, underscore the importance of sodium regulation in AD pathology and suggest that other electrolytes like chloride and potassium may also play significant roles in AD.

This study has notable strengths. To our knowledge, it is the first to systematically explore the association between serum and CSF sodium with AD pathology, neurodegeneration, and cognitive decline in humans. However, several limitations should be acknowledged. First, the cross-sectional design of this study limits our ability to draw causal inferences; longitudinal studies are needed to establish whether the observed correlations reflect causal relationships. Second, serum sodium levels can be influenced by various factors, including dietary habits, particularly high salt intake, which were not fully controlled for in this study due to the study design of the ADNI

cohort. This variability should be considered in future studies. Third, our study population was predominantly of European descent, which may limit the generalizability of our findings to other ethnic groups. Future research should include more diverse populations to ensure broader applicability of the results. Fourth, the cutoff values used to define high and low serum sodium levels were specific to our study sample and may not directly translate to clinical practice. These cutoffs should be validated in clinical settings. Fifth, despite the crucial role of sodium in electrolyte homeostasis and neurological function, chloride and potassium ions play equally important roles in the maintenance of neuronal excitability, osmotic pressure regulation, and synaptic transmission, but they were not studied in depth in this study. Future studies should further explore the interactions among sodium, chloride, and potassium, especially their combined effects on AD pathogenesis and cognitive function, in order to provide a more comprehensive understanding of the role of electrolyte homeostasis in disease progression. Lastly, while our study provides important preliminary data, validation in larger cohorts with diverse study designs, including prospective studies, is crucial. Such studies should include participants with conditions that could influence serum sodium levels to fully assess the potential impacts on our findings and to explore the broader clinical implications.

In summary, this study identifies a significant association between serum and CSF sodium and AD pathology, neurodegeneration, and cognitive decline, highlighting the potential role of sodium dysregulation in AD progression. Notably, the critical interaction between serum sodium and amyloid PET underscores the importance of sodium as a factor that may influence the disease course of AD. Monitoring and managing serum sodium levels may be a promising strategy for slowing disease progression, especially in patients receiving anti-amyloid therapies. Overall, these insights open new avenues for research to further elucidate the mechanisms by which sodium contributes to AD pathology and to explore its potential as a therapeutic target in the management of AD.

AUTHOR CONTRIBUTIONS

Yu-Han Chen: Conceptualization; methodology; software; data curation; formal analysis; investigation; writing – original draft; visualization; resources. **Zhi-Bo Wang:** Data curation; resources; writing – review and editing; visualization; methodology; conceptualization; investigation; software; formal analysis; supervision. **Xi-Peng Liu:** Writing – review and editing; supervision. **Zhi-Qi Mao:** Writing – review and editing; methodology; conceptualization; funding acquisition; project administration; supervision; resources. **for the Alzheimer's Disease Neuroimagi Initiative:** Resources.

ACKNOWLEDGMENTS

We express appreciation to contributors of Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The data used in this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)database(http://adni.loni.usc.edu/).Assuch,theinvestigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or in the writing of this paper. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; BristolMyers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. CSF proteomics data used in preparation of this article were generated by the Neurogenomics and Informatics Center at Washington University (https://neurogenomics.wustl.edu/). As such, the investigators within the NGI provided data but did not participate in analysis or writing of this report. A complete listing of NGI investigators can be found at: https://neurogenomics.wustl.edu/about-us/leadership/. CSF Somalogic (7K) and Metabolomics (Metabolon HD4) data generation and QC was supported by grants from the National Institutes of Health (RF1AG074007 (PI: Yun Ju Sung), R01AG044546 (PI: Carlos Cruchaga), P01AG003991(PI: John Morris and Carlos Cruchaga), RF1AG053303 (PI: Carlos Cruchaga), RF1AG058501 (PI: Carlos Cruchaga), and U01AG058922 (PI: Carlos Cruchaga)), and the Chan Zuckerberg Initiative (CZI), and the Alzheimer's Association Zenith Fellows Award (ZEN-22-848604, awarded to Carlos Cruchaga). The recruitment and clinical characterization of research participants at Washington University were supported by NIH P30AG066444 (PI: John Morris and Carlos Cruchaga), P01AG03991(PI: John Morris and Carlos Cruchaga), and P01AG026276 (PI: John Morris and Carlos Cruchaga). This work was supported by access to equipment made possible by the Hope Center for Neurological Disorders, the Neurogenomics and Informatics Center (NGI: https://neurogenomics.wustl.edu/) and the Departments of Neurology and Psychiatry at Washington University School of Medicine. We acknowledge the use of images

 This work was supported by grants from China Brain Project (2021ZD0200407).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available in the ADNI site, http://adni.loni.usc.edu/.

CONSENT TO PARTICIPATE

Written informed consent was obtained from all ADNI participants, and ADNI received approval from the institutional review boards at all participating institutions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chen, Y.-H., Wang, Z.-B., Liu, X.-P., Mao, Z.-Q., & (2024). Elevated serum sodium is linked to increased amyloid-dependent tau pathology, neurodegeneration, and cognitive impairment in Alzheimer's disease. *Journal of Neurochemistry*, *00*, 1–15. https://doi.org/10.1111/jnc.16257