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BDNF-Met polymorphism and amyloid-beta in relation to cognitive decline in cognitively normal elderly: the SCIENCe project

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Brain-derived neurotrophic factor (BDNF) plays a role in synapse integrity. We investigated in 398 cognitively normal adults (60±8 years, 41% female, MMSE=28±1) the joint association of the Val66Met polymorphism of the BDNF gene (Met+/−) and plasma BDNF levels and abnormal cerebrospinal fluid (CSF) amyloid-beta status (A+/−) with cognitive decline and dementia risk. Age-, sex- and education-adjusted linear mixed models showed that compared to Met−A−, Met−A+ showed steeper decline on tests of global cognition, memory, language, attention and executive functioning, while Met−A+ showed steeper decline on a smaller number of tests. There were no associations between Met+ and cognitive decline. Cox models showed that compared to Met−A−, Met−A+ participants were at increased risk of dementia (HR=8.8, 95%CI: 2.8–27.9), as were Met−A+ participants (HR=6.5, 95%CI: 2.2–19.5). Lower plasma BDNF was associated with an increased risk of progression to dementia in the A+ participants. Our results imply that Met-carriage on top of amyloid-beta pathology might increase rate of cognitive decline to dementia.

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gions (Brown et al., 2020; Lu et al., 2013). Among non-demented adults, Met-carriers show diminished hippocampal activation or hippocampal volume and show worse memory performance compared to Val-homozygotes (Brown et al., 2020; Hariri et al., 2003; Miyajima et al., 2008). Particularly in non-demented individuals with evidence of cerebral Abeta accumulation, Met-carrying has been associated with cognitive decline over time (Boots et al., 2017; Lim et al., 2021; Lim et al., 2017; Lim et al., 2014; Lim et al., 2013; Lim et al., 2015). Circulating BDNF in blood has been studied as biomarkers for resilience to cognitive decline. Lower levels of BDNF in blood plasma or serum have been found to associate with cognition and regional brain volume loss, albeit less consistently (Driscoll et al., 2012; Gunstad et al., 2008b; Teixeira et al., 2010).

Cognitively normal individuals presenting with the subjective experience of cognitive decline at memory clinics (i.e., subjective cognitive decline; SC) want information on their risk of cognitive decline and dementia. To date, it is unknown whether information on BDNF Val66Met polymorphism or BDNF plasma levels would further increase the predictive value of cerebral Abeta positivity in the clinically relevant population of SC. Therefore, in the current study, we took the population of cognitively normal individuals presenting with SC at memory clinics as a starting point, and we aimed to assess the joint associations of BDNF Val66Met polymorphism and cerebral Abeta pathology with decline over time in the main cognitive domains, and with risk of incident dementia. Additionally, we explored the association of BDNF plasma levels with cognitive decline over time and risk of incident dementia.

2. Methods
2.1. Subjects

We included 398 participants with SC from the Amsterdam Dementia Cohort (van der Flier et al., 2014; van der Flier and Scheltens, 2018) and the SCIENCe project (Slot et al., 2018). Participants were referred to our memory clinic by their general practitioner or in case of second opinion by a neurologist or geriatrician for evaluation of their cognitive complaints (Slot et al., 2018). Participants were included when BDNF-genotyping and baseline cerebrospinal fluid (CSF) Abeta42 analysis were available, and a neuropsychological test battery had been administered within one year of CSF collection. Furthermore, at least one follow-up diagnosis had to be available after a minimum of 6 months. Participants visited the Alzheimer Center Amsterdam, Amsterdam UMC, between February 2002 and January 2018 for a comprehensive dementia diagnostic screening including physical, neurological and neuropsychological evaluation. In a multidisciplinary consensus meeting SC was assigned when both clinical and cognitive testing were within normal limits, criteria for mild cognitive impairment (MCI) or dementia were not met, and no other medical conditions or a psychiatric diagnosis possibly associated with cognitive deficits were present. Informed consent was provided by all participants. The medical ethical committee of the Amsterdam UMC approved the study.

2.2. Neuropsychological assessment

Cognitive functioning was evaluated using a standardized neuropsychological test battery covering the main cognitive domains (Slot et al., 2018). The Mini-Mental State Examination (MMSE) was used to assess global cognition. The Dutch version of the Rey Auditory Verbal Learning Test (RAVLT; immediate recall, delayed recall) and Visual Association Test A (VAT) were used to assess memory. Animal fluency and the picture naming condition of VAT (VAT naming) were used to assess language. Digit span forward, Trail-Making-Test (TMT) A, Stroop word-naming and Stroop color-naming were used to assess attention. TMT B, digit span backwards and Stroop color-word naming were used to assess executive functioning. The Stroop and TMT test scores were natural log transformed and inverted in order to obtain normally distributed data in which a lower score represents a worse cognitive performance.

2.3. Clinical follow-up

Participants were clinically followed-up over time. Mean±standard deviation (SD) follow-up duration was 3.2±2.5 years, with a median of 3 visits (range: 2–12). Diagnosis was re-evaluated at each visit at an interdisciplinary consensus meeting including medical doctors and neuropsychologists. Clinical progression was defined as change in diagnosis to any type of dementia, according to international diagnostic or research consensus criteria (Gorno-Tempini et al., 2011; McKhann et al., 2011; Rascovsky et al., 2011; Roman et al., 1993). Progression time is calculated as the time difference between the baseline visit date at which the CSF Abeta42 biomarker was obtained and the date at which dementia was diagnosed.

Repeated neuropsychological assessment was available for most of the participants (n = 359; 90% with at least one follow-up neuropsychological assessment). Total number of neuropsychological assessments was 1358 for our 398 participants.

2.4. CSF analysis

CSF samples were obtained by lumbar puncture. Abeta42 levels were measured by innotest ELISA (n = 395; Fujirebio, Ghent, Belgium) (Mulder et al., 2010) or by Elecsys (n = 3) (Willemse et al., 2018). Laboratory technicians were trained for the analytical procedure and blinded for clinical diagnoses. The innotest Abeta42 levels were corrected for the drift in the levels that occurred over the years (Tijms et al., 2018). The Elecsys Abeta42 levels were transformed into the Innotest equivalents using the formula Innotest Abeta (pg/mL) = (Elecsys Abeta (pg/mL) + 365) / 1.87 (Willemse et al., 2018). Subsequently, we dichotomized the CSF Abeta42 levels < 813 pg/mL as Abeta positive (A+), and CSF Abeta42 levels ≥ 813 pg/mL as Abeta negative (A–) (Tijms et al., 2018).

2.5. Genetic analysis

Samples of all participants were genotyped using the Illumina Global Screening Array (GSAsharedCUSTOM_20018389_A2). Population substructure (principal components 1–5) was calculated using PLINK (version 1.9). The BDNF Val66Met variant was genotyped on the array (rs26256). Genotype rate was 99.98%. Met-homozygote and Met-heterozygote participants were classified as Met-carriers (Met+) and Val-homozygotes were classified as non-carriers (Met–).

2.6. Plasma analyses

For a subset (n = 198; 50%), baseline EDTA plasma samples were available. EDTA plasma was obtained by venipuncture. Tubes were centrifuged at 1,800 x g for 10 minutes, and stored in 0.5mL aliquots at −80°C. Prior to analysis, samples were thawed at room temperature and centrifuged at 14,000 xg for 10 minutes. Subsequently, plasma BDNF levels were measured in duplicates using the Simoa BDNF Discovery Kit (Quanterix, Lexington, USA), according to manufacturer’s instructions.
2.7. Statistics

Statistical analysis was performed using IBM SPSS version 26 for windows and graphs were constructed using R version 3.6.1. Participants were grouped according to a 4-level variable based on Met-carriage (Met+/Met-) and CSF Abeta status (A+/A-). The Met-A- was considered the reference group in our analyses. Baseline group differences were assessed using one-way ANOVA or T-tests, chi-squared tests or non-parametric equivalents as appropriate. Post-hoc comparisons were Bonferroni-adjusted. We used linear mixed models (LMM) to investigate the association between our four-level Met/A variable and neuropsychological test performance over time. We included Met/A, time and the interaction term Met/A × time as fixed factors, age, sex and education as co-variates, and neuropsychological test scores as dependent variables (separate models for each neuropsychological test). Neuropsychological test scores were Z-transformed prior to statistical analyses. For visualization, we plotted raw neuropsychological test scores over time, color coded for each Met/A group with superimposed average slopes per group (not corrected for possible confounders age, sex and education). Next, we formally tested if Met+/A- and A+/A- interact, by building a three-way interaction LMM, with neuropsychological test score as dependent variable and terms for age, sex, education, A-status (+/ or –), Met-carriage (+ or –), time, A’-time, Met-time, A’Met, and A’Met-time. Additionally, we tested a p for trend including our Met/A variable as a continuous variable (with 1 representing Met-A-, 2 representing Met-A+, 3 representing Met-A- and 4 representing Met-A++), to test if effect sizes increase with an increase in value in the Met/A variable.

Next, we used Cox proportional hazard models adjusted for age, sex and education, to investigate the association between our Met/A (our 4-level variable) and risk of dementia (dichotomous variable: dementia at follow-up: yes/no). The time variable was time to progression in case of clinical progression to dementia, or time to last visit for those that remained non-demented upon follow-up. Lastly, we studied the associations between plasma BDNF with cognitive performance over time, and risk of dementia. Since there is no cut-off for plasma BDNF abnormality available, we used the plasma BDNF levels (ln-transformed and Z-transformed) on a continuous scale in our statistical analyses. We stratified the cohort for CSF Abeta status (A+/A-), and subsequently performed age-, sex- and education-adjusted LMMs and Cox proportional hazard models. For all LMMs analyses a random intercept and a random slope for time were used. LMM analyses were corrected for multiple testing using the 10% false discovery rate (FDR) procedure (Benjamini and Yekutieli, 2001), rendering p < 0.05_FDR statistically significant. As a sensitivity analysis, we re-ran the LMM and Cox models incorporating principal components 1 through 5 as additional possible confounders. In these sensitivity analyses, 31 participants were excluded due to family relations (n = 3), population outliers (n = 27) or quality control failure (n = 1).

3. Results

3.1. Study cohort

Baseline characteristics of our study cohort of 398 SCD participants are presented in Table 1. Participants were on average 60±8 years old, 164 (41%) were female and average MMSE was 28±1. By design, average baseline neuropsychological test scores were within the normal range. In our cohort, n = 28 (7%) were Met-A+, n = 115 (29%) Met-A-, n = 58 (15%) Met-A+ and n = 197 (49%) Met-A-. These groups differed in age and sex (both: p < 0.001), with older participants in both A- groups and a higher proportion of females in the Met-A+ group compared to the Met-A- and Met-A- groups. There was no significant difference in plasma BDNF concentration between the four groups (p = 0.425), nor when comparing plasma BDNF concentrations among Met+ and Met-participants, independent of Abeta status (p = 0.116).

3.2. Met-carriage and Abeta status in relation to cognitive decline

Fig. 1 presents plots of neuropsychological test performance over time by Met/A group. Linear mixed models adjusted for age, sex and education showed that there were no baseline differences in cognitive test performance between the Met-A- group and the 3 groups Met-A+, Met-A- and Met-A+. There were however interactions with time, showing that compared to the Met-A- group, the Met-A+ group had steeper decline during follow-up on several neuropsychological tests (7 out of 12 tests, p < 0.05_FDR) covering global cognition (MMSE), and the cognitive domains memory, executive functioning and attention, but not language (Table 2). Moreover, the Met-A+ showed steeper decline on almost all cognitive tests (11 out of 12 tests, p < 0.05_FDR), covering global cognition and all major cognitive domains memory, language, executive functioning, and attention (Table 2). By contrast, the Met-A- group did not show steeper decline on any of the administered tests compared to the Met-A- group. Sensitivity analyses in which we additionally corrected for genetics principal components gave largely similar results, except that the Met-A- group no longer showed steeper cognitive decline over time compared to the Met-A+ group on two of the administered tests (MMSE and Stroop color word naming; supplementary table 2).

Next, we tested if Met and A have interactive or additive effects in predicting rate of cognitive decline. We observed a significant interaction effect for Met/A in longitudinal performance on VAT (p = 0.017; test for memory) and Stroop word naming (p = 0.023; test for attention), but not on the other administered neuropsychological tests. We did observe a significant p for trend for increasing effect sizes with an increase in value for Met/A in relation to longitudinal cognitive performance on almost all cognitive tests (10 out of 12 tests; Table 2).

3.3. Met-carriage and Abeta status in relation to clinical progression

During follow-up, 29 (7%) participants progressed to a diagnosis of dementia (n = 19 to AD-dementia, n = 5 to frontotemporal dementia, n = 2 to vascular dementia, n = 1 to dementia with lewy bodies, n = 2 progressive supranuclear palsy), after an average follow-up duration of 4.4±3.6 years (progression diagnosis per Met/A group shown in supplementary table 3). Most participants progressed within the Met-A+ group (n = 10, 36%), followed by the Met-A- group (n = 11, 19%; Table 1).

Kaplan-Meier curves visualizing unadjusted progression to dementia by Met/A group are provided in Fig. 2. Cox proportional hazard models adjusted for age, sex and education showed that Met+A+ had a 8.8-fold (95% confidence interval (CI) of HR: 2.8 – 27.9, p < 0.001) higher risk of dementia as compared to Met-A-. The risk estimate in the Met-A+ group was HR = 6.5 (95%CI: 2.2–19.5, p = 0.001). The Met-A+ group was not at increased risk of dementia compared to the Met-A- group (p = 0.952). Additionally adjusting the COX analysis for the genetics principal components did not change the results (Met-A+: HR = 8.9, 95% CI: 2.7–30.1, Met-A+: HR = 6.4, 95% CI: 1.9–21.8, Met-A+: HR = 0.9, 95%CI: 0.2–3.8).

3.4. Plasma BDNF in relation to cognition and clinical progression

The subset with available plasma BDNF was comparable to the total cohort in terms of age (60±9 years), sex (n = 78 (39%) fe-
Table 1
Baseline demographics and clinical characteristics

|                                | Overall (n = 398) | Met+ A+ (n = 28) | Met+ A- (n = 115) | Met- A+ (n = 58) | Met- A- (n = 197) |
|--------------------------------|------------------|-----------------|------------------|-----------------|------------------|
| Demographics and clinical data |                  |                 |                  |                 |                  |
| Age, years, mean (SD)          | 60.1 (8.4)       | 62.7 (9.3)      | 60.1 (8.1)       | 64.9 (6.6)      | 58.3 (8.3)       |
| Sex – Female, n (%)            | 164 (41%)        | 20 (71%)        | 40 (35%)         | 27 (47%)        | 77 (39%)         |
| Education, range 1 – 7, mean (SD) | 5.5 (1.2)  | 5.4 (1.3)       | 5.6 (1.1)        | 5.6 (1.1)       | 5.4 (1.3)        |
| VAT                            | 126/17/255       | 26/20           | 100/15/0         | 0/0/58          | 0/0/197          |
| Plasma BDNF (ng/mL), mean (SD) | 19.7 (17.5)      | 13.7 (7.6)      | 18.6 (17.3)      | 17.3 (10.6)     | 22.0 (20.0)      |

Clinical follow-up

|                                |                  |                 |                  |                 |                  |
| Median number of visits [range] | 3 [2 – 12]       | 3 [2 – 10]      | 3 [2 – 9]        | 3 [2 – 12]      | 3 [2 – 10]       |
| Duration – years, mean (SD)    | 3.2 (2.5)        | 3.8 (2.0)       | 3.4 (2.7)        | 3.0 (2.6)       | 3.0 (2.2)        |
| Incident dementia – n (%)      | 29 (75%)         | 10 (36%)        | 3 (3%)           | 11 (19%)        | 5 (3%)           |
| Time to progression – years, mean (SD) | 4.4 (3.6)     | 5.4 (3.9)       | 3.5 (3.1)        | 4.8 (3.9)       | 2.0 (1.5)        |

Cognitive measures, mean (SD)

| Global cognition               |                  |                 |                  |                 |                  |
| MMSE                           | 28.3 (1)         | 28.0 (1)        | 28.4 (2)         | 28.2 (1)        | 28.3 (1)         |
| Memory                         |                   |                 |                  |                 |                  |
| RAVLT immediate recall         | 41 (9)           | 40 (8)          | 42 (9)           | 40 (7)          | 41 (9)           |
| RAVLT delayed recall           | 8.3 (3)          | 7.8 (3)         | 8.6 (3)          | 7.3 (3)         | 8.5 (3)          |
| VAT                            | 12 (1)           | 11 (1)          | 12 (1)           | 12 (1)          | 12 (1)           |

Language

| Category fluency animals       |                  |                 |                  |                 |                  |
| TMTB                           | 88 (36)          | 90 (51)         | 84 (30)          | 99 (46)         | 87 (33)          |
| Digit span backward            | 9.2 (3)          | 9.5 (3)         | 9.1 (3)          | 9.7 (3)         | 9.0 (3)          |
| Stroop color word naming       | 104 (31)         | 104 (27)        | 101 (28)         | 109 (30)        | 104 (23)         |

Attention

| Digit span forward             | 13 (2.9)         | 13 (3.0)        | 13 (2.7)         | 13 (2.7)        | 13 (3.1)         |
| TMTA                           | 37 (15)          | 35 (14)         | 36 (18)          | 39 (12)         | 36 (14)          |
| Stroop word naming             | 46 (11)          | 45 (8)          | 46 (11)          | 44 (7)          | 46 (13)          |
| Stroop color naming            | 62 (15)          | 62 (11)         | 61 (12)          | 61 (12)         | 63 (17)          |

Data is presented as mean (SD), n (%) or median [range: min – max], for the total cohort and stratified on the 4-level variable BDNF genotype * cerebrospinal fluid amyloid-beta status. Education scoring is according to the Verhage (1965) system. Plasma BDNF was available for n = 198 (50%). Availability of the baseline cognitive measures ranged from n = 363 (91%) to n = 393 (99%). Groups were compared using one-way ANOVA, Kruskal Wallis or Chi-Squared tests as appropriate.

Met, V686M-Met-allele; A, cerebrospinal fluid amyloid-beta status; MMSE, Mini-Mental State Examination; RAVLT, Dutch version of the Rey Auditory Verbal Learning Test; VAT, Visual Association Task; TMT, Trail Making Test.

* p < 0.05

Table 2
Baseline and longitudinal associations between Met-carriage combined with CSF amyloid-beta status and neuropsychological test performance

|                                | Met-A- | Met-A+ | p for trend | p for trend | p for trend |
|--------------------------------|--------|--------|-------------|-------------|-------------|
|                                | Baseline | Annual change | Baseline | Annual change | Baseline | Annual change | Baseline | Annual change | Baseline | Annual change |
| Global cognition               |         |         |             |             |             |         |         |             |             |             |
| MMSE                           |         |         |             |             |             |         |         |             |             |             |
| Memory                         |         |         |             |             |             |         |         |             |             |             |
| RAVLT immediate recall         |         |         |             |             |             |         |         |             |             |             |
| RAVLT delayed recall           |         |         |             |             |             |         |         |             |             |             |
| VAT                            |         |         |             |             |             |         |         |             |             |             |
| Language                       |         |         |             |             |             |         |         |             |             |             |
| Category fluency animals       |         |         |             |             |             |         |         |             |             |             |
| Executive functioning          |         |         |             |             |             |         |         |             |             |             |
| TMTB                           |         |         |             |             |             |         |         |             |             |             |
| Digit span backwards           |         |         |             |             |             |         |         |             |             |             |
| Stroop color word naming       |         |         |             |             |             |         |         |             |             |             |
| Attention                      |         |         |             |             |             |         |         |             |             |             |
| Digit span forward             |         |         |             |             |             |         |         |             |             |             |
| TMTA                           |         |         |             |             |             |         |         |             |             |             |
| Stroop word naming             |         |         |             |             |             |         |         |             |             |             |
| Stroop color naming            |         |         |             |             |             |         |         |             |             |             |

Data is presented as β (standard error). Linear mixed models including terms for the group (Met/A), time, interaction of group * time, neuropsychological test and covariates age, sex and education were conducted to assess associations between group and neuropsychological test performance. The interaction term group * time represents the estimated annual change in test performance. TMT and Stroop were natural log-transformed. TMT and Stroop scores were inverted, so that for all neuropsychological tests lower scores correspond to worse performance. All neuropsychological test scores were transformed to z-scores. The last two columns represent a p-value for trend, to indicate if there is a step-wise increase for steeper rates of decline over the 4 groups Met-A-, Met-A+, Met-A-, Met-A+, calculated by using the Met/A variable on a continuous scale instead of factorial.

Met, V686M-Met-allele; A, cerebrospinal fluid amyloid-beta status; MMSE, Mini-Mental State Examination; RAVLT, Dutch version of the Rey Auditory Verbal Learning Test; VAT, Visual Association Task; TMT, Trail Making Test.

* p < 0.005

1 p < 0.05
Fig. 1. Neuropsychological test performance over time for our Met/A participants
Slopes represent unadjusted average neuropsychological trajectories for our 4 groups Met+A+ (dark red), Met+A- (dark blue), Met-A+ (light red) and Met-A- (light blue), with 95% confidence interval. Raw neuropsychological test values were plotted, unadjusted for possible confounders age, sex and education. Note that for TMT and Stroop tests, higher values imply worse performance. We reversed the y-axes of these tests for better visualization. Met, Val66Met-allele, A, cerebrospinal fluid amyloid-beta status; MMSE, Mini-Mental State Examination; RAVLT, Dutch version of the Rey Auditory Verbal Learning Test; VAT, Visual Association Task; TMT, Trail Making Test.

male) and education (5.5±1.2), as well as in the distribution of the Met/A (n = 18 (9%) Met+A+, n = 56 (28%) Met+A-, n = 26 (13%) Met-A+ and n = 98 (50%) Met-A).

Stratified for CSF Abeta status (A+/A-), we did not find any association between baseline plasma BDNF and neuropsychological test performance at baseline nor with cognitive decline over time (supplementary table 1). Cox proportional hazards models however, showed that among A+ participants, lower plasma BDNF levels were associated with a 3.7-fold (95% CI of HR: 1.1–13.1) higher risk of dementia. There was no effect of plasma BDNF on dementia risk among the A- participants.
4. Discussion

The present study suggests that cognitively unimpaired, Abeta positive individuals with SCW who additionally carry the BDNF Val66Met polymorphism have the steepest rates of decline in the domains of global cognition, memory, language, executive functioning and attention, and carry the highest risk of dementia. Abeta positive individuals who do not carry the BDNF Val66Met polymorphism also showed cognitive decline over time, albeit less pronounced. Our results suggest that BDNF genotyping might provide valuable prognostic information in individuals who are within the Alzheimer's continuum.

We did not observe any cross-sectional associations between Abeta status, BDNF genotype and neuropsychological test performance. This is possibly consequential to the fact that individuals had to perform within normal limits to be included in the study, and thus there was low variation in neuropsychological test scores. By contrast, we observed clear associations with cognitive decline over time. By contrast, we observed clear associations with cognitive decline over time, but only by Abeta positive individuals. Taking the Abeta negative non-Met-carriers (49% of the population) as the reference group, Abeta positive Met-carriers showed steeper rates of decline on virtually all administered neuropsychological tests covering memory, language, executive functioning and attention, whereas the Abeta positive non-Met-carriers showed decline on fewer tests and with somewhat smaller effect sizes, also confirmed in our p for trend analysis in which we showed that effect sizes increase with an increase in Met/A value from Met-A to Met+ A+. Other studies, which were mainly conducted in the Australian population-based cohort AIBL, showed that particularly the Abeta positive group that additionally carried the Val66Met polymorphism showed greatest cognitive decline over time, in the domains of episodic memory, executive functioning and language (Lim et al., 2016; Lim et al., 2017; Lim et al., 2014; Lim et al., 2013; Lim et al., 2015), for which we also found indications. We extend on these former findings, by additionally showing associations with decline in attention. An important difference between our study and previous studies is that we used individual tests, instead of composite scores for cognitive domains. Some tests might be more sensitive to pick up the earliest cognitive decline, which is essential when studying trajectories of cognitive decline in cognitively unimpaired individuals. To illustrate, the previous studies administered only digit span forward and digit symbol (from the Wechsler Adult Intelligence Scale–Revised) as measure for attention, and in agreement to their findings we did not find associations for the digit span forward test either. However, we observed joint Abeta pathology and Met-carrying associated decline on other tests for attention, namely TMT A, Stroop word-naming and Stroop color-naming.

We also showed that Abeta positive individuals who additionally carry the Val66Met polymorphism had an increased risk of dementia, as compared to the Abeta negative non-Met-carriers. The Abeta positive non-Met-carriers also had an increased, yet less pronounced, risk of dementia. To our knowledge this is the first study that investigates the association of BDNF-genotype, Abeta status and clinical progression in a SCW population, which is a clinically highly relevant population. All participants presented with SCW at our memory clinic, where their subjectively reported decline could not be objectified, as their test performance remained within normal limits (Jessen et al., 2020; Jessen et al., 2014; Slot et al., 2018). They worry about their cognition, and they would therefore especially benefit from accurate risk prognosis. Of note, one previous study investigated the BDNF-genotype-associated risk of clinical progression in SCW and found that Val66Met-carryage increased the risk of progression to MCI and AD, but they did not take Abeta status into account (Bessi et al., 2019). Another study found APOE ε4 and BDNF Met-carryage to be associated with cognitive decline (Cechova et al., 2020), which supports our findings as well, as APOE ε4 might be a proxy for Abeta status, since APOE ε4 carriers have a high risk of being Abeta positive (Jansen et al., 2019). Our findings suggest that BDNF genotyping may particularly have value in addition to Abeta status. It is well known that cerebral amyloidosis increases the risk of dementia, yet at the same time – it is difficult to translate findings on group levels to the individual, as some are more resilient to deal with Abeta pathology than others. Our findings suggest that non Met-carryage is related to this resilience of the brain, or the other way around – that Met-carryage diminishes resilience. This is also in line with studies that show an effect of physical activity on BDNF plasma levels; illustrating that interventions aiming to boost resilience affect BDNF (Dinoff et al., 2017; Nascimento et al., 2015). If this genetic Val66Met variant of BDNF indeed diminishes resilience to cognitive decline and increases risk of dementia, one would expect this genetic variant to be present more frequently in individuals with dementia or AD. However, genome-wide association studies (GWAS) on AD show little evidence for Met-carryage as risk factor for AD (de Rojas et al., 2021; Jansen et al., 2019). Difference in power might explain this discrepancy in findings between GWAS studies and more direct studies on cognitive decline like the current study and the ones conducted in the AIBL cohort. Large, direct studies of BDNF genotype on cognitive decline are needed.

Since Met-carryage was associated with lowered levels of BDNF protein in the hippocampus (Allen et al., 2011; Hock et al., 2000) and lowered BDNF levels in the hippocampus have been associated with worse memory function (Minichillo, 2009), we hypothesized that lowered plasma BDNF levels might be associated with cognitive decline. Indeed, we found that low plasma BNF was associated with higher risk of dementia, but in Abeta positive individuals only. In apparent contradiction with this finding, we did not find any association of plasma BDNF with rates of cognitive decline over time. Earlier studies on blood-based BDNF and cognitive de-

![Fig. 2. Kaplan-Meier survival curves visualizing clinical progression to dementia for the Met/A participants. Curves present the observed clinical progression over time, with separate lines for the 4 groups Met+ A+ (dark red), Met+ A− (dark blue), Met− A+ (light red) and Met− A− (light blue). The vertical tick marks represent individuals who have been censored. Met, Val66Met-allele; A, cerebrospinal fluid amyloid-beta status.](image-url)
cline to dementia were similarly inconclusive (Driscoll et al., 2012; Gunstad et al., 2008a; Teixeira et al., 2010).

Amongst the strengths of the current study is that we investigated a relatively large sample of a well-defined and clinically relevant population. Furthermore, we had a standardized battery of neuropsychological tests covering the major cognitive domains and had extensive follow-up data of our participants. A limitation of the current study is that we had plasma available from a subset only (n = 198; 50%), limiting statistical power. Furthermore we could not control for factors that might influence BDNF plasma levels, such as physical activity, depression, metabolic syndrome and cardiovascular health (Brunoni et al., 2008; Cain et al., 2017; Dinoff et al., 2017; Golden et al., 2010; Nascimento et al., 2015). Also, due to the small prevalence of Met/Met homozygotes in this cohort (only 4%), we could not consider a dose-effect of the Val66Met polymorphism. Furthermore, longer follow-up time of our participants is needed, since only a small proportion of the individuals progressed to dementia which resulted in wide confidence intervals for some of our analyses. Although results should be interpreted with care, we had largely comparable observations for our two separate LMM and Cox analyses. Independent studies with concomitant registration of all possible confounding factors is needed to further study associations between plasma BDNF and cognitive decline.

5. Conclusion

To conclude, we showed that among individuals with SCD, Met-carriage on top of cerebral Abeta pathology might exacerbate decline in the main cognitive domains and increase risk of clinical progression to dementia. Plasma BDNF was associated with increased risk of clinical progression to dementia, in amyloid positive individuals only. These results imply that BDNF could be related to resilience to cognitive decline due to cerebral Abeta pathology, and further research is needed to investigate the potential of Val66Met and plasma BDNF as prognostic markers.

6. Credit author statement

Author contributions: K.A.v.d.B., I.M.W.V., P.S., C.E.T., and W.M.v.d.F. contributed to study concept and design. All authors contributed to data acquisition and analysis. K.A.v.d.B., I.M.W.V., and W.M.v.d.F. contributed to drafting the text and figures. All authors critically evaluated and approved the manuscript.

7. Verification

This manuscript has not been previously published and is not under consideration by any other journal. All authors approved the manuscript and this submission.

Disclosure statement

K.A.v.d.B., I.M.W.V., J.L.E., S.j.v.d.L., and I.J. have nothing to disclose. N.D.P is consultant to Boehringer Ingelheim, Aribio, and Amylyx. He is co-PI of a study with Fuji Film Toyama Chemical. He is CEO and co-owner of the Brain Research Center, The Netherlands. P.S. has received consultancy fees (paid to the institution) from AC Immune, Alkermes, Ailylam, Alzheon, Anavex, Biogen, Brainstorm Cell, Cortexyme, Denali, EIP, ImmunoBrain Checkpoint, GemVax, Genentech, Green Valley, Novartis, Novo Nordisk, PeopleBio, Renew LLC, Roche. He is PI of studies with AC Immune, CogRx, Fuji1-film/Toyama, IONIS, UCB, and Vivoryon. He is a part-time employee of Life Sciences Partners Amsterdam. He serves on the board of Brain Research Center and New Amsterdam Pharma. Research of C.E.T. is supported by the European Commission (Marie Curie International Training Network, grant agreement No 860197 (MIRIADE, and JPND), Health Holland, the Dutch Research Council (ZonMW), Alzheimer Drug Discovery Foundation, The Selfridges Group Foundation, Alzheimer Netherlands, Alzheimer Association. C.E.T and W.M.v.d.F are recipients of ABOARD, which is a public-private partnership receiving funding from ZonMW (#7330595007) and Health–Holland, TOPsector Life Sciences & Health (PPP-allocation: #LSHM201016). ABOARD also receives funding from Edwin Bouw Fonds and Gieskes-Strijbisfonds. Research programs of W.M.v.d.F. have been funded by ZonMW, NWO, EU-FP7, EU-JPND, Alzheimer Nederland, CardioVascular Onderzoek Nederland, Health–Holland, TOPsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Pasman stichting, Biogen MA Inc, Boehringer Ingelheim, Life-MI, AVID, Roche BV, Fujifilm, Combinostics.

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Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi: 10.1016/j.neurobiolaging.2021.08.018.

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