Association of creatine kinase with Alzheimer's disease pathology: A cross-sectional study

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To the Editor: Creatine kinase (CK), also called creatine phosphokinase, is primarily located in the cytoplasm and mitochondria. It can be used to diagnose cardiac diseases such as myocardial infarction, viral myocarditis, and pericarditis because it is a vital kinase directly related to intracellular energy operation, muscle contraction, and adenosine triphosphate (ATP) regeneration. Several studies have confirmed in recent years that serum biomarkers such as elevated CK are associated with Alzheimer's disease (AD) and its related pathological protein.[1] Previous research indicated that systemic conditions, particularly cardiovascular and cerebrovascular diseases, are significant risk factors for cognitive impairment, and dysfunction of peripheral organs may also contribute to cognitive decline and AD.[2] However, the connection between CK and AD remains unknown. Therefore, to investigate the association between CK and cerebrospinal fluid (CSF) AD pathology biomarkers, we analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a global multi-centered database.

Participants from the ADNI database (https://adni.loni.usc.edu/) were involved in this study after excluding participants who lacked available necessary baseline or CK data. The ADNI database is accessible to researchers upon application. The ADNI collected participant data on clinical history, biochemical markers, genetics, and neuroimaging at baseline and during follow-up as well as the neurological, physical, and neuropsychological examination results. Blood, CSF, and urine samples were collected at baseline and multiple follow-up visits to detect biomarkers. The institutional review boards approved this multi-site longitudinal biomarker research project, and participants provided written informed consent (https://adni.loni.usc.edu/).

The data on CK (FLDNAME: RCT14), CSF β-amyloid$_{1–42}$ (Aβ), and phosphorylated tau-181 (P-tau) of the participants in this study were extracted from the ADNI-1 subgroup. Previous research on the AT(N) framework indicated that CSF Aβ cut-offs were considered at 976.6 pg/mL (categorized as Aβ+ <976.6 pg/mL; and Aβ– ≥976.6 pg/mL) as well as CSF P-tau cut-offs at 21.8 pg/mL (categorized as T+ >21.8 pg/mL; and T– ≤21.8 pg/mL).[3]

In this study, to examine the intergroup differences, we used chi-squared analysis for categorical variables, and student's *t*-test and one-way analysis of variance (ANOVA) for continuous variables with normal distribution. We further used multiple linear regression models to investigate the relationship between CK levels and CSF AD biomarkers. Box diagram and scatter diagram were conducted to visualize data. Our study reported a conventional and significant two-sided *P*-value threshold of 0.05 and a 95% confidence interval (CI). R Studio (version 4.2.1, www.rstudio.com/) was used for statistical analyses and diagram generation.

A total of 1607 participants were included in this study, including 443 participants with normal cognitive function (CN), 853 participants with mild cognitive impairment (MCI), and 311 participants with AD. For all included participants, the mean age was 73.8 (7.2) years,

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891 (55.44%) of them were male, and the mean education experience was 15.9 (2.86) years. The detailed information on demographic characteristics, biomarkers, and AD-related indicators in three groups was presented in Supplementary Table 1, http://links.lww.com/CM9/B878.

The comparison results of CK levels in different age, gender, *APOE ε4* status, cognitive status, and AD diagnosis groups were showed in Supplementary Figure 1, http://links.lww.com/CM9/B878. The male group had a higher level of CK than the females (107.5 ± 65.6 U/L *vs.* 94.3 ± 52.5 U/L; P <0.001; Supplementary Figure 1A, http://links.lww.com/CM9/B878). Compared with middle-aged participants, elderly participants (109.3 ± 61.0 U/L *vs.* 119.5 ± 66.8 U/L; $P = 0.020$; Supplementary Figure 1B, http://links. lww. com/CM9/B878) had a lower level of CK. And AD diagnosis participants had a lower level of CK than non-AD participants (103.5 ± 57.8 U/L *vs.* 112.3 ± 62.7 U/L; $P = 0.010$, Supplementary Figure 1C, http://links.lww.com/CM9/B878). AD participants had a significantly lower level of CK than MCI participants (103.5 ± 57.8 U/L *vs.* 115.5 ± 65.4 U/L; $P = 0.006$; Supplementary Figure 1E, http://links.lww.com/CM9/B878); however, there was no significant difference in CK levels between CN and AD (106.6 ± 57.1 U/L *vs.* 103.5 ± 57.8 U/L, P >0.05; Supplementary Figure 1E, http://links.lww.com/CM9/B878) as well as CN and MCI (106.6 ± 57.1 U/L *vs.* 115.5 ± 65.4 U/L, P >0.05; Supplementary Figure 1E, http://links.lww.com/CM9/B878). Specifically, there was no statistically significant difference in CK level between any *APOE ε4* status groups (*APOE ε4* negative = 111.7 ± 62.3 U/L; *APOE ε3/ε4* = 109.1 ± 61.1 U/L; *APOE ε4/ε4* = 110.6 ± 63.3 U/L; all P >0.05; Supplementary Figure 1D, http://links.lww.com/CM9/B878). The Aβ+ group had a lower level of CK than Aβ− group (106.8 ± 61.7 U/L *vs.* 114.2 ± 64.1 U/L; $P = 0.025$, Supplementary Figure 1F, http://links.lww.com/CM9/B878), and the difference between Aβ− and Aβ+ groups was statistically significant. When grouped by CSF P-tau, compared with T− group, T+ had a significantly lower level of CK (116.4 ± 67.3 U/L *vs.* 104.9 ± 58.7 U/L; $P = 0.005$; Supplementary Figure 1G, http://links. lww. com/CM9/B878). After excluding the influence of collinearity on the results, we then used a linear regression model to examine the relationship between CK and Aβ and P-tau, and did not find the significant linear relationship between CK and Aβ ($\beta = 0.044$, 95% CI: −0.019 to 0.106; $P = 0.173$; Supplementary Figure 1H, http://links.lww.com/CM9/B878); however, a decrement of CK associated with increased level of P-tau was found ($\beta = -0.068$, 95% CI: −0.132 to −0.003; $P = 0.039$; Supplementary Figure 1I, http://links.lww.com/CM9/B878).

It is well known that CK levels can indicate cardiovascular diseases such as myocardial infarction and myocarditis. Furthermore, studies have shown that cardiovascular disease co-morbidities are closely linked to dementia.[4] There is an association between metabolic abnormalities and cardiovascular disease, and previous research indicates that cardiometabolic diseases may also increase the risk of dementia.[5] In addition, previous research has demonstrated that the stabilization of heart function can prevent brain structure changes and brain dysfunction and that the improvement of heart function can also, to a certain extent, improve brain function, demonstrating the close relationship between the heart system and brain function.[6] This study focuses on peripheral metabolic marker CK, which is relevant to diagnosing cardiovascular disease *in vivo*. This marker may indicate how cardiac activity affects reduced metabolic function, brain health, and subsequent cognitive decline. The brain has an extremely high energy requirement, and CK promotes cognitive function, dendrite generation, and cell motility by producing large amounts of adenosine triphosphate (ATP) during brain activation. As an essential component of energy metabolism, CK is associated with neurological disorders. Alterations in ATP-metabolizing proteins, such as CK, are associated with early AD mitochondrial dysfunction. Recent research by Sandebring–Matton *et al*[7] has found large deposits of B-type CK in the hippocampal pyramidal cells and frontal cortex of AD patients, which may be related to abnormal creatine metabolism in oligodendrocytes. In addition, research indicates that CK, as a protective factor, plays a role in cognitive decline and the onset of dementia.[8] It also suggests that increasing CK levels may be a cognition-protective means for enhancing cognitive function. In our results, CK levels were significantly lower in the AD population than in the MCI population, suggesting that lower levels of CK may be associated with complete cognitive impairment. However, no significant differences were found between the CN group and the MCI or AD groups, respectively. This may be due to the fact that the paticipants in CN group were older than those in MCI group, and CK levels may be affected by age. Therefore, future studies should be conducted in participants with comparable age distribution to verify our inference.

CK catalyzes the conversion of adenosine diphosphate (ADP) and creatine phosphate into ATP and creatine and plays a crucial role in regulating the energy supply for muscle contraction, particularly cardiac muscle contraction, by maintaining a relatively stable ATP pool. In heart failure patients, pathological hypertrophy and myocardial remodeling are closely associated with deficient ATP levels and CK-related responses. Meanwhile, published research indicates that changes in central CK levels can result in alterations in central nervous system function and ATP dysfunction, which may influence the altered brain health environment.[9] Another study revealed that oxidation of CK in AD led to the disruption of CSF AD pathology proteins and that AD patients' brains exhibited decreased CK activity.[10] As there are no clear serological markers for the diagnosis and prognosis of cognitive impairment, peripheral CK levels can be considered a non-invasive method and a serological marker for diagnosing cardiovascular diseases and cognitive impairment. However, this needs to be further demonstrated in future research. In addition, the level of CK, which also reflects the metabolic status of the body, particularly creatine and energy metabolism, can aid in the secondary prevention of cognitive impairment.

In conclusion, we investigated the relationship between CK levels and AD in this study. The result of intergroup differences analysis identified that CK levels were associated with age, gender, AD diagnosis, and CSF AD biomarkers. The linear regression model demonstrated a significant correlation between P-tau level increases and CK level decreases. The correlation between CK and AD should be investigated in more details in future studies to determine whether CK and CK-related cardiometabolic disorders can be used as serological diagnostic or prognostic markers to provide new insights into AD.

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Conflicts of interest

None.

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