J Chin Med Assoc

ORIGINAL ARTICLE

Serum brain-derived neurotrophic factor levels as a predictor for Alzheimer disease progression

Meng-Ju Tsai[a,b], Yung-Shuan Lin[a–d], Chun-Yu Chen[a,b,d], Wei-Ju Lee[b,d,e,f,g], Jong-Ling Fuh[a,b,d,*]

[a]Division of General Neurology, Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Institute of Brain Science, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [d]Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [e]Neurological Institute, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; [f]Dementia Center, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; [g]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan, ROC

Abstract

Background: Brain-derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of Alzheimer's disease (AD), and decreased peripheral levels of this protein are associated with an increased risk of developing the disease. This study focuses on whether serum BDNF levels could be used as a predictor of AD progression.

Methods: In this longitudinal observational study, we recruited cognition normal participants (N = 98) and AD (N = 442) from the Clinic at the Taipei Veterans General Hospital. We conducted a mini-mental status exam, a 12-item memory test, a categorical verbal fluency test, and a modified 15-item Boston naming test. A Serum BDNF level and apolipoprotein E (*APOE*) allele status were measured. The AD patients were followed prospectively. Based on the difference of MMSE scores, these patients were divided into fast decliners (decline ≥ 3/y) and slow decliners (MMSE decline < 3/y). Logistic regression was conducted to examine the impact of serum BDNF levels and other factor on the likelihood of AD patients being slow decliners. Pearson's correlation was used to estimate the relationship between serum BDNF levels and the score of neuropsychological tests.

Results: In a logistic regression model containing serum BDNF levels, age, sex, *APOE4* carrier status, education levels, and baseline MMSE score, higher serum BDNF levels were associated with a slower rate of cognitive decline in the AD group. Serum BDNF levels positively correlated with the results of multiple neuropsychological tests.

Conclusion: BDNF is a protective factor against AD progression and likely plays a role in establishing a link between AD pathology and clinical manifestations.

Keywords: Alzheimer's disease; Brain-derived neurotrophic factor; Cognitive decline; Disease progression; Predictor

1. INTRODUCTION

Alzheimer's disease (AD) is now recognized as a continuum that includes cognitively normal (CN), mild cognitive impairment (MCI), and dementia.[1] In clinical practice, such as physician-patient communication or advance care planning, and in trial design, such as stratification of patients or setting of endpoints,[2] understanding the trajectory of the disease course is important.

An ideal biomarker could be beneficial for serving this purpose. Several conditions should be met for this biomarker: non-invasive, easily obtainable, reliable, cheap, well-validated, and correlated with AD pathology.[3] As a blood-based sample with a readily available immunoassay, serum brain-derived neurotrophic factor (BDNF), indicated to be correlated with the central BDNF level,[4] fits the first four conditions compared to neuroimaging or cerebrospinal fluid biomarker tests.

BDNF belongs to the neurotrophin family and might play an important role in the pathophysiology of AD. The downstream cascades of BDNF binding to its receptor contribute to many aspects of neural circuit formation, including neuronal differentiation, growth, and synaptic plasticity.[5] BDNF levels were the highest in the hippocampal region of brain and in mice, the BDNF-Tropomyosin receptor kinase B (TrkB) pathway is essential for hippocampal long-term potentiation and related to long-term memory development.[6,7] BDNF modulates both the presynaptic and postsynaptic areas in the cyclic adenosine monophosphate (cAMP)-responsive element binding protein 1 (CREB)-dependent memory-forming model.[8–11] BDNF exerts ability of reducing amyloid β (Aβ) generation and tau protein phosphorylation. In reverse, Aβ and tau overexpression causes BDNF down-regulation.[12] In clinical studies, lower levels of BDNF in the cerebrospinal fluid are associated with the progression from MCI to AD.[13]

It has been shown that BDNF can cross the blood-brain barrier toward peripheral tissues.[14] In the peripheral system, BDNF levels can be measured using plasma or serum samples and corresponding bioassays, and the two types of sources represent two different pools of BDNF.[15] Researchers reported mixed

*Address correspondence. Dr Jong-Ling Fuh, Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei 112, Taiwan, ROC. E-mail address: jlfuh@vghtpe.gov.tw (J.-L. Fuh).

Conflicts of interest: Dr. Jong-Ling Fuh, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 960-965.

Received May 25, 2023; accepted August 13, 2023.

doi: 10.1097/JCMA.0000000000000991

results from studies involving plasma BDNF samples. In a 2-year follow-up study, plasma BDNF levels were neither different between healthy elderly subjects and MCI patients nor related to cognition or functional decline.[16] In another study, MCI patients have higher BDNF levels, and BDNF has excellent discrimination accuracy when compared to healthy control subjects and MCI subjects.[17] However, serum BDNF results are more consistent. The levels of BDNF are increased in AD patients with slow cognitive decline[18] and associated with a lower risk of cognitive decline in the MCI group and a lower risk for dementia among the dementia-free group.[19] These studies are limited by relatively small sample sizes (only two had more than 400 participants) and rarely focus on AD progression.

Due to this evidence, we aim to examine BDNF's role in AD progression and, subsequently, the relationship between serum levels of BDNF and cognitive function on a larger scale.

2. METHODS

2.1. Participants

We prospectively recruited CN participants and those with AD from the Neurology Outpatient Clinic at the Taipei Veterans General Hospital. The CN participants were volunteers with no subjective or objective impairments in cognitive function. Patients with probable AD dementia with amnestic presentation were included in this study based on the core clinical criteria established by the Alzheimer's Association and the National Institute on Aging in 2011[20] and eligible for inclusion (N = 597). Subsequent to the diagnosis, the AD group was followed up annually in 2 years and those who undergo no further follow-up examination (N = 155) were excluded. We excluded patients with cognitive impairment with atypical presentation, extensive white matter lesion, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) by *NOTCH3* genotyping, and other etiologies, such as acute consciousness changes due to systemic disease, drug intoxication, central nervous system infection, neurological deficits following head trauma, or major depression based on the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders*.[21] Before participating in the study, all the participants and their caregivers provided informed consent. The Institutional Review Board of Taipei Veterans General Hospital approved this research program.

2.2. Clinical evaluation and procedures

Participants underwent a standardized clinical evaluation that included a clinical interview, physical examination, neuropsychological evaluation, laboratory tests, and computed tomography or magnetic resonance imaging upon recruitment. The mini-mental status exam (MMSE) was used to assess general cognitive function.[22] To assess short-term memory, executive function, and language function, the 12-item memory test, categorical verbal fluency test (VF), and modified 15-item Boston naming test (BNT) were used. MMSE and VF test were repeated when the AD group was followed up. The results from the second-year follow-up were used for whole group analysis whenever available.

2.3. Measurement of serum BDNF levels

At baseline, fresh venous blood samples were collected in polypropylene tubes. We allowed the samples to clot at room temperature for 30 minutes before centrifuging them and storing them at –80°C for biochemical analysis. Serum BDNF levels were measured in duplicate using the Human BDNF Immunoassay Quantikine enzyme-linked immunosorbent assay (ELISA) kit (DBD00; R&D Systems, Minneapolis, MN, USA), according to the instructions and protocols provided by the manufacturer. All samples from each participant were measured on the same plate to avoid interpolate variation and the coefficients of variance (CVs) of all samples were below than 15%.

2.4. DNA analysis

Please refer to the Supplementary Material (http://links.lww.com/JCMA/A206) for DNA analysis procedures.

2.5. Statistical analysis

To establish the differences between demographic profiles and neuropsychological evaluation results between the CN and AD groups, independent two-sample *t* tests and chi-square test were conducted. These patients were divided into fast decliners (MMSE decline ≥ 3/y) and slow decliners (MMSE decline < 3/y).[23,24] The demographic profiles and neuropsychological evaluation tests of slow and fast decliners were compared using independent two-sample *t* tests and chi-square tests. Considering that the kurtosis of the serum BDNF levels was 1.104, a natural log transformation was performed before further analysis. The difference in serum BDNF levels between sexes was tested using an independent two-sample t-test. Pearson's correlation was used to estimate the relationship between serum BDNF levels and the participants' age and neuropsychological evaluation results. Logistic regression was used to examine the impact of serum BDNF levels, age, sex, *APOE4* carrier status, education levels, and baseline MMSE score on the likelihood of patients with AD being slow decliners. An analysis of subgroups was conducted in two aspects. First, for AD participants who had complete 2-year follow-up, we analyzed the results from the first and second follow-up separately. Second, we divided the AD participants into mild-moderate severity group (baseline MMSE score ≥ 15) and severe group (baseline MMSE score < 15)[25] before logistic regressions were performed between fast and slow decliners. Statistical analyses were performed using SPSS software version 26 (IBM, Inc., Armonk, NY, USA), and statistical significance was set at $p < 0.05$.

3. RESULTS

3.1. Participants

A total of 540 study participants were enrolled, including 442 AD patients and 98 CN participants. Table 1 summarizes the background characteristics of the participants. The two groups

Table 1

Demographic data, serum BDNF levels, and cognitive test performance of the study participants

Characteristics	CN (N = 98)	AD (N = 442)	*p*
Age	71.6 (8.0)	79.5 (7.0)b	<0.001
Sex			
Male[a]	40 (40.8%)	227 (51.4%)	0.059
APOE ε4 carrier[a]	15 (15.3%)	160 (36.2%)	<0.001
Education (y)	12.3 (4.8)	9.6 (4.6)b	<0.001
Serum BDNF levels	10.1 (0.3)	9.9 (0.4)b	<0.001
MMSE	28.4 (1.7)	18.4 (5.3)b	<0.001
12-item memory test	8.0 (1.9) (N = 72)	1.1 (1.8)b (N = 436)	<0.001
Verbal fluency	13.2 (2.8) (N = 71)	6.5 (2.9)b (N = 438)	<0.001
Boston naming test	14.4 (1.0) (N = 70)	11.5 (2.8)b (N = 439)	<0.001

Data presented as mean and SD in parentheses unless noted.

AD = Alzheimer's disease; *APOE* = apolipoprotein E; BDNF = brain-derived neurotrophic factor; CN = cognitively normal; MMSE = Mini-Mental State Examination.

[a]Presented as the number of participants and percentages in parentheses.

[b]$p < 0.001$ vs CN.

showed significant differences in age, *APOE4* carrier status, and years of education. The CN group was the younger than the AD group (CN 71.6 ± 8.0, AD 79.5 ± 7.0; $p < 0.001$). There was a greater proportion of *APOE4* carriers in the AD group (36.2%) than in the CN group (15.3%) ($p < 0.001$). The CN group had higher educational years than the AD group (CN 12.3 ± 4.8, AD 9.6 ± 4.6; $p < 0.001$). The sex distribution between the groups did not show any significant differences (male proportion in CN 40.8%, AD 51.4%; $p = 0.059$).

3.2. Neuropsychological evaluations

There were significantly lower scores for AD patients in the MMSE, 12-item memory test, VF, and BNT than CN participants (MMSE: CN 28.4 ± 1.7, AD 18.4 ± 5.3, $p < 0.001$; 12-item memory test: CN 8.0 ± 1.9, AD 1.1 ± 1.8, $p < 0.001$; VF: CN 13.2 ± 2.8, AD 6.5 ± 2.9, $p < 0.001$; BNT: CN 14.4 ± 1.0, AD 11.5 ± 2.8, $p < 0.001$).

3.3. Serum BDNF levels

The mean ± SD of natural log-transformed serum BDNF levels were 10.1 ± 0.3 in the CN group, 9.9 ± 0.4 in the AD group and 9.9 ± 0.4 in the whole group. The AD group had lower serum BDNF levels than the CN group ($p < 0.001$). The serum BDNF level was higher in female participants (10.0 ± 0.4) than male participants (9.9 ± 0.4) ($p < 0.001$). Overall, the level of serum BDNF decreased with increasing age ($r = –0.144$; $p < 0.001$).

3.4. Serum BDNF levels and neuropsychological evaluations

Serum BDNF levels showed positive correlations with MMSE scores ($r = 0.116$; $p = 0.007$), 12-item memory test scores ($r = 0.134$; $p = 0.003$), and VF scores ($r = 0.129$; $p = 0.004$). No correlation was found between the serum BDNF levels and BNT scores ($p = 0.345$).

3.5. Serum BDNF levels and MMSE decline rate in AD patients

All AD patients received the first-year follow-up and 335 (335/442 = 75.8%) patients received the second-year follow-up. The mean following period was 23.1 ± 8.3 months. Of these patients, 95 (21.5%) experienced a rapid decline and 347 (78.5%) experienced a slow decline. Table 2 summarizes the characteristics of the two groups. There was a lower level of education among slow decliners (9.4 ± 4.7 vs 10.6 ± 4.5 years; $p = 0.023$) than among fast decliners. There were no significant differences between the two groups in terms of age, sex, *AOE4* carrier status, or MMSE scores at baseline. Slow decliners had a higher serum BNDF level than fast decliners (9.9 ± 0.4 vs 9.8 ± 0.5; $p = 0.006$).

In the logistic regression model, 6.8% (Nagelkerke R^2) of the variance in the decline rate was explained. After adjusting for age, sex, *APOE4* carrier status, education levels, and baseline MMSE score, the odds ratio (OR) of slow decliner was 2.37 (95% CI, 1.326-4.230) for a unit increase in serum BDNF levels. Increased age was associated with slow decline (OR, 1.04; 95% CI, 1.003-1.071), while education was associated with a lower OR of slow decline (OR, 0.95; 95% CI, 0.895-0.997) (Table 3).

A logistic regression was conducted on the 335 patients who received both the first and second follow-up surveys based on demographic factors such as age, sex, APOE4 carrier status, education, baseline MMSE score, and serum BDNF levels.

During first follow-up, the mean following period was 12.6 ± 5.2 months. Of these patients, 85 (25.4%) experienced a rapid decline and 250 (74.6%) experienced a slow decline. There was no difference noticed between rapid and slow decliners in terms of age, sex, *APOE4* carrier status, education levels, baseline MMSE score, or serum BDNF levels. Logistic regression model indicated only increased age associated with slow decline (OR, 1.04; 95% CI, 1.004-1.075) (Table 4). During second-year follow-up, the mean following period was 25.5 ± 7.1 months. Of these patients, 71 (18.2%) experienced a rapid decline and 274 (81.8%) experienced a slow decline. The slow decliners were older (79.7 ± 6.4 vs 77.0 ± 9.2 years; $p = 0.035$) and had higher serum BDNF levels (10.0 ± 0.4 vs 9.8 ± 0.5; $p = 0.017$).

Table 2

Comparison of demographics, the carrier status of *APOE*, and the results of neuropsychological tests between slow and fast decliners

Characteristics	Slow decliner (N = 347)	Fast decliner (N = 95)	*p*
Age	79.8 (6.5)	78.5 (8.7)	0.177
Sex			
Male[a]	174 (50.1%)	53 (55.8%)	0.329
APOE ε4 carrier[a]	131 (37.8%)	29 (30.5%)	0.194
Education (y)	9.4 (4.7)	10.6 (4.5)	0.023
Serum BDNF levels	9.9 (0.4)	9.8 (0.5)	0.006
MMSE	18.2 (5.5)	19.2 (4.4)	0.091
12-item memory test	1.2 (1.8) (N = 342)	1.1 (1.9) (N = 94)	0.718
Verbal fluency	6.6 (2.9) (N = 345)	6.0 (2.9) (N = 93)	0.111
Boston naming test	11.5 (2.8) (N = 345)	11.5 (2.7) (N = 94)	0.987

Data presented as mean and SD in parentheses unless noted.
APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; MMSE = Mini-Mental State Examination.
[a]Presented as the number of participants and percentages in parentheses.

Table 3

Logistic regression model for predicting slow decline in AD patients using serum BDNF levels

Parameter	B (SE)	Wald	Significance	OR (95% CI)
Age	0.036 (0.017)	4.586	0.032	1.036 (1.003-1.071)
Sex	–0.065 (0.252)	0.067	0.795	0.937 (0.572-1.535)
APOE ε4 carrier	0.369 (0.258)	2.040	0.153	1.446 (0.872-2.397)
Years of education	–0.057 (0.028)	4.217	0.040	0.945 (0.895-0.997)
Baseline MMSE	–0.018 (0.024)	0.576	0.448	0.982 (0.938-1.029)
Serum BDNF levels	0.862 (0.296)	8.487	0.004	2.368 (1.326-4.23)
Constant	–9.241 (3.37)	7.532	0.006	

AD = Alzheimer's disease; *APOE* = apolipoprotein E; B = beta coefficient; BDNF = brain-derived neurotrophic factor; MMSE = Mini-Mental State Examination; OR = odds ratio; Wald = Wald statistics.

Table 4

Logistic regression model for predicting slow decline in AD patients using serum BDNF levels, first-year follow-up

Parameter	B (SE)	Wald	Significance	OR (95% CI)
Age	0.038 (0.017)	4.698	0.030	1.039 (1.004-1.075)
Sex	0.069 (0.266)	0.068	0.794	1.072 (0.636-1.807)
APOE ε4 carrier	–0.027 (0.269)	0.010	0.921	0.974 (0.575-1.648)
Years of education	–0.001 (0.03)	0.002	0.963	0.999 (0.942-1.058)
Baseline MMSE	0.007 (0.026)	0.069	0.793	1.007 (0.957-1.059)
Serum BDNF levels	0.164 (0.313)	0.274	0.601	1.178 (0.638-2.173)
Constant	–3.668 (3.555)	1.065	0.302	

AD = Alzheimer's disease; *APOE* = apolipoprotein E; B = beta coefficient; BDNF = brain-derived neurotrophic factor; MMSE = Mini-Mental State Examination; OR = odds ratio; Wald = Wald statistics.

Logistic regression model indicated that increased serum BDNF levels (OR, 2.55; 95% CI, 1.299-5.020) and increased age (OR, 1.06; 95% CI, 1.019-1.102) were associated with slow decline (Table 5).

The mild-moderate severity group contained 349 (79.0%) patients and severe group 93 (21.0%) patients. In the mild-moderate severity group, the slow decliners had higher serum BDNF levels (10.0 ± 0.4 vs 9.8 ± 0.5; p = 0.003). Logistic regression model conveys similar results with the whole group analysis: higher serum BDNF levels were associated with slow decline (OR, 2.605; 95% CI, 1.392-4.877), increased age was associated with slow decline (OR, 1.05; 95% CI, 1.011-1.086) and education associated with a lower OR of slow decline (OR, 0.94; 95% CI, 0.883-0.998) (Table 6). In the severe group, no difference was noticed considering age, sex, *APOE4* carrier status, education levels, baseline MMSE score, or serum BDNF levels between rapid and slow decliners. Logistic regression model revealed no significant effect of these variables on decline rate.

4. DISCUSSION

This study had two major findings. First, increased serum BDNF levels were associated with a slower rate of cognitive decline in the AD group. Second, serum BDNF levels positively correlated with better results of multiple neuropsychological tests.

A previous 1-year follow-up study of patients with AD reported higher serum BDNF levels were associated with slower cognitive decline.[18] With an extended follow-up period of an average of 23 months, our study revealed a similar result. Our logistic regression model suggests that BDNF is a protective factor against rapid cognitive decline in patients with AD, especially in the mild-to-moderate severity group. In a Japanese study involving 405 dementia-free community-dwelling older adults, higher serum BDNF levels were associated with lower odds of cognitive decline following MCI.[26] It was found that higher BDNF gene expression in the dorsolateral prefrontal cortex was associated with slower cognitive decline, with the strongest effect occurring in patients with dementia.[27] It has been also demonstrated that there is a strong association between AD pathology and BDNF levels in relation to clinical presentation. The reduction in phosphorylated CREB protein leads to a decrease in BDNF expression and impaired axonal transport due to neuronal death or dysfunction results in reduced BDNF levels at the synapses.[28,29] The impaired downstream signaling pathways affects neuronal plasticity, synapse development, and cell survival, which could contribute to cognitive decline observed in AD patients.[12] In animal models, the correlation between central nervous system BDNF and cognitive performance was proved to be directly related. Compared with controls, deprivation of BDNF induced cognitive decline in rodents; in contrast, cognitive improvement was observed in rodents receiving exogenous BDNF injection.[30] In human, this connection is also detected. Lower peripheral BDNF levels were associated with smaller volume of hippocampus and worse memory,[30] and changes in the serum BDNF was revealed to mediate the effect of cognitive training.[31] More recently, BDNF was recognized as an exerkine, mediating the neurological benefits from physical exercise.[32] The current study approaches the relationship between BDNF and cognitive function from another angle, showing that BDNF is predictive in cognitive decline in AD patients. A higher BDNF level might indicate a relatively lower pathological burden on the patient's brain, thus contributing to a slower rate of cognitive decline.

Positive correlations exist between serum BDNF levels and cognitive tests such as the MMSE, 12-item memory test, and VF across the entire group. This finding is consistent with previous studies. It has been reported that BDNF levels correlated positively with total MMSE scores or concentration subcategory of MMSE in AD groups.[33–36] In the 90+ study, the expression of BDNF mRNA in Brodmann area 7 was positively correlated with the MMSE score.[37] These tests are compound measure of memory registry, store, and retrieval and executive along with other cognitive functions, reflecting a global cognitive function decline in AD. Correspondingly, in the brain of AD patients, decrease of BDNF is not limited to the hippocampus.[6] On the contrary, BNT more focus on semantic memory store,[38,39] which might explain the non-significance.

Consistent with our findings, several previous studies have demonstrated that age protects against rapid cognitive decline in patients with AD. Older patients with AD show a slower decline in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) 11 and MMSE.[40] In Chinese-speaking populations, two studies reported slower decline rates and a reduced risk of rapid cognitive decline in older patients with AD.[41,42] The pathological changes preceding clinical AD symptoms are expected to be more advanced in younger patients, which may lead to a more rapid decline in cognition.[43]

The cognitive reserve (CR) hypothesis may explain why higher education levels were associated with rapid cognitive decline in the AD group in the present study. Patients with a higher CR maintain equal cognitive performance despite having a more advanced pathology. Once the compensation mechanism is overloaded, an accelerated clinical decline will occur.[44] There is evidence that education strengthens the CR in AD patients, causing their cognitive function to deteriorate rapidly,[44] and analysis from the Amsterdam Dementia Cohort also supports this finding.[45]

Table 5

Logistic regression model for predicting slow decline in AD patients using serum BDNF levels, second-year follow-up

Parameter	B (SE)	Wald	Significance	OR (95% CI)
Age	0.058 (0.02)	8.558	0.003	1.06 (1.019-1.102)
Sex	0.251 (0.307)	0.670	0.413	1.286 (0.704-2.348)
APOE ε4 carrier	0.477 (0.325)	2.147	0.143	1.611 (0.851-3.048)
Years of education	–0.048 (0.035)	1.944	0.163	0.953 (0.89-1.02)
Baseline MMSE	–0.021 (0.031)	0.478	0.489	0.979 (0.921-1.04)
Serum BDNF levels	0.938 (0.345)	7.395	0.007	2.554 (1.299-5.02)
Constant	–11.745 (3.988)	8.674	0.003	

AD = Alzheimer's disease; *APOE* = apolipoprotein E; B = beta coefficient; BDNF = brain-derived neurotrophic factor; MMSE = Mini-Mental State Examination; OR = odds ratio; Wald = Wald statistics.

Table 6

Logistic regression model for predicting slow decline in AD patients using serum BDNF levels, mild-moderate severity group

Parameter	B (SE)	Wald	Significance	OR (95% CI)
Age	0.047 (0.018)	6.466	0.011	1.048 (1.011-1.086)
Sex	–0.104 (0.282)	0.136	0.712	0.901 (0.518-1.566)
APOE ε4 carrier	0.349 (0.284)	1.504	0.220	1.417 (0.812-2.474)
Years of education	–0.063 (0.031)	4.099	0.043	0.939 (0.883-0.998)
Baseline MMSE	0.053 (0.04)	1.733	0.188	1.054 (0.974-1.141)
Serum BDNF levels	0.958 (0.32)	8.960	0.003	2.605 (1.392-4.877)
Constant	–12.467 (3.758)	11.003	0.001	

AD = Alzheimer's disease; *APOE* = apolipoprotein E; B = beta coefficient; BDNF = brain-derived neurotrophic factor; MMSE = Mini-Mental State Examination; OR = odds ratio; Wald = Wald statistics.

According to the results of our study, female participants had higher serum BDNF levels than male participants did. In previous studies, there was no significant difference between the sexes in the general elderly population and those with depression.[46,47] The relationship between estrogen and BDNF was first established among the sex hormones. Several mechanisms may be involved in the induction of BDNF expression, including DNA tethering, activation of the CREB, histone acetylation, and DNA methylation.[48] However, all of our subjects were postmenopausal when the hormone profile differed significantly from that at reproductive age. The relationship between sex, sex hormones, and BDNF levels may require a more focused investigation in this group.

Overall, serum BDNF levels and age were negatively correlated in the entire cohort. A study in the elderly have reported that serum BDNF concentration declines with increasing age[49] and a study of 20-to 60-year-old participants found a negative correlation between plasma BDNF levels and age.[50] But the results differed when the participants were dispersed according to their age. In the Berlin aging study II, no differences were found between BNDF levels in older and younger groups (mean age, 68.7 ± 3.7 and 28.9 ± 3.1, respectively).[46] These conflicting results indicate that further research is required to understand how BDNF levels change throughout the human life.

We conducted a longitudinal study in a fair number of patients with AD, the results of which may provide supplementary material for the use of serum BDNF as an AD biomarker in clinical settings. However, this study has some limitations. First, the diagnoses of AD were based only on the clinical criteria. This may affect the credibility of diagnosis without AD-specific biomarkers including Aβ and pathologic tau. Nonetheless, we found that the AD group had worse results than CN group in all neuropsychological tests. This reinforces the precision of the patient stratification. Second, there were no longitudinal follow-up data in the CN group, which compromises the comparability between the groups.

In conclusion, we confirmed that serum BDNF plays a protective role in AD prognosis and acts as a bridge between AD pathology and clinical manifestations. By identifying serum BDNF as a potential biomarker for AD, this study contributes to our understanding of AD trajectory. Further comprehensive studies are necessary to clarify the underlying mechanism and validate role of BDNF in predicting AD progression.

ACKNOWLEDGMENTS

This study is supported by grants from the Academia Sinica of Taiwan (AS-BD-108-2; AS-KPQ-111-KNT), National Health Research Institutes, Taiwan (PH-112-GP-08, NHRI-11A1-CG-CO-05-2225-1), National Science and Technology Council, Taiwan (NSTC 111-2321-B-001 -010 -; 111-2314-B-075 -069 -; 111-2321-B-A49-011-, 111-2634-F-A49-014-). Taipei Veterans General Hospital (V111C-216, V112C-016), Taichung Veterans General Hospital (TCVGH-1093402C, TCVGH-1103401C, TCVGH-1103401D), and the Brain Research Center, National Yang-Ming University from The Featured Areas Research Center. Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A206.

REFERENCES

1. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al; Contributors. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018;14:535–62.
2. Tam A, Laurent C, Gauthier S, Dansereau C. Prediction of cognitive decline for enrichment of Alzheimer's disease clinical trials. *J Prev Alzheimers Dis* 2022;9:400–9.
3. O'Bryant SE, Hobson V, Hall JR, Waring SC, Chan W, Massman P, et al; Texas Alzheimer's Research Consortium. Brain-derived neurotrophic factor levels in Alzheimer's disease. *J Alzheimers Dis* 2009;17:337–41.
4. Ibrahim AM, Chauhan L, Bhardwaj A, Sharma A, Fayaz F, Kumar B, et al. Brain-derived neurotropic factor in neurodegenerative disorders. *Biomedicines* 2022;10:1143.
5. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci* 2013;14:7–23.
6. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. *Front Cell Neurosci* 2019;13:363.
7. Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. *Handb Exp Pharmacol* 2014;220:223–50.
8. Dringenberg HC. The history of long-term potentiation as a memory mechanism: Controversies, confirmation, and some lessons to remember. *Hippocampus* 2020;30:987–1012.
9. Nicoll RA. A Brief history of long-term potentiation. *Neuron* 2017;93:281–90.
10. Lisman J, Yasuda R, Raghavachari S. Mechanisms of CaMKII action in long-term potentiation. *Nat Rev Neurosci* 2012;13:169–82.
11. Benito E, Barco A. CREB's control of intrinsic and synaptic plasticity: implications for CREB-dependent memory models. *Trends Neurosci* 2010;33:230–40.
12. Gao L, Zhang Y, Sterling K, Song W. Brain-derived neurotrophic factor in Alzheimer's disease and its pharmaceutical potential. *Transl Neurodegener* 2022;11:4.
13. Forlenza OV, Diniz BS, Teixeira AL, Radanovic M, Talib LL, Rocha NP, et al. Lower cerebrospinal fluid concentration of brain-derived neurotrophic factor predicts progression from mild cognitive impairment to Alzheimer's disease. *Neuromolecular Med* 2015;17:326–32.
14. Tarassova O, Ekblom MM, Moberg M, Lovden M, Nilsson J. Peripheral BDNF response to physical and cognitive exercise and its association with cardiorespiratory fitness in healthy older adults. *Front Physiol* 2020;11:1080.
15. Gejl AK, Enevold C, Bugge A, Andersen MS, Nielsen CH, Andersen LB. Associations between serum and plasma brain-derived neurotrophic factor and influence of storage time and centrifugation strategy. *Sci Rep* 2019;9:9655.
16. Balietti M, Giuli C, Casoli T, Fabbietti P, Conti F. Is blood brain-derived neurotrophic factor a useful biomarker to monitor mild cognitive impairment patients? *Rejuvenation Res* 2020;23:411–9.
17. Ng TKS, Coughlan C, Heyn PC, Tagawa A, Carollo JJ, Kua EH, et al. Increased plasma brain-derived neurotrophic factor (BDNF) as a potential biomarker for and compensatory mechanism in mild cognitive impairment: a case-control study. *Aging (Albany NY)* 2021;13:22666–89.
18. Laske C, Stellos K, Hoffmann N, Stransky E, Straten G, Eschweiler GW, et al. Higher BDNF serum levels predict slower cognitive decline in Alzheimer's disease patients. *Int J Neuropsychopharmacol* 2011;14:399–404.
19. Weinstein G, Beiser AS, Choi SH, Preis SR, Chen TC, Vorgas D, et al. Serum brain-derived neurotrophic factor and the risk for dementia: the Framingham Heart Study. *JAMA Neurol* 2014;71:55–61.
20. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
21. American Psychiatric Association D-TF. *Diagnostic and statistical manual of mental disorders: DSM-5™*. 5th ed. Washington, DC, USA: American Psychiatric Publishing, a division of American Psychiatric Association; 2013.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.

23. Carcaillon L, Peres K, Pere JJ, Helmer C, Orgogozo JM, Dartigues JF. Fast cognitive decline at the time of dementia diagnosis: a major prognostic factor for survival in the community. *Dement Geriatr Cogn Disord* 2007;23:439–45.
24. O'Hara R, Thompson JM, Kraemer HC, Fenn C, Taylor JL, Ross L, et al. Which Alzheimer patients are at risk for rapid cognitive decline? *J Geriatr Psychiatry Neurol* 2002;15:233–8.
25. Henneges C, Reed C, Chen YF, Dell'Agnello G, Lebrec J. Describing the sequence of cognitive decline in Alzheimer's disease patients: results from an observational study. *J Alzheimers Dis* 2016;52:1065–80.
26. Fujiwara Y, Ihara K, Hachisu M, Suzuki H, Kawai H, Sakurai R, et al. Higher serum brain-derived neurotrophic factor levels are associated with a lower risk of cognitive decline: a 2-year follow up study in community-dwelling older adults. *Front Behav Neurosci* 2021;15:641608.
27. Buchman AS, Yu L, Boyle PA, Schneider JA, De Jager PL, Bennett DA. Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. *Neurology* 2016;86:735–41.
28. Sharma V, Singh TG, Kaur A, Mannan A, Dhiman S. Brain-derived neurotrophic factor: a novel dynamically regulated therapeutic modulator in neurological disorders. *Neurochem Res* 2023;48:317–39.
29. Amidfar M, de Oliveira J, Kucharska E, Budni J, Kim YK. The role of CREB and BDNF in neurobiology and treatment of Alzheimer's disease. *Life Sci* 2020;257:118020.
30. Piepmeier AT, Etnier JL. Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance. *J Sport Exerc Psychol* 2015;4:14–23.
31. Nicastri CM, McFeeley BM, Simon SS, Ledreux A, Hakansson K, Granholm AC, et al. BDNF mediates improvement in cognitive performance after computerized cognitive training in healthy older adults. *Alzheimers Dement (N Y)* 2022;8:e12337.
32. Rody T, De Amorim JA, De Felice FG. The emerging neuroprotective roles of exerkines in Alzheimer's disease. *Front Aging Neurosci* 2022;14:965190.
33. Laske C, Stransky E, Leyhe T, Eschweiler GW, Wittorf A, Richartz E, et al. Stage-dependent BDNF serum concentrations in Alzheimer's disease. *J Neural Transm (Vienna)* 2006;113:1217–24.
34. Konukoglu D, Andican G, Firtina S, Erkol G, Kurt A. Serum brain-derived neurotrophic factor, nerve growth factor and neurotrophin-3 levels in dementia. *Acta Neurol Belg* 2012;112:255–60.
35. Lee JG, Shin BS, You YS, Kim JE, Yoon SW, Jeon DW, et al. Decreased serum brain-derived neurotrophic factor levels in elderly Korean with dementia. *Psychiatry Investig* 2009;6:299–305.
36. Navarro-Martinez R, Fernandez-Garrido J, Buigues C, Torralba-Martinez E, Martinez-Martinez M, Verdejo Y, et al. Brain-derived neurotrophic factor correlates with functional and cognitive impairment in non-disabled older individuals. *Exp Gerontol* 2015;72:129–37.
37. Michalski B, Corrada MM, Kawas CH, Fahnestock M. Brain-derived neurotrophic factor and TrkB expression in the "oldest-old," the 90+ study: correlation with cognitive status and levels of soluble amyloid-beta. *Neurobiol Aging* 2015;36:3130–9.
38. Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia* 2004;42:1212–22.
39. Wright LM, De Marco M, Venneri A. Current understanding of verbal fluency in Alzheimer's disease: evidence to date. *Psychol Res Behav Manag* 2023;16:1691–705.
40. Bernick C, Cummings J, Raman R, Sun X, Aisen P. Age and rate of cognitive decline in Alzheimer disease: implications for clinical trials. *Arch Neurol* 2012;69:901–5.
41. Zhao Q, Zhou B, Ding D, Teramukai S, Guo Q, Fukushima M, et al. Cognitive decline in patients with Alzheimer's disease and its related factors in a memory clinic setting, Shanghai, China. *PLoS One* 2014;9:e95755.
42. Pan CC, Chu CS, Chen CL, Chuang YC, Chen NC. Factors affecting rapid cognitive decline in patients with Alzheimer's disease: a longitudinal follow-up study. *Int J Environ Res Public Health* 2021;18:8576.
43. Koychev I, Gunn RN, Firouzian A, Lawson J, Zamboni G, Ridha B, et al; Deep and Frequent Phenotyping study team. PET tau and amyloid-beta burden in mild Alzheimer's disease: divergent relationship with age, cognition, and cerebrospinal fluid biomarkers. *J Alzheimers Dis* 2017;60:283–93.
44. Scarmeas N, Albert SM, Manly JJ, Stern Y. Education and rates of cognitive decline in incident Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006;77:308–16.
45. van Loenhoud AC, Groot C, Bocancea DI, Barkhof F, Teunissen C, Scheltens P, et al. Association of education and intracranial volume with cognitive trajectories and mortality rates across the Alzheimer disease continuum. *Neurology* 2022;98:e1679–91.
46. Kronenberg G, Gertz K, Schoner J, Bertram L, Liman T, Steinhagen-Thiessen E, et al. BDNF serum concentrations in 2053 participants of the Berlin Aging Study II. *Neurobiol Aging* 2021;101:221–3.
47. Elfving B, Buttenschon HN, Foldager L, Poulsen PH, Andersen JH, Grynderup MB, et al. Depression, the Val66Met polymorphism, age, and gender influence the serum BDNF level. *J Psychiatr Res* 2012;46:1118–25.
48. Chan CB, Ye K. Sex differences in brain-derived neurotrophic factor signaling and functions. *J Neurosci Res* 2017;95:328–35.
49. Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, et al. A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. *Front Aging Neurosci* 2014;6:69.
50. Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, et al. The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiol Aging* 2005;26:115–23.