Plasma Brain-Derived Neurotropic Factor Levels Are Associated with Aging and Smoking But Not with Future Dementia in the Rotterdam Study

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Abstract.
Background: Brain-derived neurotropic factor (BDNF) plays a vital role in neuronal survival and plasticity and facilitates long-term potentiation, essential for memory. Alterations in BDNF signaling have been associated with cognitive impairment, dementia, and Alzheimer's disease. Although peripheral BDNF levels are reduced in dementia patients, it is unclear whether changes in BDNF levels precede or follow dementia onset.
Objective: In the present study, we examined the association between BDNF plasma levels and dementia risk over a follow-up period of up to 16 years.
Methods: Plasma BDNF levels were assessed in 758 participants of the Rotterdam Study. Dementia was assessed from baseline (1997–1999) to follow-up until January 2016. Associations of plasma BDNF and incident dementia were assessed with Cox proportional hazards models, adjusted for age and sex. Associations between plasma BDNF and lifestyle and metabolic factors are investigated using linear regression.
Results: During a follow up of 3,286 person-years, 131 participants developed dementia, of whom 104 had Alzheimer's disease. We did not find an association between plasma BDNF and risk of dementia (adjusted hazard ratio 0.99; 95% CI 0.84–1.16). BDNF levels were positively associated with age (B = 0.003, SD = 0.001, $p = 0.002$), smoking (B = 0.08, SE = 0.01, $p = < 0.001$), and female sex (B = 0.03, SE = 0.01, $p = 0.03$), but not with physical activity level (B = –0.01, SE = 0.01, $p = 0.06$).
Conclusion: The findings suggest that peripheral BDNF levels are not associated with an increased risk of dementia.

Keywords: Aging, Alzheimer's disease, brain-derived neurotropic factor, dementia, genetic epidemiology

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INTRODUCTION

Brain-derived neurotropic factor (BDNF) is the most widely distributed neurotropic factor, that supports physiological functioning in the central nervous system and the periphery [1–3]. It plays a vital role in neuronal survival and plasticity of cholinergic and dopaminergic neurons in the cortex [4–8] and facilitates hippocampal and cortical long-term potentiation, essential for memory acquisition and consolidation [9–11].

BDNF's neurotropic effects are exerted by binding to the tyrosine receptor kinase B (TrkB). Breakdown of the BDNF-TrkB signaling pathway has been associated with poorly differentiated neurons, loss of synaptic connectivity, and cognitive impairment [12]. Reduced serum BDNF has been related to smaller hippocampal volumes as well as poorer memory performance in healthy elderly. Higher levels of BDNF, on the other hand, have been related to better learning and memory [13, 14].

The BDNF-TrkB signaling pathway is also implicated in the pathogenesis of Alzheimer's disease (AD) [15]. Postmortem, AD patients show decreased levels of BDNF and its receptor in the frontal cortex and hippocampus [16] and reduced expression of the BDNF gene in the hippocampus and the entorhinal cortex [17], compared to neurologically non-impaired controls. The hippocampus, frontal and entorhinal cortex are consistently affected in the earliest stages of the disease.

Despite consistent findings in pathological studies, the findings of clinical studies investigating the association of BDNF with AD or mild cognitive impairment (MCI) have been far from consistent. While various studies reported lower peripheral BDNF levels in AD patients compared to healthy controls, other studies showed an inverse or no association [18–22]. A meta-analysis of 15 cross-sectional and case-control studies showed significantly lower peripheral serum BDNF levels in AD patients compared to controls [23]. No differences in peripheral BDNF levels were found between patients diagnosed with MCI and healthy controls [23]. Of note is that change in peripheral BDNF levels could only be detected in later stages of disease progression [23]. Investigating plasma-based markers, Elahi et al. found elevated BDNF levels in late-onset AD patients, that were strongly associated with cognition and gray matter volumes [24].

Because of the cross-sectional design of these case control studies, it is impossible to disentangle whether changes in BDNF levels precede or follow the cognitive decline and onset of dementia. Cohort studies investigating the association between peripheral BDNF levels and future cognitive decline and dementia risk are scarce. Weinstein et al. found that higher peripheral BDNF levels in older adults were protective against the development of AD [25]. However, the association between BDNF and the risk for incident dementia was limited to specific subgroups, i.e., women, older participants (> 80 years), and participants with at least a college degree [25]. In AD patients, higher BDNF serum levels were predictive of relatively slower cognitive decline in the following year [26]. Longitudinal studies of cognitive decline in healthy elderly did not provide evidence for an association between peripheral BDNF and rate of decline over 10 years [27, 28].

Besides genetic variation, age, and sex, a proportion of the observed variation in BDNF levels can be attributed to lifestyle factors, (co)morbidities, and the presence of depressive symptoms. Sleep deprivation, depression, diabetes mellitus, and stress have been associated with decreased levels of BDNF [29–33], whereas physical activity, smoking, coronary artery disease, and caloric restriction are associated with elevated BDNF levels [13, 33, 34–41, 42].

In light of the conflicting results regarding the association between BDNF levels and risk of dementia, we examined the long-term association between BDNF plasma levels and dementia risk over a follow-up period up to 16 years and addressed the association between plasma BDNF, associated comorbidities and a large number of lifestyle exposures.

MATERIALS AND METHODS

Setting

This study was embedded within the prospective, population-based Rotterdam Study, ongoing since 1990 in the city of Rotterdam in the Netherlands. The study was designed to study risk factors and determinants of disease in the elderly population. The Rotterdam Study started with an invitation to 10,215 inhabitants of Rotterdam, aged 55 years and older. Of the invitees, 7,983 (78%) people agreed to participate in the first examinations. The participants were interviewed at home and participated in elaborate physical examinations at the Rotterdam Study research facility in the Ommoord district in Rotterdam. The assessments were repeated every 3 to 5 years. The second follow-up assessment of the first cohort (RSI-3) was
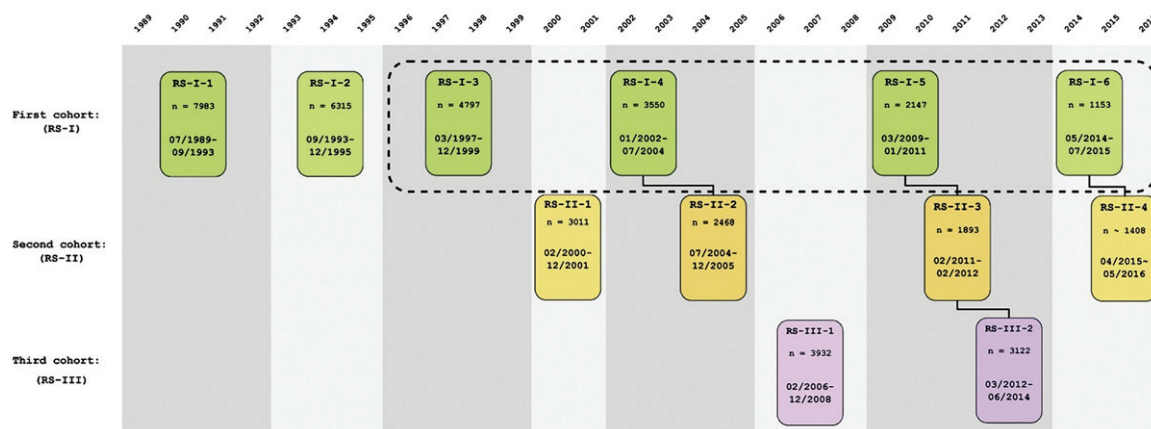
Fig. 1. Diagram of examination cycles of the Rotterdam Study (RS) [43]. RS-I-1 refers to the baseline examination of the original cohort. RS-I-2, RS-I-3, RS-I-4, RS-I-5, and RS-I-6 refer to re-examinations of the original cohort members. The follow-up examinations within the dashed border are included in the present study. RSI-3 was used as baseline.

used as baseline in the present study. A diagram of the cohort cycles of the Rotterdam Study is depicted in Fig. 1. Further details on the objectives and design of the Rotterdam Study have been described elsewhere [43].

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Participants

From 1997 to 1999, plasma BDNF levels were measured in blood samples collected at the second follow-up examination of the first cohort (RSI-3) that is considered the baseline measurement for the current study. From the 4,797 individuals who participated in the second follow-up examination, 971 participants were randomly selected for BDNF assessment. Plasma BDNF values below the lower detection limit (11 pg/mL; N = 191; 19.76%) or more than three standard deviations above the average plasma BDNF value (N = 1) were considered outliers

and were excluded from the analyses. Participants diagnosed with dementia at baseline (N = 14) were excluded from the analyses. The data of seven people were excluded from analyses because insufficient data were available to ascertain dementia status at baseline. In total, the data of 758 participants were analyzed, including the data of 131 participants who developed dementia during follow-up. See Fig. 2 for a flowchart of participant selection.

Assessment of plasma BDNF

Fasting blood samples were obtained at the research center. Citrate plasma (5 mL) was collected and stored at −80°C. In 2008, 200 μL of citrate plasma from each participant was sent to Myriad RBM, Austin, Texas (http://www.myriadrbm.com) where a multiplex immunoassay on a human multi-analyte profile was performed [44]. Samples were run in duplicates according to the manufacturer's published protocols [45] and met all parameters of quality control as defined by the Clinical Laboratory Standards Institute [46]. Intra-assay variation and percentage missing did not exceed 10%. Plasma BDNF levels are expressed in picogram per milliliter (pg/mL). The minimum and maximum detectable dosages were 11 pg/mL and 26500 pg/mL respectively.

Assessment of dementia

Participants were screened for dementia at baseline and follow-up examinations, using a cognitive assessment including the Mini-Mental State Examination (MMSE) [47] and the Geriatric Mental Schedule
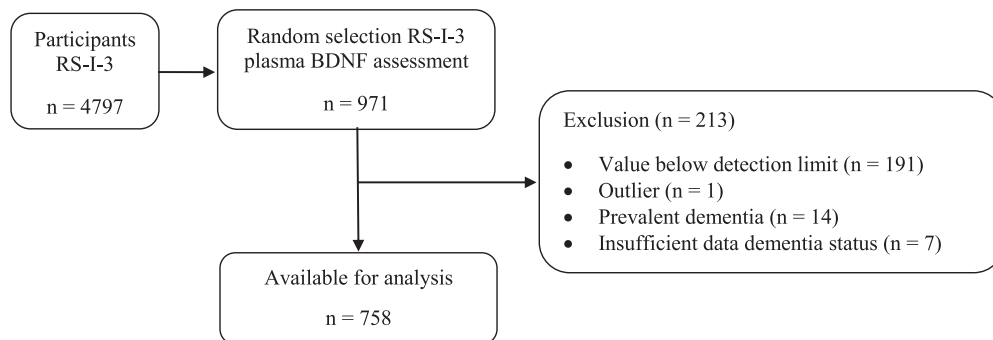
Fig. 2. Flowchart of participant selection from the second follow-up measurement in cohort 1 of the Rotterdam Study (RS-I-3).
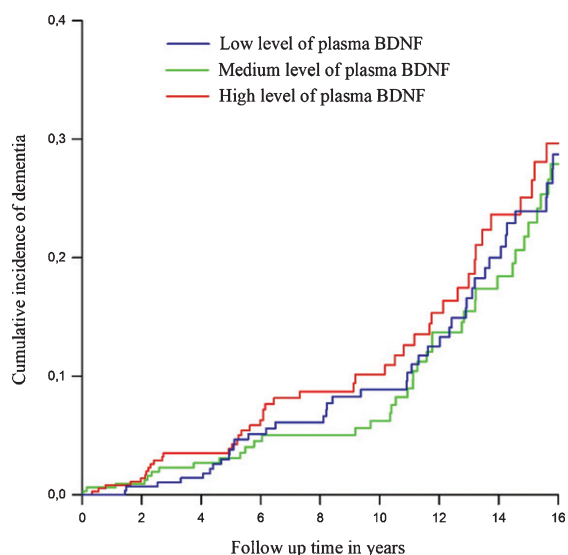

Fig. 3. Cumulative incidence curves of dementia per tertile of plasma Brain Derived Neurotrophic Factor (BDNF), adjusted for age and sex. Tertile 1 represent the lowest levels of plasma BDNF, tertile 2 medium levels and tertile 3 the highest levels.

(GMS) organic level [48]. Participants with a MMSE score lower than 26 or GMS organic level higher than 0 subsequently underwent further investigation and an informant interview including the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX) [49]. A consensus panel led by a consultant neurologist established the final diagnosis dementia or probable AD according to standard criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders III-revised) (American Psychiatric Association, 1987) and AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) [51].

During follow-up, the cohort was under continuous surveillance for dementia incidence through electronic linkage of the database of the Rotterdam Study with medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. Follow-up for incident dementia is virtually complete until January 1, 2016 (97.6% of potential person-years).

Assessment of APOE

Information on *APOE* was obtained using polymerase chain reaction on coded DNA samples. *APOE* ε4 carrier status was defined as carrier of one or two ε4 alleles. Missing values for *APOE* ε4 carrier status (3.83%) were imputed using regression analyses based on age and sex.

Assessment of physical activity

Levels of daily physical activity (PA) were assessed at baseline with the Zutphen Physical Activity Questionnaire [52]. The questionnaire was translated into Dutch and validated in a sample of the Zutphen Elderly Study Population [52]. The test-retest reliability of this questionnaire is 0.93 and its correlation with doubly labelled water, the gold standard for measuring PA, is 0.61 [53]. The questionnaire contains questions on walking, cycling, sports, gardening, hobbies, and housekeeping and inventoried the frequency and duration of these activities performed in the previous week. To quantify activity intensity, we assigned metabolic equivalent of task (MET) units to all activities mentioned in the questionnaire according to the 2011 updated version of the Compendium of Physical Activities [54]. Finally, we multiplied MET-values of specific activities with time (in hours) per week spent on that activity to calculate

MET·h·week of total PA. Standardized values of total MET-hours of physical activity per week and number of MET-hours spent on moderate to vigorous physical activity were used for analyses. Detailed information on the collection of PA data has been described previously [55].

Assessment of depressive symptoms and anxiety

We measured depressive symptoms using the validated Dutch version of the Center for Epidemiology Depression Scale (CES-D) [56, 57]. Participants were asked to self-report how often they experienced various depressive symptoms during the previous week. Possible scores ranged from 0 (rarely or never) to 3 (most or all of the time). For items with positive affect, the response categories were reversed. Total scores were summed to a total depressive symptoms score ranging from zero to 60. The psychometric properties of the scale were found to be good in an older population [57]. The presence of feelings of anxiety was derived from item 10 on the CES-D on which participants were asked how often they had felt anxious during the previous week. Anxiety was than coded as *No* = 'never' versus *Yes* = 'sometimes' or 'most or all of the time'. Missing values for depressive symptoms (5.94%) and anxiety (1.72%) were imputed using regression analyses based on age and sex.

Other measurements

Systolic blood pressure was calculated as the average of two measurements at the right brachial artery using a random-zero sphygmomanometer. Serum glucose, total cholesterol, and high-density lipoprotein (HDL)-cholesterol levels were acquired by an automated enzymatic procedure (Boehringer Mannheim System). To assess diabetes mellitus all participants, except those on anti-diabetic medication, received a glucose drink of 75 mg in 200 mL water. Participants were classified as having diabetes mellitus if they used any anti-diabetic medication or when the pre-load or post-load serum glucose levels were at or above 11.1 mmol/l. Education level was defined as low (primary, unfinished secondary and lower vocational), middle (secondary or intermediate vocational) and high (higher vocational or university). Body mass index (BMI) was calculated by dividing participants' weight in kilogram by the height in meters. At baseline all participants were asked about their medication use, past and current smoking habits and current alcohol consumption.

Smoking status was categorized into current smoker, former smoker and never smoked. Alcohol consumption was defined as gram per day. Missing values for smoking status (1.06%) were imputed using regression analyses based on age and sex.

Statistical analyses

We examined the association between plasma BDNF and incident dementia in the total sample using Cox proportional hazards models. Plasma BDNF was entered per standard deviation (SD) into the models. To adjust the estimation of the proportional hazard for the competing risk of death an additional competing risk regression was performed [58]. We also studied plasma BDNF in tertiles, using the lowest tertile as reference. The underlying timescale in the Cox proportional hazards models was the follow-up time, which was defined from the date of blood sample collection (1997–1999) until 1 January 2016. Participants were censored within this period when they were diagnosed with dementia, died, or were lost to follow-up, whichever came first. Analyses were adjusted for age and sex. The proportional hazards assumption was tested with the Schoenfeld residuals test and log-log plots of the survival function, both procedures confirmed that the assumption was met. No outliers were identified. To control bias due to risk factors and co-morbidities that may influence circulating BDNF, educational level, total- and HDL cholesterol, glucose level, presence of diabetes mellitus, body mass index, systolic blood pressure, depressive symptoms, anxiety (y/n), alcohol consumption, smoking status, physical activity level, and *APOE ε*4 carrier status, are investigated as potential confounders. None of the additional covariates qualified as confounder as they did not change the estimate of the model with more than 1%. To investigate possible effect modification by Apolipoprotein E, the (multiplicative) interaction between sex, education, smoking and *APOE ε*4 carrier status, and plasma BDNF on dementia risk was tested using interaction terms.

We used a linear regression model to examine the influence of metabolic and lifestyle factors on plasma BDNF levels in the randomly drawn sub-cohort. Effects of medication use on plasma BDNF were studied as potential confounders, including the effects of ACE-inhibitors, anti-hypertensive and anti-thrombotic drugs, serum lipid reducing agents, anti-diabetic, anti-Parkinson, anti-epileptic, anti-inflammatory and anti-rheumatic medication,

systemic corticosteroids, psycholeptic- and psycho-analeptic agents. Plasma BDNF levels showed a non-normal distribution, with a positive skewness and elevated kurtosis. As log10 transformation did not change the results, analyses on the non-transformed BDNF values are presented. Analyses were performed using Stata/SE version 16 (StataCorp LLC, College Station, TX, USA).

RESULTS

Baseline characteristics of the study population are shown in Table 1. During a total follow up of 3,286 person-years of the total sample, 131 participants of the total set developed dementia, of whom 104 were diagnosed with AD, and 27 were diagnosed with other types of dementia including vascular dementia and Parkinson's disease dementia. The incidence rate of 40 cases per 1000 person-years in the present sample lies within the range of the estimated incidence rates in Western Europe for people between the age of 60 and 90 + that varies from 3.1 to 122.4 [59, 60]. The average plasma BDNF level is 138.81 pg/mL, with a standard deviation of 160.41 pg/mL. Group means and standard deviations are provided in Table 2.

Cross-sectional associations with BDNF level

Linear regression analyses on the association between metabolic and lifestyle factors and plasma BDNF in the sub-cohort (Table 3) indicated a positive relation with age (B = 0.003, SE = 0.001, $p = 0.002$), female sex (B = 0.03, SE = 0.01, $p = 0.03$), and current smoking (B = 0.08, SE = 0.01, $p < 0.001$). The association between plasma BDNF level and standardized baseline levels of physical activity (B = –0.01, SE = 0.01, $p = 0.06$) did not reach significance. Total model: $F(15,742) = 2.97$, $p \leq 0.001$. Plasma BDNF levels at baseline of participants who developed incident AD during follow-up are higher (M = 0.15, SD = 0.16) than those of participants that were diagnosed with other dementia types during follow-up (M = 0.09, SD = 0.10) F(1) 4.08, $p = 0.045$.

Effects of medication use on plasma BDNF were studied and included the effects of ACE-inhibitors, anti-hypertensive and anti-thrombotic drugs, serum lipid reducing agents, anti-diabetic, anti-Parkinson, anti-epileptic, anti-inflammatory and anti-rheumatic medication, systemic corticosteroids, psycholeptic- and psycho-analeptic agents. No effect of medication on plasma BDNF was observed.

Table 1
Baseline characteristics of the study population

	Total $N = 758$	Incident dementia $N = 131$	No dementia $N = 627$	p
Age, y	73.19 (7.47)	75.76 (7.44)	72.75 (7.44)	< 0.001
Women	419 (55.28%)	81 (61.83%)	338 (53.91%)	< 0.001
Plasma BDNF, pg/mL	139.57 (162.88)	138.27 (148.65)	139.84 (165.81)	0.92
Physical Activity (total METh)	87.96 (49.10)	88.64 (47.76)	87.82 (49.42)	0.86
Apolipoprotein E ε4 carrier	216 (28.50%)	48 (36.64%)	168 (26.79%)	0.003
Apolipoprotein E ε4 homozygote	12 (1.65%)	7 (22.58%)	5 (0.80%)	< 0.001
Systolic blood pressure	143.37 (20.66)	140.44 (20.22)	143.98 (20.72)	0.72
Diastolic blood pressure	74.77 (10.97)	72.94 (10.09)	75.15 (11.11)	0.04
Middle level of education	324 (42.74%)	41 (31.30%)	283 (45.14%)	0.004
High level of education	61 (8.05%)	14 (10.69%)	47 (7.50%)	0.22
Depressive symptoms	4.12 (6.31)	5.52 (7.24)	3.83 (6.06)	0.005
Body mass index	26.62 (3.97)	26.62 (3.35)	26.62 (4.09)	0.99
Anxiety	50 (6.60%)	13 (9.92%)	37 (5.90%)	0.09
Glucose, mmol/L	5.87 (1.43)	5.80 (1.15)	5.88 (1.49)	0.55
Total cholesterol, mmol/L	5.81 (0.97)	5.82 (0.91)	5.81 (0.98)	0.93
HDL-cholesterol, mmol/L	1.41 (0.40)	1.45 (0.41)	1.40 (0.40)	0.13
MMSE	27.68 (1.92)	27.30 (2.03)	27.76 (1.88)	0.01
Current smoking	121 (15.96%)	13 (9.92%)	108 (17.22%)	0.04
Former smoking	367 (48.42%)	64 (48.85%)	303 (48.33%)	0.91
Alcohol intake g/day	11.82 (16.45)	11.31 (13.96)	11.93 (16.93)	0.69

Means and standard deviations, number and percentage reported. *P*-values are based on univariate analysis of variance and Pearson's chi-square test. Anxiety is expressed as self-reported presence of anxious feelings yes/no. BDNF, brain-derived neurotropic factor; pg/mL, picogram per milliliter, METh, metabolic equivalent of task hour; mmol/L, millimole per liter; g/day, gram per day; BMI, body mass index; HDL, high density lipoprotein; MMSE, Mini-Mental State Examination.

Table 2
Average plasma BDNF values stratified by group

	N	Plasma BDNF	p
Women	339	142.17 (163.48)	
Men	419	136.37 (162.32)	0.63
No dementia	627	139.84 (165.81)	
Incident dementia all cause	131	138.27 (148.65)	0.92
Incident Alzheimer's disease	104	151.49 (157.33)	
Incident dementia other	27	87.35 (95.07)	0.045
Carrier of *APOE* ε4 allele	216	138.75 (134.72)	
Non carrier of *APOE* ε4 allele	542	139.90 (170.29)	0.93
Low level of education	369	134.18 (141.20)	
Middle level of education	323	148.57 (187.02)	
High level of education	60	112.06 (118.90)	0.21
Current smoker	121	190.12 (212.92)	
Former smoker	367	134.69 (157.79)	
Never smoked	270	123.56 (138.28)	0.00
Low level of physical activity	249	149.78 (169.39)	
Moderate level of physical activity	249	146.69 (184.45)	
High level of physical activity	249	123.55 (132.48)	0.15

Group means and standard deviations reported. *P*-values are based on univariate comparison of group means. Level of physical activity is expressed in tertile groups of the total number of Metabolic Equivalent of Task hours. BDNF, brain-derived neurotropic factor expressed in pg/mL (picogram per milliliter); *APOE* ε4, Apolipoprotein E ε4.

Table 3
Summary of regression analysis predicting variation in BDNF plasma level in the sub-cohort N = 758

Variable	B	SE(B)	β	p
Age	0.003	0.001	0.11	0.002
Sex	0.03	0.01	0.03	0.09
Middle level of education	0.02	0.01	0.06	0.13
High level of education	–0.01	0.02	–0.01	0.80
Body mass index	–0.001	0.00	–0.04	0.32
Diabetes mellitus	–0.01	0.01	–0.04	0.24
Total cholesterol	0.01	0.01	0.09	0.06
Systolic blood pressure	0.00	0.00	–0.04	0.23
APOE ε4 status	0.001	0.01	0.002	0.94
Depressive symptoms	–0.002	0.001	–0.07	0.09
Anxiety	0.01	0.03	0.02	0.65
Alcohol	0.00	0.00	0.03	0.39
Current smoking	0.08	0.01	0.18	<0.001
Former smoking	0.02	0.01	0.07	0.13
Standardized physical activity	–0.01	0.01	–0.07	0.06

APOE ε4, Apolipoprotein E ε4.

Survival analyses: BDNF and the risk of dementia

The Cox proportional hazard analysis of the risk of dementia did not show evidence for a relation between the level of plasma BDNF at baseline and

Table 4
Association between plasma BDNF level and risk of dementia

	Incident dementia n/N 131/758 HR (95% CI)	Incident Alzheimer's disease n/N 104/758 HR (95% CI)
Plasma BDNF	0.99 (0.84 – 1.16) χ^2 (3) = 2.88 p = 0.41	1.06 (0.92 – 1.23) χ^2 (3) = 3.60 p = 0.31

Adjusted for age and sex. Plasma BDNF values are standardized. BDNF, Brain-derived neurotropic factor.

risk of dementia (Table 4). The observed hazard ratio (HR) per SD increase in plasma BDNF is 0.99 (95% CI 0.84–1.55) χ^2 (3) = 2.88 p = 0.41. Adjustment for the competing risk of death in the competing risk regression only altered the sub distribution hazard of plasma BDNF on the risk of dementia 0.95 (95% CI 0.80–1.13) χ^2 (3) = 15.73 p = 0.001. Analysis per tertile of plasma BDNF levels, using the first tertile as reference, did also not show any significant differences in dementia risk for those with different levels of plasma BDNF at baseline [HR moderate versus low 0.91 (95% CI 0.65 – 1.29); HR high versus low 1.08 (95% CI 0.78 – 1.49). Figure 2 shows the cumulative incidence curves of dementia per tertile of plasma BDNF, adjusted for age and sex.

Congruent hazard ratios were found for the incidence of AD: HR 1.06 (95% CI 0.92–1.23) $\chi^2(3) = 3.60$ $p = 0.31$ (Table 4). Additional adjustment for education level, metabolic factors (total cholesterol, HDL-cholesterol, glucose, BMI, systolic blood pressure), diabetes mellitus, depressive symptoms, anxiety (y/n), alcohol consumption, smoking status, physical activity level, or *APOE* ε4 carrier status did not change the association between plasma BDNF and dementia risk. When testing for effect modification, no evidence for multiplicative interactions between plasma BDNF level and *APOE* ε4 carrier status, education level, sex or smoking status was found.

DISCUSSION

In our cohort study with a follow-up period of up to 16 years, we did not find an association between BDNF levels and dementia risk. We found that a higher plasma BDNF level at baseline is associated with higher age, female sex and higher prevalence of smoking. Plasma BDNF was not associated with total physical activity level or amount of moderate to vigorous activity.

Our findings with regard to dementia risk are in contrast with the only other follow-up study on the relation between peripheral BDNF and future dementia risk, in which higher serum BDNF levels were associated with a lower incidence of dementia over a follow-up period of 10 years [25]. However, when conducting a sensitivity analysis, Weinstein et al. concluded the association was confined to specific subgroups of participants, i.e., women, older participants (>80 years) and participants with at least a college degree. In the present study, subgroup analyses did not yield different results. Our results also deviate from the observed elevations in plasma BDNF in patients with AD reported by Elahi et al [24]. Although the cumulative incidence rate of dementia for those with the highest level of plasma BDNF is elevated compared to lower levels of plasma BDNF, no significant differences in dementia risk are observed. The discrepancy might be related to the course of AD, suggesting that peripheral BDNF concentrations change as a result of AD pathology and mark disease progression and severity of the cognitive deficit [61].

The absence of an association between BDNF and dementia risk is in line with the findings of longitudinal studies investigating cognitive decline. For instance, Nettiksimmons et al. and Driscoll et al. found no prospective association between blood BDNF levels and cognitive decline in healthy older adults [27, 28]. Our results also correspond with the Mendelian Randomization studies that have so far failed to establish a robust association between polymorphisms of the BDNF gene and AD [62].

We found a positive association between age and plasma BDNF, in line with two previous reports in younger age groups [63, 64], but in conflict with several studies, in comparable age groups, reporting a negative association [25, 65–67] or no association [21, 68–71]. The findings on the association between age and BDNF level therefore seem unclear, while age is the major determinant of a wide variety of diseases in the population.

Of note is that we found that current smoking is also associated with elevated blood plasma BDNF levels. This finding is in accordance with results of previous large cross-sectional and longitudinal studies [25, 33, 67, 72]. The fact that the direction of the association between plasma BDNF levels and both smoking and aging, is similar, is as anticipated, given that both are drivers of inflammation, disease and mortality. This association supports the hypothesis that BDNF is a key regulator in the neuroimmune axis [73]. On the one hand, inflammatory responses are known to cause a reduction in BDNF expression, a process that may lead to impairments in neuroplasticity and cognition [73, 74]. On the other hand, anti-inflammatory processes also require the regulation of BDNF signaling pathways that promote neuroprotection and survival [73, 75].

Strengths of the present study are the use of plasma BDNF as predictor of dementia risk, the extended follow-up period of up to 16 years, and the availability of information on multiple confounders.

However, it is important to note that the detection limits and average plasma BDNF levels obtained by the multiplex immunoassay used in the present study differ from those obtained by more sensitive single-molecule arrays [76, 77]. The reliability of our assessment is warranted by adherence to standard operating procedures [45] and quality control [46] and is strengthened by the replication of the positive association between circulating BDNF and smoking [25, 33, 67, 72].

In conclusion, the current study sheds new light on the association between plasma BDNF and the neuropathology of dementia. The results indicate that alterations in peripheral plasma BDNF levels do not increase the risk of dementia. The positive association between plasma BDNF levels and age and smoking, both drivers of dementia risk, raises the question whether larger studies are needed.

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