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Elevated Homocysteine Levels and Hypertension Relate to Cognitive Impairment via Increased White Matter Hyperintensity Volume

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Abstract.
Background: Recent studies have identified a relationship between elevated homocysteine levels and hypertension (HTN) with Alzheimer's disease (AD), but its pathogenesis remains unclear.
Objective: To evaluate elevated homocysteine levels and HTN as risk factors for cognitive impairment (CI) and determine their relationship with white matter hyperintensity (WMH) volume.
Methods: A total of 521 subjects were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and divided into two groups according to the diagnostic criteria of the ADNI database. The CI group included 370 subjects, consisting of 122 with AD and 248 with mild CI, while the cognitively normal (CN) group contained 151 subjects. The history of HTN, homocysteine levels, WMH volume and Mini-Mental State Examination (MMSE) scores were analyzed.
Results: The study found that patients with CI had higher homocysteine levels than those with CN. Additionally, WMH volume was significantly correlated with homocysteine levels in CI patients, and MMSE scores decreased as WMH volume increased. Further analysis revealed that CI patients with HTN had significantly higher homocysteine levels than those without

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[2]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of the 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/wpcontent/uploads/how to apply/ADNI Acknowledgment List.pdf

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HTN. Furthermore, the correlation between WMH volume and homocysteine levels was significant only in CI patients with HTN and not in those without HTN. In CN patients, there was no correlation between WMH volume and homocysteine levels in either the HTN or non-HTN groups, and no difference was observed in homocysteine levels.
Conclusions: It is indicated that elevated homocysteine levels in conjunction with HTN are associated with the increased volume of WMHs and CI.

Keywords: Alzheimer's disease, homocysteine, hypertension, white matter hyperintensities

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and is characterized by gradual memory loss, cognitive impairment (CI), a progressive decline in daily activities, abnormal behavior, and social impairment [1, 2]. The pathogenesis of AD is complex and varied, and recent studies have identified increased homocysteine levels as a potential biomarker for AD [3]. Hypertension (HTN) is also a major vascular risk factor for AD morbidity and worsening of prognosis [4]. Previous research has shown that high homocysteine levels are associated with cognitive decline in elderly hypertensive patients [5] and may interact with cardiovascular diseases such as HTN to increase white matter hyperintensity (WMH) volume [6]. WMHs have been reported in AD and are linked with CI [7].

This study aimed to assess the effects of homocysteine levels and HTN on WMH volume in patients with CI and cognitively normal (CN) individuals from the ADNI database. We sought to investigate whether the synergistic effect of homocysteine levels with HTN on cognitive function might be mediated through WMH volume.

MATERIALS AND METHODS

ADNI database

The original data for this study were collected from the ADNI database (http://www.adni-info.org), which was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, led by Principal Investigator Michael W. Weiner, MD. The goal of the initiative was to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD. All participating agencies have approved the use of the ADNI database, and written informed consent was obtained from all participants at each site. This study was also approved by the relevant leader or participant of the initiative.

Participants

A total of 521 subjects were included in this study, with 370 in the CI group and 151 in the CN group. General inclusion criteria for the different patient groups were as follows: CN subjects: MMSE scores between 24–30 (inclusive), a CDR of 0, nondepressed, non-mild cognitive impairment (MCI), and nondemented. MCI subjects: MMSE scores between 24–30 (inclusive), a memory complaint, objective memory loss measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. Mild AD: MMSE scores between 20–26 (inclusive), CDR of 0.5 or 1.0, and meets NINCDS/ADRDA criteria for probable AD.

All participants underwent 1.5-tesla anatomical brain MRI scans as part of the ADNI study. Blood samples were collected in the morning after overnight fasting and before breakfast at the time of their baseline MRI scan. Total homocysteine levels in plasma samples were measured using an enzyme immunoassay [8]. Participants were classified as having HTN or not based on their self-reported history of HTN.

WMH volume measurement

The details of this method are published [9]. In brief, this method performs WMH detection using a Bayesian Markov random field (MRF) method established by vectors of three image intensities (PD, T1, and T2) associated with the image pixels, with the goal of determining a binary label for each image voxel that indicates the presence or absence of WMH at that voxel. This is accomplished by utilizing the three image intensity vectors that maximize the posterior probability of the labels given the image intensity

data. Within Bayes' theorem modified by MRF, the prior probability of a specific label depends both on the spatial prior—the prior probability that WMHs occur at a given pixel as well as the contextual prior (i.e., the conditional probability of each voxel given the labels at neighbors of that voxel). The likelihood depends on the statistical distribution of the (PD, T1, T2) image intensities relative to the underlying labels.

Neurological evaluations

The Mini-Mental State Examination (MMSE) scale is a widely used tool for dementia screening because it can comprehensively, accurately, and rapidly reflect the mental state and degree of cognitive impairment in subjects. The scale includes seven domains: time orientation, place orientation, immediate memory, attention and computation, delayed memory, language, and visual space. A total of 30 questions are included on the scale. One point is awarded for each correct answer, while zero points are given for any wrong or unknown answers.

Statistical methods

The correlations of WMH volume with MMSE score and homocysteine levels were analyzed using IBM SPSS 25.0 statistical analysis software. Pearson correlation coefficients were calculated for variables that followed a normal distribution, while Spearman's rank correlation coefficients were calculated for variables that did not follow a normal distribution. Patients with CI and those who were CN were divided into groups for homocysteine level difference analysis. Data that met the assumptions of normality and homogeneity of variance were analyzed using one-way analysis of variance (ANOVA), while nonparametric tests were used for data that did not meet these assumptions.

RESULTS

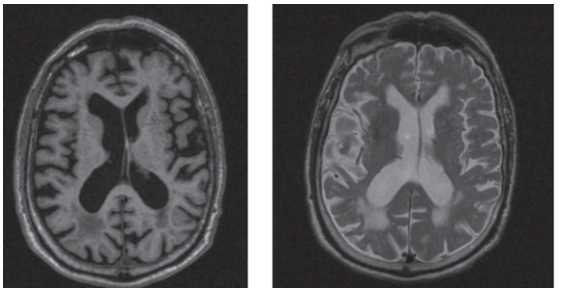
General information

A total of 370 patients with CI and 151 CN patients were analyzed. There were significant differences between the two groups in terms of sex (female ratio in CI: 58.6%, CN: 48.3%), mean homocysteine levels (CI: 10.9 ± 3.03, CN: 10.2 ± 2.73), WMH volume (CI: 0.942 ± 1.896, CN: 0.588 ± 1.274), MMSE scores (CI: 25.6 ± 3.3, CN: 29.1 ± 1.0), diastolic blood pressures (CI: 74.7 ± 9.5, CN: 72.8 ± 10.3), cerebrospinal fluid (CSF) amyloid-β 42 ($A\beta_{42}$) (CI: 155.1 ± 50.6, CN: 207.8 ± 57.2), CSF tau (CI: 110.5 ± 60.4, CN: 70.1 ± 29.8), CSF p-tau (CI: 38.0 ± 18.7, CN: 24.2 ± 14.2), apolipoprotein 4 (*APOE4*) carriage (CI: 57.6%, CN: 28.5%), and body mass index (BMI) (CI: 25.7 ± 3.75, CN: 26.5 ± 44.2). Mean age (CI: 75.8 ± 7.0, CN: 76.5 ± 5.0), systolic blood pressure (CI: 136.0 ± 17.3, CN: 133.2 ± 16.7), diabetes mellitus (CI: 6.8%, CN: 7.9%), smoking (CI: 25.4%, CN: 31.1%), and dyslipidemia (CI: 15.7%, CN: 12.6%) were not significantly different between the CI and CN groups (Table 1, all $p < 0.05$).

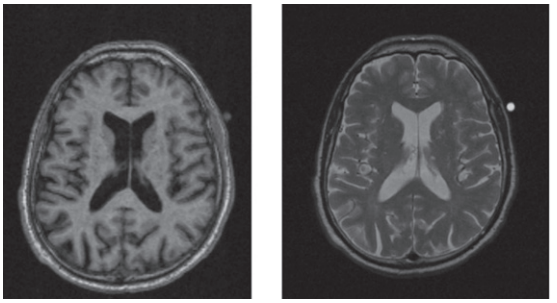
Table 1
Basic information of CI and CN subjects

Variables	CI Group, N = 370	CN, N = 151	*p*
Age (y)	75.8 ± 7.0	76.5 ± 5.0	0.558
Female sex, *n* (%)	217 (58.6%)	73 (48.3%)	0.002
Education (y)	15.3 ± 3.0	15.7 ± 2.9	0.116
Homocysteine (μM)	10.9 ± 3.0	10.2 ± 2.7	0.010
WMH volume (ml)	0.942 ± 1.896	0.588 ± 1.274	0.006
MMSE score	25.6 ± 3.3	29.1 ± 1.0	0.000
Systolic blood pressure (mm Hg)	136.0 ± 17.3	133.2 ± 16.7	0.098
Diastolic blood pressure (mm Hg)	74.7 ± 9.5	72.8 ± 10.3	0.034
CSF Aβ42 (pg/ml)	155.1 ± 50.6	207.8 ± 57.2	0.000
CSF Tau (pg/ml)	110.5 ± 60.4	70.1 ± 29.8	0.000
CSF P-tau (pg/ml)	38.0 ± 18.7	24.2 ± 14.2	0.000
APOE4 carriage, *n* (%)	213 (57.6%)	43 (28.5%)	0.000
BMI	25.7 ± 3.8	26.5 ± 4.2	0.032
Diabetes mellitus, *n* (%)	25 (6.8%)	12 (7.9%)	0.631
Smoking, *n* (%)	94 (25.4%)	47 (31.1%)	0.182
Dyslipidemia, *n* (%)	58 (15.7%)	19 (12.6%)	0.367

WMH, white matter hyperintensity, MMSE, Mini-Mental State Examination, CSF, cerebrospinal fluid, $A\beta_{42}$, amyloid-β 42, BMI, body mass index, CI, cognitive impairment, CN, cognitively normal.



MRI pictures of WMH in CI (T1 and T2)



MRI pictures of WMH in CN (T1 and T2)

Fig. 1. Magnetic resonance imaging (MRI) in cognitively impaired (CI) and cognitively normal (CN) subjects. T1 and T2 pictures of brain cross-section MRI of typical patients with CI and CN. WMH, white matter hyperintensities.

Homocysteine levels and abnormal WMH volume are associated with CI

In this study, both serum homocysteine levels and WMH volume were found to be increased in patients with CI compared to CN patients (Table 1 and Fig. 1, $p < 0.05$). In the binary logistic regression analysis, after adjusting for confounding factors such as gender, age, diabetes, hypertension, smoking, years of education, and BMI, homocysteine levels and WMH volume were significantly associated with CI (Supplementary Table 1, $p < 0.05$). Correlation analysis using Pearson's or Spearman's rank correlation coefficients revealed that homocysteine levels were positively correlated with WMH volume in CI patients (Fig. 2, $p < 0.01$), and WMH volume was negatively correlated with MMSE scores (Fig. 2, $p < 0.01$). However, no significant correlations were found in CN patients (Fig. 2, $p > 0.05$).

Association between homocysteine levels and HTN with WMH and CI

This study found that homocysteine levels were significantly higher in patients with CI and HTN than in patients without HTN (Table 2, $p < 0.05$). However, there was no significant difference in homocysteine levels between hypertensive and nonhypertensive CN patients (Table 3, $p > 0.05$). Furthermore, homocysteine levels were found to be more significantly correlated with WMH volume in CI patients with HTN than in those without HTN (Fig. 3).

DISCUSSION

Our study found that patients with CI had high levels of homocysteine, which is consistent with

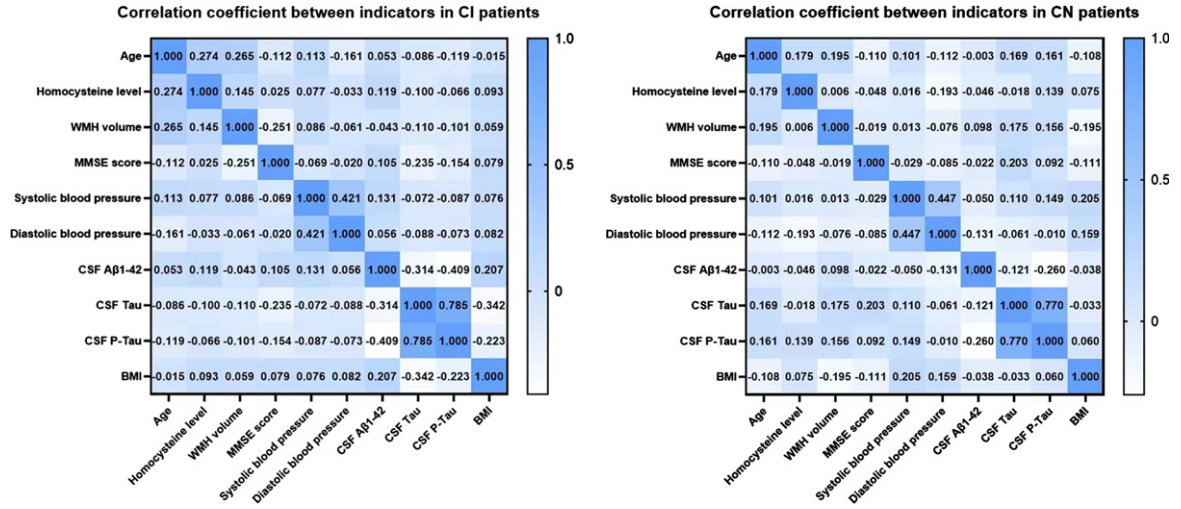


Fig. 2. Correlation coefficients for relationships among the indicators in cognitive impaired (CI) and cognitively normal (CN) patients. The heatmap represents the correlation coefficients for the relationships among the indicators of the patients; the darker the color, the higher the correlation. The left panel represents the CI patients, and the right panel represents the CN patients. WMH, white matter hyperintensities; MMSE, Mini-Mental State Exam; CSF, cerebrospinal fluid; BMI, body mass index.

Table 2
Basic information of CI patients with and without HTN

Variables	HTN, N = 203	NO HTN, N = 167	*p*
Age (y)	76.8 ± 6.5	74.6 ± 7.3	0.003
Female sex, *n* (%)	82 (40.4%)	75 (44.9%)	0.382
Homocysteine (μM)	11.5 ± 3.3	10.2 ± 2.6	0.000
WMH volume (ml)	0.951 ± 1.559	0.931 ± 2.243	0.109
MMSE score	25.4 ± 3.4	25.7 ± 3.1	0.577
Systolic blood pressure (mm Hg)	138.3 ± 16.9	133.1 ± 17.3	0.001
Diastolic blood pressure (mm Hg)	75.1 ± 9.6	74.2 ± 9.4	0.484
CSF $A\beta_{42}$ (pg/ml)	156.0 ± 48.0	154.2 ± 53.3	0.311
CSF Tau (pg/ml)	106.4 ± 55.7	114.6 ± 64.9	0.367
CSF P-tau (pg/ml)	36.6 ± 17.8	39.5 ± 19.5	0.363
APOE4 carriage, *n* (%)	121 (59.6%)	92 (55.1%)	0.382
BMI	26.4 ± 4.0	24.9 ± 3.3	0.000
Diabetes mellitus, *n* (%)	20 (9.9%)	5 (3.0%)	0.009
Smoking, *n* (%)	51 (25.1%)	43 (25.7%)	0.891
Dyslipidemia, *n* (%)	37 (18.2%)	21 (12.6%)	0.137

Table 3
Basic information of CN subjects with and without HTN

Variables	HTN, N = 76	NO HTN, N = 75	*p*
Age (y)	77.1 ± 4.9	75.8 ± 5.1	0.123
Female sex, *n* (%)	43 (56.6%)	35 (46.7%)	0.223
Homocysteine (μM)	10.5 ± 2.9	9.8 ± 2.6	0.225
WMH volume (ml)	0.767 ± 1.635	0.408 ± 0.718	0.688
MMSE score	29.1 ± 0.9	29.1 ± 1.1	0.488
Systolic blood pressure (mm Hg)	139.7 ± 16.4	126.5 ± 14.2	0.000
Diastolic blood pressure (mm Hg)	75.2 ± 10.1	70.4 ± 10.0	0.006
CSF $A\beta_{42}$ (pg/ml)	207.2 ± 55.9	208.4 ± 59.2	0.895
CSF Tau (pg/ml)	69.6 ± 26.2	70.6 ± 33.7	0.754
CSF P-tau (pg/ml)	24.2 ± 10.1	24.2 ± 17.7	0.153
APOE4 carriage, *n* (%)	22 (28.9%)	21 (28%)	0.897
BMI	27.4 ± 4.3	25.5 ± 3.9	0.006
Diabetes mellitus, *n* (%)	7 (9.2%)	5 (6.7%)	0.563
Smoking, *n* (%)	23 (30.3%)	24 (32%)	0.818
Dyslipidemia, *n* (%)	12 (15.8%)	7 (9.3%)	0.232

previous studies linking elevated plasma total homocysteine levels to the risk of dementia and AD [10, 11]. In this study, the results showed a significantly higher volume of WMH in CI versus CN subjects, which was negatively correlated with the MMSE scores, indicating that an increased WMH volume is associated with worse cognitive function [12]. We also found that homocysteine levels were positively correlated with WMH volume, suggesting that homocysteine may lead to cognitive dysfunction by increasing WMH volume. Additionally, our study revealed that CI patients with a history of HTN had higher homocysteine levels, and the correlation between homocysteine levels and WMH volume was stronger, suggesting that HTN exacerbates the impact of homocysteine on WMH volume and further damages cognitive function.

A previous study identified high homocysteine levels as an independent risk factor for cardiovascular disease. However, recent studies have demonstrated that increased homocysteine levels are also a risk factor for cognitive decline and the development of AD. For example, Ravaglia et al. [13] found that as homocysteine levels increased, MMSE scores decreased. Oulhaj et al. [14] discovered that homocysteine levels could predict the conversion of MCI to AD and the progressive decline in cognitive function in AD patients. Moreover, a few studies have indicated that elevated plasma homocysteine levels are associated with brain WMH volume [15, 16], which is linked to various neurological disorders, including cognitive decline [17]. Consistent with these findings, we found that homocysteine levels were higher in CI patients than in CN groups and that homocysteine levels were positively correlated with WMH volume in CI patients, but no direct correlation was found between homocysteine levels and MMSE scores. In addition, we found that WMH volume was higher in

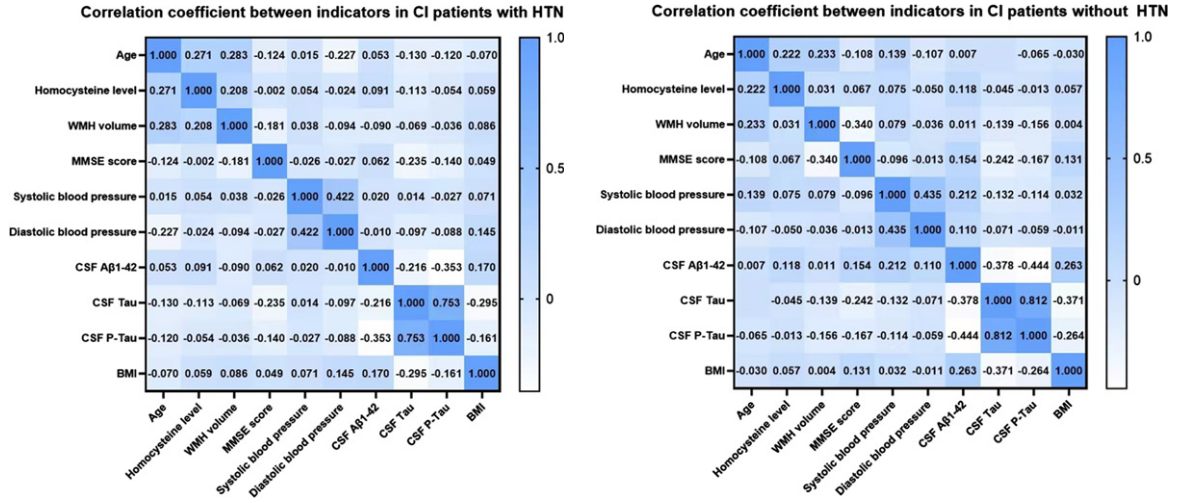


Fig. 3. Correlation coefficients for relationships among the indicators in cognitively impaired (CI) patients with and without hypertension (HTN). The left panel represents patients with CI combined with HTN, and the right panel represents patients with CI without HTN. WMH, white matter hyperintensities; MMSE, Mini-Mental State Exam; CSF, cerebrospinal fluid; BMI, body mass index.

patients with CI than in the CN group, and WMH volume was correlated with MMSE scores in patients with CI. These findings suggest that homocysteine levels may be a risk factor for cognitive dysfunction and may affect cognitive function by influencing WMH volume.

In hypertensive patients, the presence of WMH volume in brain imaging may lead to CI [18]. Patients treated for HTN exhibited significantly reduced cognition compared to others, and that association was mediated by higher WMH volume [19]. High homocysteine levels are also an independent risk factor for HTN and can promote the development of essential HTN and CI [20, 21]. Recent findings suggest that high homocysteine levels and severe cerebrovascular loss are associated with WMH volume, possibly explaining the effect of high homocysteine levels on HTN-induced CI [22]. Our results showed that homocysteine levels were higher in patients with CI with HTN than in those without HTN, but no effect of HTN on WMH volume or cognitive function was found, and the correlation between homocysteine levels and WMH volume was higher in patients with CI with HTN than in patients without HTN. These results suggest that the presence of HTN may synergistically exacerbate the effects of homocysteine levels on cognitive function.

We collected data on patients with a history of HTN taking antihypertensive medication and conducted statistical analysis, finding no differences in outcomes between patients who took the medication and those who did not (Supplementary Table 2),

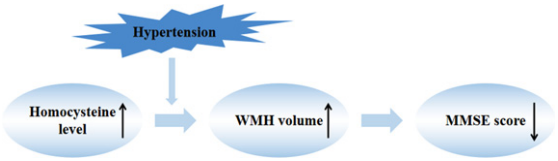


Fig. 4. The relationships of homocysteine levels and hypertension with cognitive function in cognitively impaired patients. Homocysteine levels may either directly affect cognitive function or possibly indirectly by affecting white matter hyperintensities (WMH) volume, and both pathways are regulated by hypertensive factors. MMSE, Mini-Mental State Exam.

thereby ruling out the possible influence of antihypertensive medication on our results.

Given these results, we propose that reducing homocysteine levels in patients with CI may improve or prevent cognitive dysfunction. Studies have demonstrated that B vitamin deficiency can lead to high homocysteine levels [23], and supplementation with folic acid and B vitamins can reduce homocysteine levels and enhance cognitive function [24–26], representing a viable adjunct to traditional drug therapy. For cognitively normal elderly individuals, supplementing folic acid and B vitamins and reducing homocysteine levels may be a promising strategy for preventing AD.

In addition, there are some limitations in this study. There may be unexpected selection bias in the ADNI database, and the sample size is small, so it is necessary to conduct large-scale external verification of the current study. In addition, the models of MRI machines used by the subjects were not uniform,

which had a certain impact on the calculation of WMH volume. Future studies should include large-scale external validation research and explore specific mechanisms for these findings.

In summary, elevated homocysteine levels and HTN were related to the increased WMH volume and CI (Fig. 4).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-230687.

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