The Journal of Prevention of Alzheimer's Disease 12 (2025) 100210

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Serum BDNF and progression to MCI in cognitively normal older adults: A prospective cohort study

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ARTICLE INFO

Keywords:
Brain-derived neurotrophic factor (BDNF)
Neurotrophins
Cognitively normal
Mild cognitive impairment (MCI)
Alzheimer's disease

ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the mammalian brain. Preclinical studies suggest that BDNF influences the pathophysiology of Alzheimer's disease. In humans, higher blood BDNF levels have been associated with a lower risk of dementia. However, the relationship between serum BDNF levels and the progression to mild cognitive impairment (MCI) in cognitively normal (CN) individuals remains uncertain.

Objectives: To examine whether higher serum BDNF levels in CN older adults are associated with a reduced incidence of MCI over a 4-year follow-up period and to identify potential moderators of this relationship.

Design: Longitudinal analyses were conducted using follow-up data from the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease, an ongoing prospective cohort study. Data were collected from January 1, 2014, to May 31, 2021, and analyzed from May 1, 2023, to September 30, 2023.

Setting: Community and memory clinic setting.

Participants: A total of 274 CN older adults aged 55–90 years were included at baseline.

Measurement: Progression to MCI over the 4-year follow-up period.

Results: Among the 274 participants, 26 developed MCI during follow-up. The high BDNF group had a significantly lower incidence of MCI compared to the low BDNF group (hazard ratio [HR], 0.27; 95 % confidence interval [CI], 0.11–0.69; $P = 0.006$). This association persisted even after adjusting for BDNF Val66Met polymorphism, amyloid PET positivity, vascular risk factors, cholesterol levels, triglycerides, homocysteine, BMI, smoking, alcohol, TBI history, CES-D, and MMSE scores (HR, 0.14; 95 % CI, 0.05–0.40; $P < 0.001$). Subgroup analyses further revealed that the association was significant only in women (HR, 0.12; 95 % CI, 0.03–0.48; $P = 0.002$), individuals aged <75 years (HR, 0.16; 95 % CI, 0.03–0.77; $P = 0.022$), those with less than a college degree (HR, 0.23; 95 % CI, 0.07–0.74; $P = 0.013$), and amyloid PET-negative (HR, 0.29; 95 % CI, 0.11–0.72; $P = 0.014$) individuals.

Conclusions: These findings suggest a protective role of BDNF against clinical progression to MCI in cognitively healthy older individuals. This effect appears to be more prominent in women, as well as in relatively younger, less educated, and amyloid PET-negative individuals.

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https://doi.org/10.1016/j.tjpad.2025.100210
Received 27 January 2025; Received in revised form 9 April 2025; Accepted 19 May 2025

1. Introduction

Brain derived neurotropic factor (BDNF) is the most abundant and extensively researched neurotrophin in the mammalian brain [1,2]. It protects neurons from stress and neurotoxicity, and supports neurogenesis, development, and differentiation of neurons [3]. Furthermore, BDNF production and signaling are associated with neurophysiological processes such as long-term potentiation (LTP) [4,5]. During the aging process, BDNF levels increase in response to oxidative stress, providing partial antioxidant defense [6,7].

Preclinical studies suggest that BDNF influences the pathophysiology of Alzheimer's disease (AD) [8]. For example, BDNF/TrkB signaling has been shown to directly influence amyloid precursor protein (APP) processing [9–11], and BDNF has demonstrated protective effects against Aβ-induced toxicity by inhibiting hyperphosphorylation of tau [12,13].

In humans, directly measuring BDNF levels in the brain is challenging. Instead, BDNF levels in blood are used as a proxy, as supported by animal studies demonstrating that BDNF can cross the blood-brain barrier bidirectionally and that peripheral and central BDNF levels are closely associated [14–17]. Regarding human studies, higher blood BDNF levels have been associated with a slower rate of cognitive decline in AD dementia [18], and a reduced risk of conversion to dementia [19,20]. However, it remains uncertain whether blood BDNF levels are associated with the risk of progression to mild cognitive impairment (MCI), which is considered as a pre-dementia state or a high risk stage of dementia, in cognitively normal (CN) individuals [21]. Given that various modifiable lifestyle factors, including physical and cognitive activities, and dietary habits, can increase blood BDNF levels [8,22,23], elucidating the association between BDNF levels and progression to MCI is very meaningful in terms of the prevention of late-life cognitive decline.

In this study, we aimed to investigate whether higher serum BDNF levels are associated with a reduced likelihood of progressing to MCI over a four-year follow-up period in CN older adults. We additionally aimed to explore whether basic demographic factors (i.e., sex, age, and education), apolipoprotein E ε4 (APOE4) genotype, and the presence of Aβ pathology moderate the association of BDNF with the progression to MCI.

2. Methods

2.1. Participants

This study included 274 CN older adults who participated in the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study initiated in 2014 [24]. Data were collected from January 1, 2014 to May 31, 2021, and the data were analyzed from May 1, 2023 to September 30, 2023.

Volunteers were recruited through advertisements on an online homepage, posters, and brochures provided at four recruitment sites (two university hospitals and two public centers for dementia prevention around Seoul, South Korea) and word of mouth (recommended by other participants, family members, friends, or acquaintances). All subjects were aged between 55 and 90 years, had clinical dementia rating (CDR) score of 0, and an absence of MCI or dementia at baseline. The following exclusion criteria were also applied: 1) significant neurological or general medical conditions affecting mental function, 2) major psychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia, and alcohol use disorder, 3) hearing or visual impairment, communication or behavioral problems limiting imaging, blood testing, or clinical assessment, 4) illiteracy, and 5) participation in other studies involving experimental drugs. This study was approved by the Institutional Review Board of Seoul National University Hospital (C-1401-027-547) and the Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center (26-2015-60) in Seoul, Republic of Korea. The study protocol adhered to the principles of the current version of the Declaration of Helsinki. All participants provided written informed consent. The Supplementary Fig. 1 shows the overall process for the selection of study participants among individuals who provided informed consent.

2.2. Clinical assessments

All participants underwent standardized clinical and neuropsychological assessments conducted by trained board-certified psychiatrists and neuropsychologists following the KBASE assessment protocol [24] at baseline. Participants were also followed annually with the same clinical and neuropsychological assessments for up to 4 years. The KBASE assessment protocol incorporates the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) [25–27]. At each follow-up visit, progression to MCI was defined when a participant met the following criteria for MCI including: 1) cognitive complaints by a participant or an informant; 2) objective cognitive impairments; 3) independence in functional activities; 4) absence of dementia; and a CDR score of 0.5. Regarding Criterion 2, the age-, education-, and gender-adjusted z-score was < -1.0 for at least one of eight neuropsychological tests in the KBASE assessment protocol: [24] Word List Memory, Word List Recall, Word List Recognition, Constructional Recall, Verbal fluency, 15-item Boston Naming Test, Contructional Praxis and Stroop Color-Word Test. At each visit, the severity of depressive symptoms was also assessed using the Center for Epidemiological Studies Depression scale (CES-D), and global cognition was also evaluated using the mini-mental state examination (MMSE). Vascular risk factors (VRFs), such as hypertension, diabetes, hyperlipidemia, coronary heart disease, transient ischemic attacks (TIA), and strokes, were systematically assessed for each participant. The presence or absence of these VRFs, current smoking and alcohol consumption, and a history of traumatic brain injury (TBI) was determined based on data collected by trained nurses through systematic interviews, reliable informant reports, and review of medical records. To quantify overall clinical cerebrovascular risk, we computed composite vascular risk factor score (VRS) by summing the number of VRFs present, yielding scores ranging from 0 to 6 [28]. Additionally, baseline measurements of body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared).

2.3. Measurement of serum BDNF and other blood biomarkers

Blood samples were collected via venipuncture in the morning (8 to 9 a.m.) after an overnight fast at baseline. Serum BDNF levels were measured from previously frozen (stored at −80°C), with the commercially available Quantikine® ELISA Human Free BDNF Immunoassay (DBD00, R&D Systems, USA), following the manufacturer's protocol. Absorbance was recorded using a SpectraMax 190 ELISA Reader (Molecular Devices, China). In addition, levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (TG), and total homocysteine (tHcy) were measured, as these factors could potentially influence the association between BDNF levels and cognitive function [29,30]. Total cholesterol, HDL-cholesterol, LDL-cholesterol, and TG levels were assessed using a colorimetric method with the ADVIA 1800 Auto analyzer (Siemens, USA), while serum homocysteine levels were measured by chemiluminescence immunoassay (CIA) on the ADIVA Centaur system (Siemens Healthcare, USA). Genomic DNA was extracted from whole blood samples for apolipoprotein E genotyping, following established protocols [31]. APOE4 positivity was defined as the presence of at least one ε4 allele. The BDNF Val66Met (rs6265) single nucleotide polymorphism (SNP) was quantified using the Qubit Fluorometer, and sample purity was evaluated using Nanodrop (Thermo Fisher Scientific, Waltham, MA). Individuals with Met/Met or Val/Met genotypes were classified as Met carriers of the BDNF Val66Met polymorphism. Detailed experimental procedures are described in a prior study [32].

2.4. Measurement of cerebral Aβ deposition

All participants underwent simultaneous three-dimensional (3D) [11C] Pittsburgh compound B (PiB)-positron emission tomography (PET) and 3D T1-weighted MRI using a 3.0T Biograph mMR (PET-MR) scanner (Siemens, Washington, DC, USA), following the manufacturer's instructions at baseline. The details of PiB-PET acquisition and preprocessing were previously described [33]. The automatic anatomic labeling algorithm and the region combining method [34] were used to delineate regions of interest (ROIs) for characterizing PiB retention levels in the frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal regions. A global cortical ROI comprising these smaller ROIs was also defined. The global Aβ retention value, expressed as the standardized uptake value ratio (SUVR) for the global cortical ROI, was calculated by dividing the mean voxel value of the global cortical ROI by a mean reference range [34,35]. The inferior cerebellar gray matter in the spatially unbiased infratentorial template (SUIT) for the cerebellar atlas [36] was used as the reference region. Participants were categorized as amyloid positive if the global Aβ retention value exceeded 1.19, and as amyloid negative if the value was 1.19 or lower [37].

2.5. Statistical analyses

We conducted a series of multivariable Cox proportional hazard models to investigate the association between high and low BDNF groups (categorized by the median value of participants' serum BDNF levels) and the risk of MCI (dichotomous variable: MCI at follow-up: yes/no). Additionally, we examined the relationship between serum BDNF levels and the incidence of MCI, treating serum BDNF levels as a continuous variable. Due to the non-normal distribution of serum BDNF levels, log-transformed values were used for this analysis. Initial analyses were adjusted for age, sex, education, and APOE4 positivity (Model A). Model B included additional adjustments for amyloid PET positivity, VRS, tHcy, total cholesterol, HDL- and LDL- cholesterol, TG, and BMI, current smoking status, current alcohol use, and TBI history, and BDNF Val66Met polymorphism along with the covariates in Model A. Lastly, Model C included adjustments for CES-D and MMSE (z-score), in addition to the covariates in Model B. The time variable was defined as the time to progression in case of progression to MCI, or time to last visit for those who remained CN upon follow-up. To account for potential informative censoring due to loss to follow-up or death, we applied inverse probability of censoring weights (IPCW) using the covariates included in Model C, and additionally conducted Cox proportional hazards analyses with the weighted model [38]. We also performed a stratified analysis using Model C to investigate whether the influence of serum BDNF levels on MCI progression varied according to sex (male vs. female), age (<75 years vs. ≥75 years), education (no college degree vs. at least a college degree), APOE4 positivity (negative vs. positive), and amyloid PET positivity (negative vs. positive). Statistical analysis was performed using R version 4.3.3.

3. Results

3.1. Participant characteristics

Baseline characteristics of the participants are presented in Table 1. The high serum BDNF group had lower tHcy levels and higher total cholesterol, LDL-cholesterol, TG levels, and BMI compared to the low serum BDNF group. Of the 274 participants, 148 completed the 4-year follow-up during the data collection period, while 126 did not. Among the 126 individuals, 1 participant died, 113 dropped out before the end of data collection, and 12 had not yet reached the 4-year mark since the baseline assessment. As shown in Supplementary Table 1, there were no significant differences in most baseline characteristics between those who completed the 4-year follow-up and those who did not.

3.2. Association of serum BDNF levels and the likelihood of progressing to MCI

During the 4-year follow-up period, 26 participants developed MCI (17 amnestic MCI and 9 non-amnestic MCI). As shown in Table 2 and Fig. 1, the high serum BDNF group had significantly less frequent progression to MCI than the low serum BDNF group after adjusting for age, sex, education, and APOE4 positivity [hazard ratio (HR), 0.27; 95 % confidence interval (CI), 0.11–0.69; $P = 0.006$] (Table 2, Model A). This relationship remained significant even after additional adjustment for amyloid PET positivity, VRS, metabolic variables, BMI, smoking, alcohol, TBI history, and BDNF Val66Met polymorphism [HR, 0.13; 95 % CI, 0.04–0.37; $P < 0.001$] (Table 2, Model B). The association between serum BDNF levels and MCI progression also remained significant after further adjustment for global cognition and depression scales [HR, 0.14; 95 % CI, 0.05–0.40; $P < 0.001$] (Table 2, Model C). This trend was also observed in the weighted Cox regression analysis (Supplementary Table 2). The analyses treating serum BDNF levels as a continuous variable (log-transformed) also showed similar results across all models as show in Supplementary Table 3.

3.3. Moderators for the association between BDNF and the progression to MCI

Exploratory subgroup analyses showed that the risk of progression to MCI was significantly lower in the high serum BDNF group only among women [HR, 0.12; 95 % CI, 0.03–0.48; $P = 0.002$], participants under 75 years of age [HR, 0.16; 95 % CI, 0.03–0.77; $P = 0.022$], those with less than a college degree [HR, 0.23; 95 % CI, 0.07–0.74; $P = 0.013$], and individuals who were amyloid negative [HR, 0.29; 95 % CI, 0.11–0.72; $P = 0.014$] (Table 3).

4. Discussion

The present study showed that CN older adults with higher serum BDNF levels progressed to MCI less frequently. This finding is in line with previous reports which demonstrated that higher BDNF levels were associated with a lower risk of transitioning to dementia [19,20]. Taken together, higher serum BDNF levels may exert a continuous protective effect against clinical progression in non-demented older individuals with a wide cognitive spectrum from CN to MCI.

Regarding the mechanism by which BDNF protects against cognitive progression, BDNF could contribute to maintaining cognition by increasing neurogenesis, synaptic plasticity, and dendritic density, which may counteract brain pathologies [39–42]. Specifically, BDNF/TrkB signaling activates pathways related to neurogenesis, synaptogenesis, and neuronal survival [43–45]. Additionally, the active form of BDNF, modified BDNF (mBDNF), may play a protective role against cognitive decline by enhancing LTP, a crucial mechanism for synaptic strengthening and memory formation, through the reduction of GABA-ergic interneuron activation in the hippocampus [46–48].

Given that BDNF Val66Met polymorphism has been associated with cognitive decline across the spectrum of AD [49–51]. When we examined the association between serum BDNF and progression to MCI, therefore, we controlloed for the polymorphism positivity as a additional covariate in Model B and C. Even after controlling for the BDNF Val66Met polymorphism, higher BDNF levels were associated with less frequent progerssion to MCI suggestiong that serum BDNF work independently of the polymorphism status. As shown in Table 1, the proportion of Val66Met positive individuals was also not significantly different between low and high BDNF groups. Our findings align with previous studies, which indicate that there is no significant association between the BDNF Val66Met polymorphism and blood BDNF levels [52,53].

In the present study, higher serum BDNF levels were associated with a lower risk of MCI progression even after controlling for amyloid PET

Table 1
Baseline characteristics of the subjects.

Characteristic	Low Serum BDNF	High Serum BDNF	*p*-value
Incident of MCI cases, No./ Total cases, No. (%)	20/137 (14.4)	6/137 (4.3)	
BDNF, mean (SD), ng/mL	16177.21	28367.38	
Age, mean (SD), y	69.6 (8.1)	68.5 (8.0)	0.249
Women No. (%)	65 (47.4)	77 (56.2)	0.147
College degree No. (%)	58 (42.3)	56 (40.9)	0.807
Current smoker No. (%)	7 (5.1)	13 (9.5)	0.164
Current drinker No. (%)	53 (38.7)	53 (38.7)	1.000
BMI (SD), kg/m^2	23.8 (2.9)	24.7 (3.1)	**0.011**
tHcy, mean (SD), μmol/L	14.48 (3.88)	13.47 (3.59)	**0.027**
Total cholesterol, mean (SD), mg/dL	180.90 (36.85)	191.91 (32.72)	**0.009**
HDL-cholesterol, mean (SD), mg/dL	53.29 (14.16)	55.05 (14.40)	0.309
LDL-cholesterol, mean (SD), mg/dL	106.02 (30.98)	112.83 (28.74)	**0.060**
TG, mean (SD), mg/dL	119.69 (59.71)	136.66 (64.17)	**0.024**
CES-D score, mean (SD)	8.72 (7.07)	7.58 (6.45)	0.162
MMSE, mean (SD)	26.7 (2.4)	27.3 (2.5)	**0.045**
MMSE, z-score, mean (SD)	0.1959 (0.8947)	0.3873 (0.8504)	0.070
APOE4 positive No. (%)	25 (18.2)	25 (18.2)	1.000
Amyloid PET positive No. (%)	33 (24.1)	32 (23.4)	0.888
VRS, mean (SD)	1.09 (0.92)	0.96 (0.99)	0.232
TBI history No. (%)	11 (8.0)	10 (7.3)	0.821
BDNF Met carriers No. (%)	94 (34.3)	94 (34.3)	1.000

Note. Bold values indicate statistically significant P-Values. Continuous variables (mean [SD]) were analyzed using a two-tailed unpaired Student's t test. Age, Women, College degree, Current smoker, APOE4 positivity, and Amyloid PET positivity (number [%]) were analyzed by the Chi-square test, and p-values are reported accordingly. Abbreviations: BDNF, brain-derived neurotrophic factor; BMI, body mass index; tHcy, total homocysteine; TG, triglyceride; CES-D, center for epidemiological studies depression scale; MMSE, mini-mental state examination; APOE4, apolipoprotein E ε4; VRS, vascular risk score; TBI, traumatic brain injury.

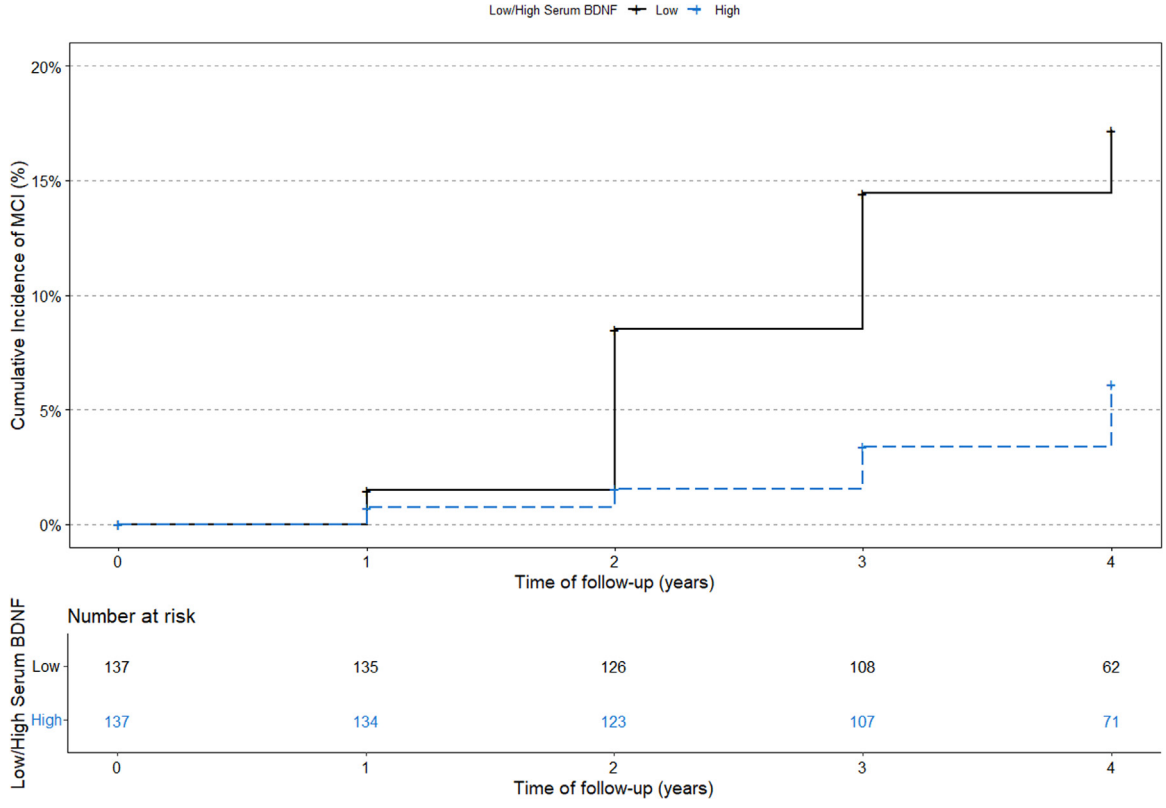

Fig. 1. Kaplan–Meier curve showing the cumulative incidence of MCI by low and high serum BDNF levels.
Note: The Kaplan–Meier curves compare the cumulative incidence of MCI between participants with low and high serum BDNF levels. The log-rank test indicates a significant difference between the curves ($P = 0.009$). Abbreviations: BDNF, brain-derived neurotrophic factor; MCI, mild cognitive impairment.

Table 2
Analyses of the association between serum brain-derived neurotrophic factor levels and the risk of incident MCI.

Model	Hazard Ratio (95 % CI)	*p*-value
Model A[a]		
Low serum BDNF	1 [Reference]	
High serum BDNF	**0.27 (0.11-0.69)**	**0.006**
Model B[b]		
Low serum BDNF	1 [Reference]	
High serum BDNF	**0.13 (0.04-0.37)**	**<0.001**
Model C[c]		
Low serum BDNF	1 [Reference]	
High serum BDNF	**0.14 (0.05-0.40)**	**<0.001**

Note. Bold values represent statistically significant HRs. Abbreviations: MCI, mild cognitive impairment; BDNF, brain-derived neurotrophic factor; APOE4, apolipoprotein E ε4; VRS, vascular risk score; tHcy, total homocysteine; TG, triglyceride; BMI, body mass index; TBI, traumatic brain injury.

[a] Model A: Adjusted for age, sex, education, APOE4 positivity

[b] Model B: Adjusted for the covariates of Model A, plus BDNF Val66Met polymorphism, amyloid PET positivity and, VRS, tHcy, total cholesterol, HDL-cholesterol, LDL-cholesterol, TG, BMI, smoking, alcohol, and TBI history.

[c] Model C: Adjusted for the covariates of Model B, plus CES-D and MMSE scores (z-scores).

Table 3
Association between serum brain-derived neurotrophic factor levels and risk of incident MCI stratified by sex, age, education, APOE4 positivity, and amyloid PET positivity.

Variable	Model	
Incident of MCI cases, No./Total cases, No. (%)	Hazard Ratio (95 % CI)	*p*-value
Women 18/142 (12.7)	**0.12 (0.03-0.48)**	**0.002**
Men 8/132 (6.7)	1.13 (0.24-5.34)	0.879
<75 y 12/188 (6.4)	**0.16 (0.03-0.77)**	**0.022**
≥75 y 14/86 (16.2)	0.50 (0.14-1.72)	0.269
No college degree 18/156 (11.5)	**0.23 (0.07-0.74)**	**0.013**
College degree 8/118 (6.8)	0.42 (0.08-2.23)	0.310
APOE4 negative 19/224 (8.5)	0.40 (0.14-1.13)	0.083
APOE4 positive 7/50 (14.0)	0.16 (0.02-1.66)	0.125
Amyloid PET negative 19/209 (9.1)	**0.29 (0.11-0.72)**	**0.014**
Amyloid PET positive 7/65 (10.8)	0.31 (0.06-1.73)	0.183

Note. Bold values represent statistically significant HRs. Model was adjusted for age (except for the age stratification), sex (except for the sex stratification), education (except for the education stratification), APOE4 positivity (except for the APOE4 stratification), amyloid PET positivity (except for the amyloid PET stratification), VRS and BDNF Val66Met polymorphism. Abbreviations: BDNF, brain-derived neurotrophic factor; MCI, mild cognitive impairment; APOE4, apolipoprotein E ε4; VRS, vascular risk score.

positivity (as shown in Models B and C). This suggests that BDNF may exert protective effects independently of Aβ pathology. Further subgroup analyses revealed that the association between higher BDNF levels and a lower frequency of MCI progression was significant in the amyloid-negative group, but not in the amyloid-positive group. Taken together, these findings suggst that BDNF might not sufficiently counteract the effect of Aβ pathology or AD-specific pathological process and may contribute to lowering risk of MCI progression through Aβ-independent process. In line with our findings, some animal studies demonstrated that BDNF introduction improved cognitive deficits without altering amyloid plaque burden and regulated neuronal atrophy, synaptic loss, and neuronal signaling, suggesting that BDNF may exert protective effects via amyloid-independent mechanisms [8,54]. However, several animal studies have proposed mechanisms through which BDNF could directly influence Aβ pathology. Nigam et al. [10] suggested that BDNF may reduce toxic Aβ production by promoting the α-secretase processing of APP. Additionally, the introduction of BDNF has been shown to enhance hippocampal LTP and mitigate the effects of Aβ and tau on neuronal loss [55–57]. Further investigations are needed to elucidate whether the effect of serum BDNF is related to Aβ deposition.

Furthermore, we observed that higher serum BDNF levels were associated with a lower risk of MCI progression only in the female group but not in the male group. This finding is consistent with a previous study which showed that decreased plasma BDNF levels were linked to impaired general cognitive function and memory exclusively in women [58]. An animal study also reported that BDNF/TrkB signaling responded more sensitively to inflammatory damage in the hippocampus in female mice, and baseline BDNF levels in the hippocampus were higher in female mice than in male mice [59]. Such sex discrepancy in the association between BDNF levels and MCI progression may be influenced by sex hormones such as estrogen and progesterone. Given conflicting results regarding the effects of sex hormones on BDNF [19,60,61], however, the possibility that other mechanisms are involved in the sex-specific contribution of BDNF to lower MCI progression should also be considered.

Additionally, the association between higher BDNF levels and a lower progression to MCI was signficant only in relatively younger individuals (less than 70 years of age), but not in older ones. This result suggests that the effect of BDNF in reducing the progression to MCI may decrease with age. In an animal study, aged rats showed less activation of BDNF/TrkB signaling, which is related to the neurotrophic effect of BDNF, compared to young rats [62].

In our study, the effect of serum BDNF levels on MCI progression was observed only in individuals with lower educational levels (i.e., less than a college degree), but not in those with higher educational levels. Education is a well-known proxy for cognitive reserve (CR), which is defined as the capacity to preserve cognitive function better in the presence of brain pathology [63,64]. Given that individuals with higher educational levels already have a sufficiently higher CR, they could maintain their cognitive function against brain pathology regardless of current BDNF levels. In contrast, as those with lower educational levels have relatively lower CR and might more depend on the present levels of BDNF for the progression to MCI.

This study has several potential limitations that should be considered. First, the four-year follow-up period may have been insufficient to fully capture the effects of serum BDNF on MCI progression, particularly subgroup-specific effects, given the relatively lower rate of MCI progression in CN individuals. In our study, only 26 (9.5 %) among 274 CN participants progressed to MCI over the 4-year follow-up period. Second, this study included only Koreans, which may limit the generalizability of the findings. Further studies including other ethnic populations are required to confirm our findings. Third, IPCW was applied to mitigate the impact of informative censoring, but potential residual bias from unmeasured variables or unmet assumptions cannot be fully excluded. Fourth, in the subgroup analysis, the sample size for some subgroups may have been insufficient to detect statistically significant results. Therefore, it

is important to interpret insignificant results from the subgroup analysis with caution. Lastly, although we controlled the confounding effect of amyloid pathology and further explored the moderation effect of amyloid pathology through subgroup analyses, the present study did not delineate the specific brain pathological processes through which BDNF exerts its protective effects against progression to MCI. Further research on neuropathological substrates underlying the effect of BDNF against clinical progression are needed.

5. Conclusions

The present study is novel in that it first demonstrated the association between higher serum BDNF and a lower risk of MCI progression in CN older individuals. Our findings suggest a protective role of BDNF against clinical progression to MCI in cognitively healthy older individuals. This role appears more prominent in women, and relatively younger, less educated, or amyloid PET-negative individuals.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Kyungtae Kim: Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Min Soo Byun:** Supervision, Investigation, Data curation. **Dahyun Yi:** Validation, Software, Project administration, Investigation, Data curation. **Joon Hyung Jung:** Validation, Data curation. **Bo Kyung Sohn:** Validation, Data curation. **Gijung Jung:** Validation, Project administration, Data curation. **Hyejin Ahn:** Validation, Project administration, Data curation. **Jun-Young Lee:** Validation, Supervision, Investigation. **Yun-Sang Lee:** Validation, Investigation. **Yu Kyeong Kim:** Validation, Investigation. **Kwangsik Nho:** Data curation, Formal analysis, Investigation, Supervision, Validation. **Dong Young Lee:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Funding

This study was supported by grants from the Ministry of Science, ICT, and Future Planning, Republic of Korea (grant no: NRF-2014M3C7A1046042, NRF-2020R1G1A1099652 & RS-2022-00165636) and grants of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant no: HI18C0630, HI19C0149 & HU23C0140), a grant from New Faculty Startup Fund from Seoul National University (grant no: RS-2023-KH136195), and a grant from the National Institute of Health, United States of America (grant no: U01AG072177). The funding source had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or decision to submit it for publication. We thank the KBASE study participants and their caregivers.

Acknowledgments

We express our gratitude to the participants and their caregivers of the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE). We also acknowledge the dedication of the clinical coordinators for their essential contributions to data collection and study coordination, as well as the collaborative efforts of the team managing data generation, storage, and project execution for KBASE.

Ethical standards

Written informed consent was obtained from all participants in this study. The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University Hospital and adhered to the principles outlined in the Declaration of Helsinki.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100210.

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