Neurotoxicity Research (2021) 39:609–617
https://doi.org/10.1007/s12640-020-00312-y

ORIGINAL ARTICLE

Serum Calcium Predicts Cognitive Decline and Clinical Progression of Alzheimer's Disease

Ling-Zhi Ma[1] · Zi-Xuan Wang[2] · Zuo-Teng Wang[1] · Xiao-He Hou[1] · Xue-Ning Shen[3] · Ya-Nan Ou[1] · Qiang Dong[3] · Lan Tan[1] · Jin-Tai Yu[3]

Received: 15 October 2020 / Revised: 6 November 2020 / Accepted: 9 November 2020 / Published online: 20 November 2020

Abstract

Relationship between serum calcium and Alzheimer's disease (AD) remains unclear. The aim of this study is to test whether serum calcium is associated with other AD-associated biomarkers and could predict clinical progression in nondemented elders. This was a longitudinal population-based study. The sample was derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, which included 1224 nondemented elders: 413 cognitively normal (CN) and 811 mild cognition impairment (MCI). Associations were investigated between serum calcium and longitudinal changes in Aβ/tau pathologic features, brain structure, cognitive function, and disease progression. Serum calcium concentrations increased with disease severity. Serum calcium predicted longitudinal cognitive decline and conversion from nondemented status to AD dementia (adjusted HR = 1.41, 95% CI 1.13–1.76). Furthermore, serum calcium levels were negatively correlated with CSF-$A\beta_{42}$ ($\beta = -0.558$, $P = 0.008$), FDG-PET ($\beta = -0.292$, $P < 0.001$), whole brain volume ($\beta = -0.148$, $P = 0.001$), and middle temporal volume ($\beta = -0.216$, $P = 0.042$). Similar results were obtained in CN and MCI groups. Higher serum calcium status (even if not hypercalcemia) may increase the risk of AD in elders. Serum calcium is a useful biomarker in predicting clinical progression in nondemented elders. More researches are needed in the future to explore the underlying mechanism.

Keywords Calcium · Alzheimer's disease · $A\beta_{42}$ · FDG-PET · Brain volume

Introduction

Alzheimer's disease (AD) is the leading cause of dementia in the elderly and is clinically defined by a gradual decline in memory and other cognitive functions. However, in Europe and the USA, less than half of people with dementia are formally diagnosed (Eichler et al. 2014). Pathological changes were inferred to be 20 years before the onset of clinical symptoms of AD. Biomarker research allows identification of high-risk groups with dementia among the general population, even in the preclinical stage (Jessen et al. 2014; Sperling et al. 2011). Calcium is considered involving in the pathophysiology of cognitive decline and AD (Betzer et al. 2018; Bussiere et al. 2019; Lacampagne et al. 2017). Previous studies have found that serum calcium ions easily diffuse into the brain through the blood–brain barrier (BBB) (Yarlagadda et al. 2007). High extracellular calcium levels may enhance calcium influx in neurons during signaling when calcium channels are opened, leading to calcium overload and, subsequently, neuronal death (Toescu et al. 2004). In addition, every clinical mutation in presenilin 1 (PS1) and presenilin 2 (PS2) genes that have been studied disrupts calcium signaling, and calcium signaling pathways are perturbed in presenilin-deficient cells (Bussiere et al. 2019; Yarlagadda et al. 2007). Deregulation of intracellular calcium signaling and disruption of intracellular calcium homeostasis may contribute to cognitive decline and the pathogenesis of dementia (Ogihara et al. 1990; Toescu et al. 2004).

✉ Lan Tan
dr.tanlan@163.com

✉ Jin-Tai Yu
jintai_yu@fudan.edu.cn

[1] Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China

[2] Department of Geriatric Medicine, the Affiliated Hospital of Qingdao University, Qingdao, China

[3] Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

However, the reported effect of serum calcium level on the AD development/progression has been inconsistent. It is reported that AD patients showed lower serum calcium than control patients in cross-sectional cohort studies (Ogihara et al. 1990; Subhash et al. 1991; Zhen et al. 2015), while, in some studies, patients with higher serum calcium levels have shown a higher incidence of AD or faster AD progression (Schram et al. 2007; Tilvis et al. 2004). One study also found that different blood calcium levels have different effects on different populations (Sato et al. 2019). Some trials have reported an association between calcium supplementation and increased risk for vascular events (Bolland et al. 2011). A permanent increase in calcium levels increases vascular risk. Vascular risk factors are related to AD (Walker and Silverberg 2008). Studies have been relatively limited, and the potential role of serum calcium as a biomarker for the presymptomatic phase of AD remains unclear.

In our research, we explored the value of serum calcium as a predictor of cognitive decline and clinical progression at the early presymptomatic stages of AD in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. We also investigated whether serum calcium levels are related to other AD biomarkers to investigate the possible mechanism of serum calcium affecting AD.

Methods

Participants

Data used in this study was obtained from the ADNI database (adni.loni.usc.edu), which was launched in 2003 as a public–private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early AD (Hendrix et al. 2015). Individuals were excluded if they had Hachinski ischemic score > 4 (a high risk of cerebrovascular disease contributing to cognitive impairment); were unable to undergo MRI; had other neurologic disorders, active depression, history of psychiatric diagnosis, alcohol or substance dependence in the last 2 years; had less than 6 years of education; or were not fluent in English or Spanish (Petersen et al. 2010). For up-to-date information, see www.adni-info.org.

There are a total of 1224 individuals (normal controls, CN = 413, MCI = 811 at baseline) with an average age of 73.5 years. We excluded participants whose data on baseline calcium were missing. We also removed the extremisms that were higher than four standard deviations (SD) above the mean or lower than four standard deviations below the mean (limited: mean ± 4SD). Finally, samples with data of cerebrospinal fluid (CSF) (n = 984 for $A\beta_{42}$, t-tau, and p-tau), amyloid PET (n = 643), brain structural measures (n = 1059), ^{18}F-fluorodeoxyglucose (FDG)-PET (n = 946), and cortical thickness (n = 652) were included in the cross-sectional analyses.

Definition of Incident AD and Cognitive Assessments

The primary endpoint was newly diagnosed AD during the follow-up period. AD patients were required to meet the criteria for probable AD defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (McKhann et al. 1984). In brief, AD group had a Mini-Mental State Examination (MMSE) score of 20–26 where lower scores suggest severe cognitive impairment (range, 0–30), and a global Clinical Dementia Rating (CDR-global) score of 0.5 to 1.0 where lower scores indicate mild cognitive impairment (range, 0–3) (Petersen et al. 2010). In our study, we stratified the MCI group into stable MCI (sMCI) with no progression to AD dementia during at least a 2-year follow-up and progressive MCI (pMCI) with progression to AD dementia during at least 2-year follow-up. Therefore, we included the following 3 groups: CN controls, sMCI group, and pMCI group. Participants without AD during the 10-year follow-up period were classified as missing or not having observed outcomes, depending on the circumstances. The composite cognitive scores referred to test results of executive function (EF) (Gibbons et al. 2012) and memory function (MEM) (Crane et al. 2012) using psychometrically optimized approaches with items from ADNI neuropsychological assessments. Briefly, EF scores were calculated by item-level data from the Trail Making Test (A and B), digit span backward, digit symbol, animal naming, vegetable naming, and the clock drawing test. Single-factor models based on item-level data from the RAVLT, the ADAS-Cog, the MMSE, and the Logical Memory test were used in the calculation of the ADNI-Mem score.

Measurement of Laboratory and Anthropometric Parameters

All data on laboratory and anthropometric parameters, as well as medical history, are downloaded from the ADNI database. Serum calcium, serum phosphorus, and triglyceride were measured. Serum calcium level was corrected in cases of hypoalbuminemia (serum Alb less than 4 g/dL), where corrected serum calcium level (mg/dL) = raw calcium level (mg/dL) + (4 − serum albumin level (g/dL)) (Payne et al. 1973). In the apolipoprotein Ɛ4 (*APOE Ɛ4*) genotyping performed at the ADNI Biomarker Core Laboratory (University of Pennsylvania), participants

carrying at least one allele were identified as *APOE ℰ4* positive status (Shaw et al. 2009). Body mass index (BMI) was calculated by dividing body weight (in kg) by height squared (in m^2). We identified the baseline co morbidities, including hypertension, type 2 diabetes mellitus (T2DM), and coronary atherosclerotic heart disease (CDH), by screening the medical information database. Self-reported health behaviors included smoking status (categorized as yes or no, both previous and current smokers are identified as yes) and alcohol consumption, calcium supplements, vitamin D supplements which is grouped in the same way.

Measurement of CSF Biomarkers

$A\beta_{42}$, t-tau, and p-tau were measured by the ADNI Biomarker Core (University of Pennsylvania) using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) with the INNOBIA AlzBio3 kit (Fujirebio, Ghent, Belgium) as described previously (Shaw et al. 2009).

Measurement of Neuroimaging

The neuroimaging data, such as standardized uptake values ratios (SUVRs) via F18-PET-AV45, regional volume, and cortical thickness on MRI, were all downloaded from the ADNI dataset (adni.loni.ucla.edu/about-data samples/image-data/). The mean florbetapir AV45 uptake (representing the Aβ retention) within each region was calculated by co-registering the florbetapir scan to the corresponding MRI. Florbetapir SUVRs were created by averaging across four cortical gray matter regions (frontal, cingulate, lateral parietal, lateral temporal) and dividing the summary by reference region. Further details of PET acquisition have been summarized previously (Apostolova et al. 2010). A detailed description of MRI imaging data acquisition and processing can be obtained (Zhang et al. 2011). MRI brain scans were acquired using 1.5-T imaging systems with a standardized protocol that included T1-weighted images using a sagittal, volumetric, magnetization-prepared rapid acquisition with gradient echo sequence. In our study, as an elective group of brain regions of interest (ROIs) regarded as the most representative region. The FDG-PET images (via averaging counts of angular, temporal, and posterior cingulate regions) were pre-processed using a series of steps to mitigate inter-scanner variability and obtain FDG-PET data with a uniform spatial resolution and intensity range for further analysis (Jagust et al. 2009).

Statistical Analysis

Chi-square tests (for categorical variables) and Mann–Whitney *U* tests (for variables with skewed distributions), and Student's *t* tests (for variables with normal distributions) were used to compare demographic, clinical, and diagnostic variables between CN and MCI groups. Logistic regression analysis was used to assess the impact of serum calcium on the risk of conversion to MCI. We tested the associations of serum calcium concentrations with longitudinal cognition using linear mixed-effects models. The baseline calcium concentration used as categorical variable in this part of analyses. The cumulative AD incidence for each group was plotted with Kaplan–Meier curves, and the effects of higher (≥ 9.9 mg/dL) or lower serum (< 9.9 mg/dL) calcium level were compared by the log-rank test (Sato et al. 2019). Multivariate Cox proportional hazards regression analysis was performed to assess the risk of new-onset AD in 3 models. To examine the relationship between calcium and AD-related biomarkers, we used multiple linear regression models at baseline. All regression analyses were adjusted for age, gender, *APOE ℰ4* status, serum phosphorus, cognitive diagnosis, education, triglyceride (TG), BMI, tobacco and alcohol use, calcium supplements, vitamin D supplements, and medical histories. These models assumed a random subject-specific intercept and a random subject-specific slope. Since all outcome variables were converted to normalize Z-scores, β coefficients refer to standardized effects. All tests were 2-sided and the criterion for statistical significance was $P < 0.05$ according to false discovery rate (FDR) correction (Yurko et al. 2020). All statistical analyses were performed using a software program (R 3.5.1).

Results

Baseline Characteristics of the Study Population

The demographic characteristics and clinical features in total nondemented elder (mean age = 73.5 years) individuals at baseline are summarized in Table 1. A total of 1224 nondemented elders were enrolled in this study. This nondemented cohort was composed of 647 low calcium individuals and 577 high calcium individuals (cutoff 9.9 mg/dL). Statistical difference was found between CN and cognitive MCI groups in age ($P < 0.001$), gender ($P = 0.003$), education levels ($P = 0.022$), and *APOE ℰ4*allele frequency ($P < 0.001$). We did not find any differences between these two groups in serum phosphorus levels, BMI, TG, smoking status, alcohol assumption, and any medical histories aspect T2DM ($P > 0.05$).

With the advance of the disease stage, the level of serum calcium showed a rising trend. The serum calcium concentration was significantly higher in the MCI group compared with CN controls ($P = 0.007$) (Fig. 1a). Higher serum calcium levels were also detected in the sMCI and

Table 1 Baseline characteristics of study participants according to diagnosis

Characteristics	CN ($n = 413$)	MCI ($n = 811$)	P
Age (years)	74.68 ± 5.69	72.94 ± 7.60	< 0.001
Gender (F/M)	203/210	326/485	0.003
Education (years)	16.31 ± 2.67	15.88 ± 2.87	0.022
APOE ε4 carriers (%)	111 (26.88)	410 (50.55)	< 0.001
Calcium (mg/dL)	9.89 ± 0.37	9.95 ± 0.37	0.018
Phosphorus (mg/dL)	3.60 ± 0.51	3.59 ± 0.53	0.720
BMI (kg/m^2)	26.83 ± 4.54	27.07 ± 4.80	0.710
Triglyceride (mmol/L)	138.09 ± 77.41	147.75 ± 110.77	0.327
Smoker (%)	116 (28.09)	224 (27.62)	0.863
Drinker (%)	12 (2.91)	21 (2.59)	0.747
Medical history			
Hypertension (%)	182 (44.07)	393 (48.46)	0.146
T2DM (%)	39 (9.44)	80 (9.86)	0.003
CDH (%)	37 (8.96)	97 (11.96)	0.112
Number of converters (%)	76 (18.40)	296 (36.50)	< 0.001

Categorical variables are reported as numbers and percentages; continuous variables are reported as means ± SDs

SD standard deviations, *CN* cognitive normal, *MCI* mild cognitive impairment, *F* female, *M* male, *APOEε4* apolipoprotein E4, *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *CDH* coronary atherosclerotic heart disease

pMCI groups compared with the CN group ($P = 0.019$ and $P = 0.037$, respectively) (Fig. 1b).

Serum calcium and longitudinal cognitive decline and clinical progression

Linear mixed-effects models were utilized to test the associations between baseline serum calcium concentration and composite cognitive decline adjusted for age, gender, *APOE ε4* status and serum phosphorus, cognitive diagnosis, education, TG, BMI, tobacco and alcohol use, calcium supplements, vitamin D supplements, and medical histories. Significant association of baseline serum calcium concentration with MEM score ($\beta = -0.020$, $P = 0.035$, longitudinally) (Fig. 2a) and executive function (EF) score ($\beta = -0.028$, $P = 0.014$, longitudinally) (Fig. 2b) were identified. Compared with the lower calcium group (< 9.9 mg/dL), the higher group (≥ 9.9 mg/dL) has faster decline rates of MEM and EF. However, there were no associations between serum calcium and MEM or EF scores at baseline.

A total of 372 (CN = 76, MCI = 296) nondemented participants developed AD during the follow-up. Figure 3 presents the results of Kaplan–Meier analyses (nondementia elders: $P = 0.030$, CN: $P = 0.022$, MCI: $P = 0.011$). The Cox proportional hazards model was developed to estimate the predictive value of serum calcium in the conversion risk from CN or MCI to incident AD dementia. Unadjusted and adjusted HRs and 95% CIs of AD compared with low calcium group are listed in Table 2. Nondementia individuals and CN and MCI individuals with high serum calcium levels would satisfy the diagnostic criteria for AD at a comparatively earlier interval (adjusted HR = 1.41,

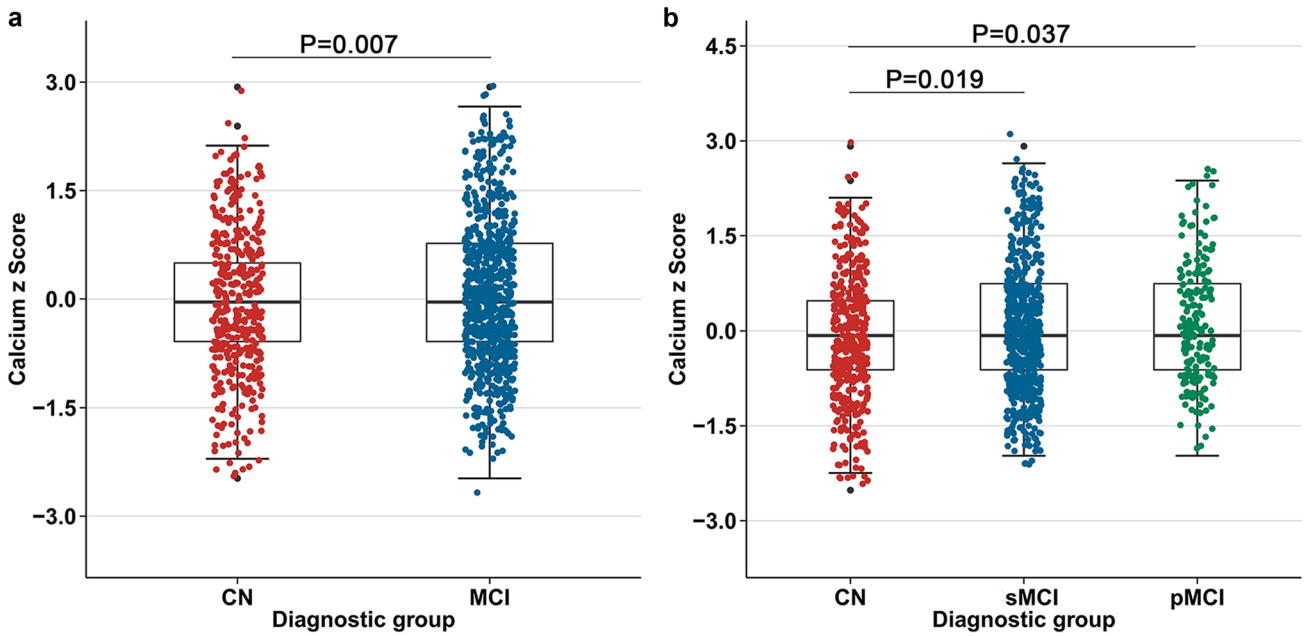

Fig. 1 Serum calcium in CN and MCI groups. The intergroup difference in serum calcium was tested using Student's *t* tests. Serum calcium concentrations were higher in the MCI group.CN cognitive normal, MCI mild cognitive impairment

Table 2 Risk of AD (HRs and 95% CIs) during follow-up

	Nondementia		CN		MCI	
	Ca < 9.9	Ca ≥ 9.9	Ca < 9.9	Ca ≥ 9.9	Ca < 9.9	Ca ≥ 9.9
Model 1*	1 (ref)	1.26 (1.02–1.57)	1 (ref)	2.36 (1.10–5.05)	1 (ref)	1.33 (1.06–1.67)
Model 2[a]	1 (ref)	1.24 (1.00–1.55)	1 (ref)	2.32 (1.08–4.96)	1 (ref)	1.32 (1.05–1.66)
Model 3[b]	1 (ref)	1.41 (1.13–1.76)	1 (ref)	2.32 (1.08–4.96)	1 (ref)	1.31 (1.04–1.64)

Unit of serum calcium is mg/dL

HR hazard ratio, *CI* confidence interval, *CN* cognitive normal, *MCI* mild cognitive impairment, *TG* triglyceride, *BMI* body mass index

*Unadjusted

[a]Adjusted for age, gender, *APOE ε4* status, and serum phosphorus

[b]Further adjusted for cognitive diagnosis, education, TG, BMI, tobacco and alcohol use, calcium supplements, vitamin D supplements, and medical histories

95% CI 1.13–1.76, HR = 2.32, 95% CI 1.08–4.96, and HR = 1.31, 95% CI 1.04–1.64, respectively) (Table 2).

Serum Calcium and Established AD Biomarkers

Multiple linear regression models were utilized to test the associations between baseline serum calcium concentration and other established AD biomarkers adjusted for age, gender, *APOE ε4* status and serum phosphorus, cognitive diagnosis, education, TG, BMI, tobacco and alcohol use, calcium supplements, vitamin D supplements, and medical histories. We found that high serum calcium level is associated with low CSF $A\beta_{42}$ ($\beta = -0.558$, $P = 0.008$), low brain metabolism measured by FDG-PET ($\beta = -0.292$, $P < 0.001$), and higher Aβ-PET ($\beta = 0.057$, $P = 0.045$) among nondemented subjects (Fig. 3b). However, there were no associations between serum calcium and CSF T-tau and P-tau levels at baseline. Correlations of higher calcium level with smaller volume of the whole brain (WB) ($\beta = -0.148$, $P = 0.002$) and middle temporal (MTL) ($\beta = -0.253$, $P = 0.015$) are also significant (Fig. 3b). Results of subgroup analyses showed that all correlations in the CN (Fig. 3d) and MCI (Fig. 3f) individuals were consistent with the results from the nondemented individuals except for the whole brain's

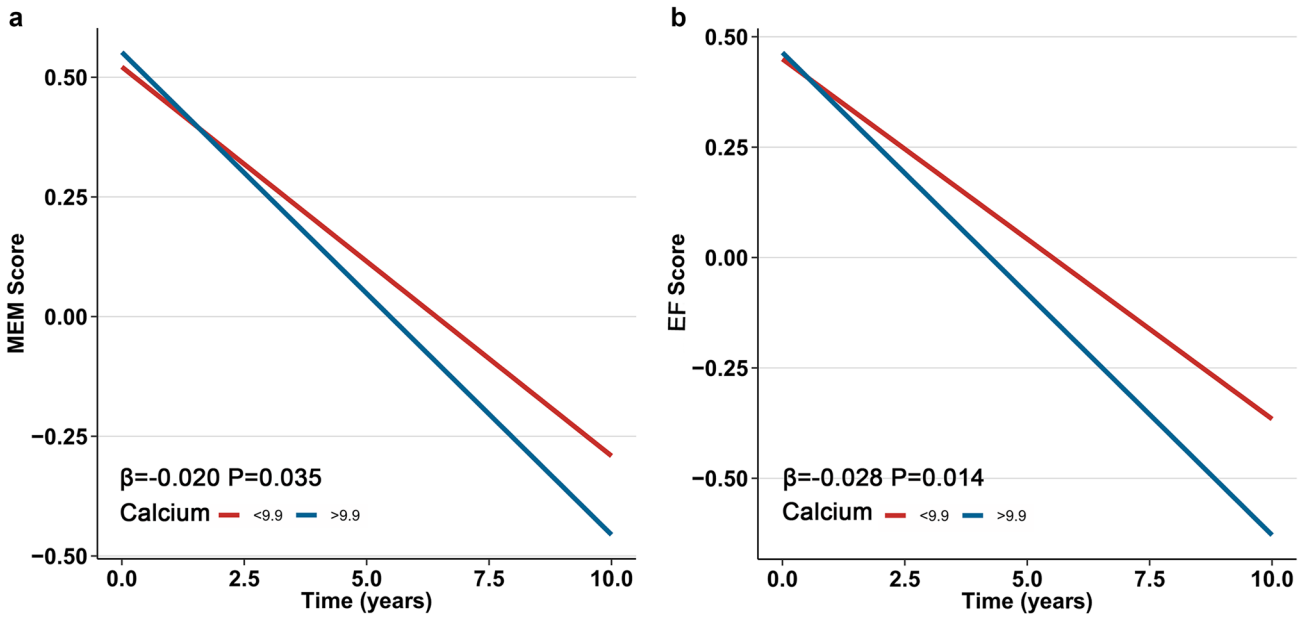

Fig. 2 Longitudinal associations between serum calcium and cognition decline. Estimated means from linear mixed-effects models adjusted for age, gender, *APOE ε4* status and serum phosphorus, cognitive diagnosis, education, TG, BMI, tobacco and alcohol use, calcium supplements, vitamin D supplements, and medical histories. MEM memory function, EF executive function *APOE* apolipoprotein E, TG triglyceride, BMI body mass index

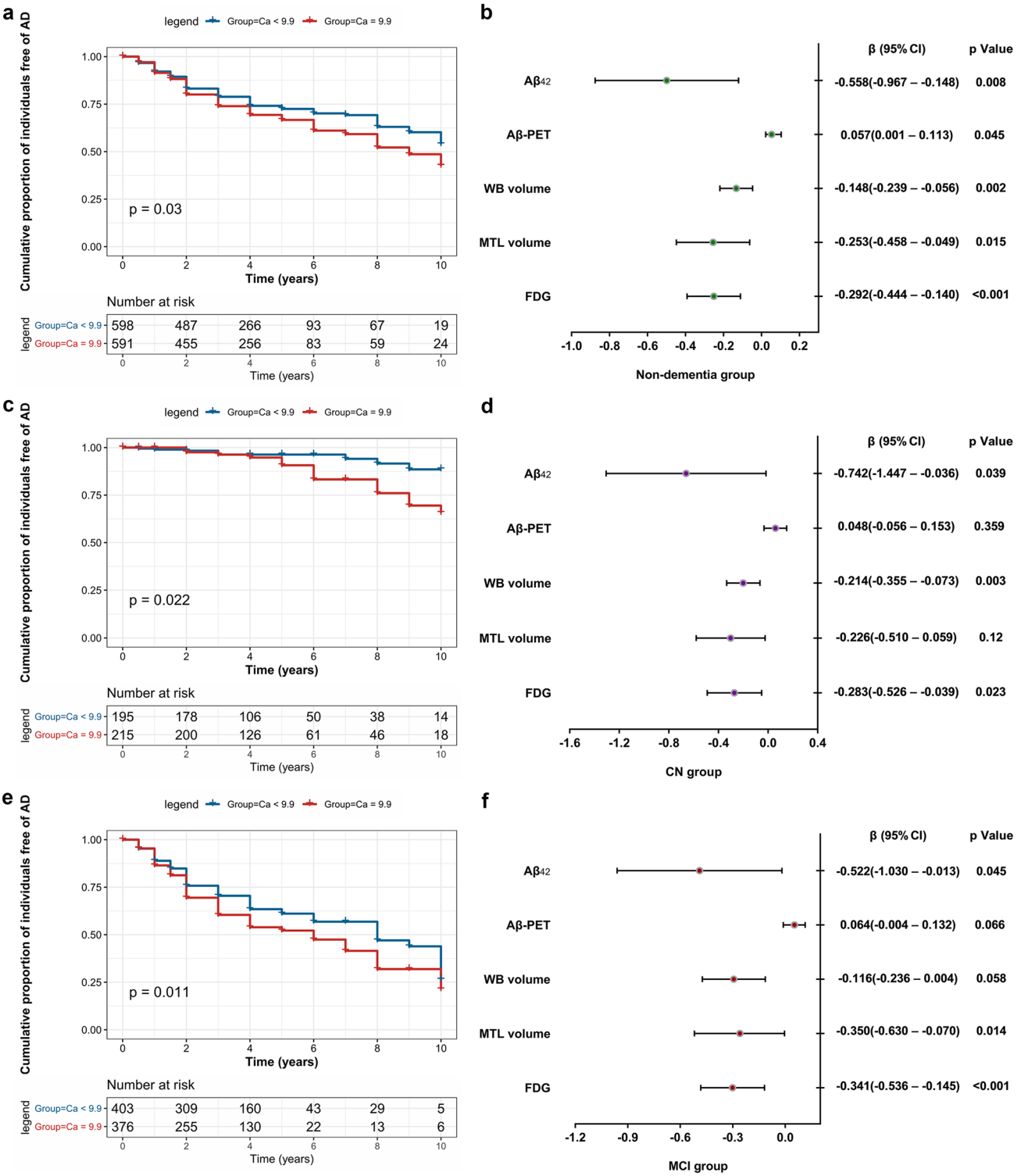

Fig. 3 Clinical progression between every pair of low calcium group and the high calcium group (cutoff 9.9 mg/dL). **a**, **c**, **e** The Kaplan–Meier curves showing cumulative probability of MCI to AD dementia progression and were ranked in the order of nondementia elders, CN, and MCI. The small crosses are censored data, with the number of objects at risk indicated at the bottom of the graph. The unadjusted *P* value for the log-rank test is shown at the bottom left. **b**, **d**, **f** Relationship between serum calcium levels and AD core biomarkers were demonstrated by estimates with β values, 95% CIs, and *P* values, which were arranged in accordance with the order mentioned above. AD Alzheimer's disease, CN normal controls, MCI mild cognitive impairment, $A\beta_{42}$ amyloid β_{42}, WB whole brain, MTL middle temporal, FDG ^{18}F-fluorodeoxyglucose, CI confidence interval

amyloid burden. All these associations still achieved significance after FDR correction. No correlation was detected between calcium concentration and cortical thickness (Supplementary Table 1).

Discussion

In the present study, we relied on a well-characterized longitudinal cohort of nondementia elders at study entry. In this cohort, we elucidated the association between serum calcium concentration and the risk of AD in the presence of baseline. Serum calcium concentration was higher in the MCI group than that in the CN group at baseline. We also found a relationship between high serum calcium concentration and increased risk for AD in the elderly, that is, the risk of AD dementia in the high calcium group (even if not hypercalcemia) is 1.33 times, compared with the low calcium group. This is consistent with our hypothesis and the results of some previous studies (Sato et al. 2019; Schram et al. 2007; Tilvis et al. 2004).

We further examined the relationship between serum calcium level and AD-related biomarkers in this nondementia sample. We now found that serum calcium was positively associated with CSF-Aβ pathology after controlling for several possible confounders. The relationship between serum calcium and Aβ pathology was further verified on Aβ-PET, and serum calcium was positively correlated with whole brain amyloid deposition. No correlation was found between high serum calcium levels and amyloid deposition in a specific brain region. These findings indicate that high levels of serum calcium do not preferentially affect Aβ metabolism in specific brain regions, which may mean that high levels of serum calcium affect all regions of the brain. No evidence for a significant relationship between serum calcium and tau pathology was found. Our study also demonstrated that serum calcium showed suggestive associations with WB volume and MTL volume. In addition, as serum calcium levels increase, metabolic levels in the entire brain decrease. The results of our study also suggested a possible mechanism for high blood calcium levels in causing the onset of AD dementia. Although Aβ plays an upstream role in the pathogenesis of AD, Aβ alone is insufficient to cause the onset of clinically detected dementia directly. However, this may be sufficient to cause downstream pathophysiologic changes such as brain atrophy that ultimately led to AD dementia (Bennett et al. 2004). We speculated that serum calcium levels influenced Aβ pathology first and subsequently reduced downstream brain atrophy rate, brain metabolism, and the risk of AD dementia.

There are many possible mechanisms that explain the beneficial effects of serum calcium on the development of AD dementia. Serum calcium is directly related to extracellular levels in the brain because calcium ions are considered to enter the brain by easy diffusion through the blood–brain barrier (Petersen et al. 2010). Meanwhile, extracellular calcium levels are closely related to intracellular calcium levels. Higher extracellular calcium status activates calcium-sensing receptors on the cell membrane, leading to increased intracellular calcium (Joborn et al. 1991). Numerous studies have demonstrated that small but long-lasting elevations of intracellular calcium ultimately lead to neuronal cell death (Hotchkiss et al. 2009; Toescu et al. 2004; Yarlagadda et al. 2007). In addition, as we guessed, Aβ is involved in this process. The formation of Aβ in the brain may be involved in the disruption of intraneuronal calcium levels. Evidence from experimental studies shows that amyloid is able to be incorporated into neuronal membranes to form calcium-permeable channels, which leads to increased intracellular calcium levels (Kawahara and Kuroda 2000).

It is worth noting that this study has some limitations. First, it may be proposed that high serum calcium levels reflect underlying disease rather than a causal relationship with decreased cognitive function. These underlying factors may include the effect of parathyroid hormone, the production of cancer-associated autoantibody, and metastasis (Bushinsky and Monk 1998). Therefore, we limited the study sample to people with normal serum calcium levels. Relatively few individuals with cancer or kidney failure in the study sample made it less likely to cause a link between serum calcium and cognitive decline. Second, serum calcium was measured only at baseline. However, it has been shown that serum calcium is maintained within a narrow range and every individual is considered to have a unique set point (Payne et al. 1973). Therefore, serum calcium is likely to remain at similar levels during follow-up. Furthermore, possible confounding factors that were not considered, such as blood vitamin D level at baseline.

Serum calcium levels are affected in many ways. Previous studies have focused on the relationship between calcium supplementation and dementia. It is believed that calcium supplementation actually increases the risk of AD (Bolland et al. 2011; Kern et al. 2016; Sato et al. 2019). The mechanism of calcium supplements in the pathogenesis of dementia could be the steep increase in serum calcium levels caused by the supplements (Bolland et al. 2010). Combined with our findings, we recommend that the elderly, especially those with long-term calcium supplementation, regularly test their serum calcium.

The main findings of this study were that serum calcium concentration (1) was elevated in MCI group compared with control groups, (2) predicted longitudinal cognitive decline and conversion from nondementia status to AD dementia, and (3) associated with CSF $A\beta_{42}$ level, Aβ-PET, FDG-PET, WB volume, and MTL volume among nondemented elderly adults. Taken together, these findings suggest that serum calcium is a potentially presymptomatic

biomarker for AD. In the preclinical stage, this biomarker may be helpful in predicting disease progression and cognitive decline in preclinical stage. Our study also provided clues to how serum calcium participated in the pathogenetic process in AD.

In conclusion, the long-term high calcium status (even if not hypercalcemia) of the elderly cannot be ignored. To better understand the effect of serum calcium levels on AD, further studies in other populations are necessary.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12640-020-00312-y) contains supplementary material, which is available to authorized users.

Author Contributions Ling-Zhi Ma, Zi-Xuan Wang, Qiang Dong, Lan Tan, and Jin-Tai Yu planed the work and drafted the manuscript; Ling-Zhi Ma, Zi-Xuan Wang, Zuo-Teng Wang, and Xiao-He Hou helped in the manuscript preparation; Ling-Zhi Ma, Zi-Xuan Wang, Xue-Ning Shen, and Ya-Nan Ou designed and has drawn the figures and pathway; Lan Tan and Jin-Tai Yu guided throughout the manuscript.

Funding 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 W81XWH-12-2-0012). 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; Bristol-Myers 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. This study was supported by grants from the National Natural Science Foundation of China (91849126, 81571245, and 81771148), the National Key R&D Program of China (2018YFC1314700), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

Apostolova LG et al (2010) 3D PIB and CSF biomarker associations with hippocampal atrophy in ADNI subjects. Neurobiol Aging 31:1284–1303. https://doi.org/10.1016/j.neurobiolaging.2010.05.003

Bennett DA et al (2004) Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. Arch Neurol 61:378–384. https://doi.org/10.1001/archneur.61.3.378

Betzer C et al (2018) Alpha-synuclein aggregates activate calcium pump SERCA leading to calcium dysregulation EMBO reports 19. https://doi.org/10.15252/embr.201744617

Bolland MJ et al (2010) Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ (Clinical Research Ed) 341:c3691. https://doi.org/10.1136/bmj.c3691

Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR (2011) Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ (Clinical Research Ed) 342:d2040. https://doi.org/10.1136/bmj.d2040

Bushinsky DA, Monk RD (1998) Electrolyte quintet: Calcium Lancet (London, England) 352:306–311. https://doi.org/10.1016/s0140-6736(97)12331-5

Bussiere R et al (2019) Upregulation of the sarco-endoplasmic reticulum calcium ATPase 1 truncated isoform plays a pathogenic role in Alzheimer's disease Cells 8. https://doi.org/10.3390/cells8121539

Crane PK et al (2012) Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Brain Imaging Behav 6:502–516. https://doi.org/10.1007/s11682-012-9186-z

Eichler T et al (2014) Rates of formal diagnosis in people screened positive for dementia in primary care: results of the DelpHi-Trial. J Alzheimers Dis 42:451–458. https://doi.org/10.3233/jad-140354

Gibbons LE et al (2012) A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. Brain Imaging Behav 6:517–527. https://doi.org/10.1007/s11682-012-9176-1

Hendrix JA et al (2015) The worldwide Alzheimer's Disease Neuroimaging Initiative: an update. Alzheimer's Dement 11:850–859. https://doi.org/10.1016/j.jalz.2015.05.008

Hotchkiss RS, Strasser A, McDunn JE, Swanson PE (2009) Cell death. N Engl J Med 361:1570–1583. https://doi.org/10.1056/NEJMra0901217

Jagust WJ et al (2009) Relationships between biomarkers in aging and dementia. Neurology 73:1193–1199. https://doi.org/10.1212/WNL.0b013e3181bc010c

Jessen F et al (2014) A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement 10:844–852. https://doi.org/10.1016/j.jalz.2014.01.001

Joborn C et al (1991) Cerebrospinal fluid calcium, parathyroid hormone, and monoamine and purine metabolites and the blood-brain barrier function in primary hyperparathyroidism Psychoneuroendocrinology 16:311–322. https://doi.org/10.1016/0306-4530(91)90017-n

Kawahara M, Kuroda Y (2000) Molecular mechanism of neurodegeneration induced by Alzheimer's beta-amyloid protein: channel formation and disruption of calcium homeostasis. Brain Res Bull 53:389–397. https://doi.org/10.1016/s0361-9230(00)00370-1

Kern J et al (2016) Calcium supplementation and risk of dementia in women with cerebrovascular disease. Neurology 87:1674–1680. https://doi.org/10.1212/wnl.0000000000003111

Lacampagne A et al (2017) Post-translational remodeling of ryanodine receptor induces calcium leak leading to Alzheimer's disease-like

pathologies and cognitive deficits. Acta Neuropathol 134:749–767. https://doi.org/10.1007/s00401-017-1733-7

McKhann G et al (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944. https://doi.org/10.1212/wnl.34.7.939

Ogihara T, Miya K, Morimoto S (1990) Possible participation of calcium-regulating factors in senile dementia in elderly female subjects. Gerontology 36(Suppl 1):25–30. https://doi.org/10.1159/000213230

Payne RB, Little AJ, Williams RB, Milner JR (1973) Interpretation of serum calcium in patients with abnormal serum proteins. BMJ 4:643–646. https://doi.org/10.1136/bmj.4.5893.643

Petersen RC et al (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 74:201–209. https://doi.org/10.1212/WNL.0b013e3181cb3e25

Sato K et al (2019) Lower serum calcium as a potentially associated factor for conversion of mild cognitive impairment to early Alzheimer's disease in the Japanese Alzheimer's Disease Neuroimaging Initiative. J Alzheimers Dis 68:777–788. https://doi.org/10.3233/jad-181115

Schram MT et al (2007) Serum calcium and cognitive function in old age. J Am Geriatr Soc 55:1786–1792. https://doi.org/10.1111/j.1532-5415.2007.01418.x

Shaw LM et al (2009) Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 65:403–413. https://doi.org/10.1002/ana.21610

Sperling RA et al (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer''s Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:280–292. https://doi.org/10.1016/j.jalz.2011.03.003

Subhash MN et al (1991) Calcium and phosphorus levels in serum and CSF in dementia. Neurobiol Aging 12:267–269. https://doi.org/10.1016/0197-4580(91)90001-z

Tilvis RS et al (2004) Predictors of cognitive decline and mortality of aged people over a 10-year period . J.Gerontol A Biol Sci Med Sci 59:268–274. https://doi.org/10.1093/gerona/59.3.m268

Toescu EC, Verkhratsky A, Landfield PW (2004) Ca^{2+} regulation and gene expression in normal brain aging Trends. Neurosci 27:614–620. https://doi.org/10.1016/j.tins.2004.07.010

Walker MD, Silverberg SJ (2008) Cardiovascular aspects of primary hyperparathyroidism. J Endocrinol Invest 31:925–931. https://doi.org/10.1007/bf03346443

Yarlagadda A, Kaushik S, Clayton AH (2007) Blood brain barrier: the role of calcium homeostasis Psychiatry (Edgmont (Pa : Township)) 4:55–59.

Yurko R, G'Sell M, Roeder K, Devlin B (2020) A selective inference approach for false discovery rate control using multiomics covariates yields insights into disease risk. Proc Natl Acad Sci USA 117:15028–15035. https://doi.org/10.1073/pnas.1918862117

Zhang D et al (2011) Multimodal classification of Alzheimer's disease and mild cognitive impairment. NeuroImage 55:856–867. https://doi.org/10.1016/j.neuroimage.2011.01.008

Zhen D et al (2015) High prevalence of vitamin D deficiency among middle-aged and elderly individuals in northwestern China: its relationship to osteoporosis and lifestyle factors. Bone 71:1–6. https://doi.org/10.1016/j.bone.2014.09.024