Plasma amyloid is associated with the rate of cognitive decline in cognitively normal elderly: the SCIENCe project

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ABSTRACT

Plasma biomarkers are promising prognostic tools in individuals with subjective cognitive decline (SCD). We aimed to investigate the relationships of baseline plasma amyloid beta (Aβ42/Aβ40 and total Tau (tTau) with rate of cognitive decline, in comparison to relationships of baseline cerebrospinal fluid (CSF) Aβ42, tTau, and phosphorylated tau181 (pTau181) with rate of cognitive decline. We included 241 subjects with SCD (age = 61 ± 9, 40% female, Mini-Mental State Examination = 28 ± 2) with follow-up (average: 2 ± 2 years, median visits: 3 [range: 1–11]) for re-evaluation of neuropsychological test performance (attention, memory, language, and executive functioning domains). Using age, gender and education-adjusted linear mixed models, we found that lower plasma Aβ42/Aβ40 was associated with steeper rate of decline on tests for attention, memory, and executive functioning, but not language. Lower CSF Aβ42 was associated with steeper decline on tests covering all domains. Associations for plasma amyloid and cognitive decline mirror those of CSF amyloid. Plasma tTau was not associated with rate of cognitive decline, whereas CSF Tau and pTau181 were on multiple tests covering all domains.

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1. Background

Deposition of amyloid in the brain is among the first pathological changes in Alzheimer's disease (AD) and occurs decades before dementia onset (Bateman et al., 2012; Dubois et al., 2016; Jack et al., 2018). Within the Alzheimer's pathobiological continuum, the recent AD research framework recognizes 6 clinical stages of severity of cognitive impairment (Jack et al., 2018). The Alzheimer’s clinical stage 2 reflects an intermediate stage wherein objective cognitive test performance is within normal limits while individuals either report an experience of cognitive decline or show subtle cognitive decline on longitudinal testing (Jack et al., 2018). Subjective cognitive decline (SCD) refers to a self-perceived change in cognitive abilities without objective evidence of decline (Jessen et al., 2014) and falls in this clinical stage 2.

Roughly one out of 4 patients visiting a memory clinic fit the description SCD. Many individuals with SCD are so-called worried well, but a subset is likely experiencing the first symptoms of AD pathological changes (i.e., Alzheimer's clinical stage 2) (Jessen et al., 2014). It is essential to identify SCD individuals who harbor preclinical AD because these individuals are at higher risk to develop dementia over time (Sierra-Rio et al., 2016; van Harten et al., 2013b; Wolfsgruber et al., 2017).

Previous studies showed that low amyloid beta (Aβ42) in the cerebrospinal fluid (CSF) or Aβ visualized on positron emission tomography (PET) is associated with cognitive decline over time in various cognitive domains in cognitively normal individuals (Donohue et al., 2014, 2017; Doraiaiswamy et al., 2014; Landau et al., 2012; Lim et al., 2014; Mielke et al., 2016; Roberts et al., 2018; Timmers et al., 2019; van Harten et al., 2013a). CSF sampling and amyloid PET have however disadvantages in terms of invasiveness of the procedures and high costs, which a blood amyloid biomarker
would overcome. Since highly sensitive laboratory techniques emerged, evidence started accumulating that plasma amyloid can become a useful biomarker for amyloid pathology (Chatterjee et al., 2019; Janelidze et al., 2016; Nakamura et al., 2018; Palmqvist et al., 2019b; Schindler et al., 2019; Verberk et al., 2018; Vergallo et al., 2019). Earlier we showed that plasma amyloid has reasonable accuracy to identify an abnormal CSF amyloid status in cognitively normal individuals with SCD (Verberk et al., 2018). Here, we investigated clinical relevance in this SCD cohort by assessing the relationship of baseline levels of plasma Aβ and total Tau (τ) with objective cognitive decline over time on neuropsychological tests covering the major cognitive domains. Furthermore, for comparison, we also assessed relationships of baseline levels of CSF Aβ, tau phosphorylated at threonine 181 (pT181), and τ with cognitive decline over time.

2. Methods

2.1. Subjects

We included 241 subjects with SCD from the ongoing SCIENCE project (Slot et al., 2018b) and Amsterdam Dementia Cohort (van der Flier et al., 2014; van der Flier and Scheltens, 2018). Between November 2000 and August 2016, participants visited the Alzheimer Center Amsterdam, Amsterdam UMC, for a thorough baseline diagnostic dementia screening including neurological, physical, and neuropsychological evaluation and brain magnetic resonance imaging. Apolipoprotein E (APOE) genotyping was performed for n = 231 (96%) subjects, from which APOE ε4 carriership was defined as having at least one APOE ε4 copy. The label of SCD was assigned in a multidisciplinary consensus meeting when clinical and cognitive testing were within normal limits and criteria for mild cognitive impairment (MCI), dementia, or other conditions potentially causing cognitive decline were not met. Participants were included in this study when a plasma sample was present in the VUMc biobank, CSF biomarkers were measured, and clinical follow-up was offered. Plasma and CSF were largely collected at the same day (n = 237, 98%) but latest within a time frame of half a year. Baseline SCD label was assigned latest within half a year of plasma and CSF collection (mostly within one month; 98%). In a subset (total n = 77; n = 49 with first assessment within one year from baseline visit), we measured the extent of self-perceived SCD using the Cognitive Change Index-self (CCI): a 20-item questionnaire (range score: 20–100) (Rattanabannakit et al., 2016).

All participants provided written informed consent to use medical data and biomaterials for research purposes. The medical ethical committee of the VU University approved the present study. The study was in accordance with the Helsinki declaration act of 1975.

2.2. Cognitive assessment

Cognitive function was assessed using a standardized neuropsychological evaluation covering the main cognitive domains (Slot et al., 2018b). Global cognition was assessed using the Mini-Mental State Examination (MMSE). Tests for the memory domain included the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) immediate recall, delayed recall, and recognition and the Visual Association Task (VAT). Tests for the attention domain included Digit Span Forward, Trail Making Test (TMT) A, Stroop word naming, and Stroop color naming. Tests for executive function included Digit Span Backward, TMT B, letter fluency test, and Stroop color word naming. The percentage of available baseline test scores are presented in Table 1. Stroop and TMT test scores were natural log transformed before analysis for normal distribution of the data. Residuals of annual change were normally distributed for all neuropsychological tests scores, except VAT.

2.3. Clinical follow-up

Clinical follow-up was available for all subjects, meaning that as at least one re-evaluation of the SCD diagnosis was performed. Upon follow-up, n = 34 (14%) showed clinical disease progression, of whom n = 23 (9.5%) to MCI, n = 4 (2%) to AD dementia, and n = 7 (3%) to non-AD dementia. At each clinical follow-up visit, cognition was re-evaluated using MMSE (at least one follow-up assessment available for n = 235 [98%]) and/or a full neuropsychological test battery (at least one follow-up assessment available for n = 212 [88%]). Before 2014, follow-up visits were performed as part of routine clinical care. From 2014 onwards, follow-up visits of most subjects were scheduled as part of annual research visits for the SCIENCE study.

Table 1

| Demographics and clinical characteristics | n | Mean | SD |
|------------------------------------------|---|------|----|
| Age, mean ± SD, y                        | 241 | 61±9 |
| Female gender, n (%)                     | 241 | 97 (40%) |
| APOE ε4 carriership                      | 231 | 85 (35%) |
| Education, mean ± SD, range 1–7          | 241 | 5±1  |
| Follow-up time, mean ± SD, y             | 241 | 2.4±2 |
| Number of visits, median (range)         | 241 | 3 (1–11) |
| Geriatric Depression Scale, mean ± SD    | 223 | 2.8±2 |
| CCI                                      | 49  | 43±15 |
| CSF biomarkers, mean ± SD                |     |      |
| Plasma Aβ42, pg/mL                       | 241 | 1023±256 |
| CSF pT181, pg/mL                         | 241 | 50±25 |
| CSF τ, pg/mL                             | 241 | 325±238 |
| Plasma biomarkers, mean ± SD             |     |      |
| Plasma Aβ42, pg/mL                       | 241 | 9.7±1.8 |
| Plasma Aβ40, pg/mL                       | 241 | 208±38 |
| Plasma Aβ42/Aβ40 ratio                   | 241 | 48±7.1 |
| Plasma pT181, pg/mL                      | 241 | 3.1±1.0 |
| Cognitive measures, mean ± SD            |     |      |
| Global cognition                         |     |      |
| MMSE                                     | 239 | 28±2  |
| Attention                                |     |      |
| Digit span forward                       | 236 | 13±3  |
| TMT A                                    | 234 | 38±15 |
| Stroop word naming                       | 219 | 46±11 |
| Stroop color naming                      | 217 | 63±15 |
| Memory                                   |     |      |
| RAVLT immediate recall                   | 227 | 41±9  |
| RAVLT delayed recall                     | 228 | 8±3   |
| RAVLT recognition                        | 227 | 28±2  |
| VAT A                                    | 231 | 12±1  |
| Language                                 |     |      |
| VAT naming                               | 229 | 12±2  |
| Category fluency animals                 | 229 | 22±6  |
| Executive functioning                    |     |      |
| TMT B                                    | 232 | 91±47 |
| Digit span backward                      | 236 | 9±3   |
| Stroop color naming                      | 217 | 105±34|
| Letter fluency test                      | 186 | 36±12 |

Data are presented as mean ± SD, number (%), or median (range). Education scoring is according to the Verhage (1965) system. The Dutch version of the CCI-self was assessed for a subset (n = 77), of whom 49 filled out the questionnaire within one year of baseline plasma sampling. Plasma Aβ42/Aβ40 ratio was calculated and multiplied by 1000.

Key: Aβ, amyloid beta; APOE, apolipoprotein E; CCI, Cognitive Change Index-self; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; pT181, tau phosphorylated at threonine 181; RAVLT, Dutch version of the Rey Auditory Verbal Learning Test; SD, standard deviation; τ, total tau; TMT, Trail Making Test; VAT, Visual Association Task.
Group average follow-up duration was 2 ± 2 years; median number of visits was 3, with a minimum of 1 and maximum of 11 visits. This resulted in a total number of cognitive evaluations of 785 for our 241 subjects. For evaluation of perceived SCD, we had a total of 190 CCI scores for 77 subjects (median number of evaluations was 2, with a minimum of 1 and a maximum of 4).

2.4. CSF analysis

CSF samples were obtained by lumbar puncture. Concentrations of the biomarkers Aβ42, pTau181, and tTau were measured using Innotest ELISAs (Fujirebio, Ghent, Belgium) (Mulder et al., 2010). Technicians were trained for the analytical procedure and were blinded for clinical diagnosis. CSF Aβ42 levels were adjusted for the drift in CSF biomarker analyses that occurred over the years (Tijms et al., 2017).

2.5. Plasma analysis

EDTA plasma samples were obtained through venipuncture (nonfasted). Tubes were centrifuged at 1800 g, aliquoted in polypropylene tubes, and stored at −80 °C in our biobank within 2 hours of collection. Plasma was analyzed using the automated Simoa HD-1 analyzer with a commercially available Simoa Human Inno preliminary standardization protocol (Andreasson et al., 2015). The instructions. The assay was in-house analytically validated according to the standardized protocol (Andreasson et al., 2015). The samples were run on 2 consecutive days by trained research personnel, with a random allocation of the samples to the runs.

CSF Aβ42 was used to normalize Aβ42 concentrations (Aβ42/Aβ40*1000; further referred to as Aβ42/Aβ40 ratio).

2.6. Statistics

Data was analyzed using SPSS for windows, version 22 (IBM), and graphs were constructed using GraphPad Prism for windows, version 7.02 or R version 3.4.2. Linear mixed models (LMM) were used to assess associations with performance on neuropsychological tests over time. This method allows for analysis of correlated data, for variability in the number of evaluations per subject, missing data points, and for differences in time intervals between evaluations, therewith taking advantage of all available data points. The 10% false discovery rate (10%FDR) procedure was applied to correct for multiple testing (Benjamini and Yekutieli, 2001), rendering a P value <0.05FDR statistically significant. Baseline plasma and CSF marker data (as continuous variables) and baseline and longitudinal neuropsychological data were standardized for comparability of effect sizes (i.e., transformed into Z-scores).

First, we performed LMM, including a main effect of time with age, gender, and education as covariates, to determine general annual change on neuropsychological test performance across the group. Subsequently, we performed LMM with terms for a plasma marker (Aβ42/Aβ40 ratio or tTau) or CSF marker (Aβ42, pTau181, or tTau; all in separate models), time, interaction of plasma or CSF marker*time, age, gender and education, and neuropsychological tests (interpreted separately, not combined into domain scores) as the dependent variables. The standardized (s)β ± SE of the biomarker (plasma or CSF) represents the association with baseline test, and the sβ ± SE of the interaction term plasma or CSF marker*time represents the association with annual change on test performance. For all models, a random intercept was included. A random slope for time was added when it increased the model fit (holds true for TMT A+B, Stroop word naming, color naming and

The interaction term CSF marker*time represents the estimated annual change in test performance. CSF markers and neuropsychological test scores were standardized by transformation into Z-scores before analysis to make effect sizes comparable. TMT and Stroop were natural log-transformed. TMT and Stroop scores were inverted, so that for all neuropsychological test scores, lower scores correspond to worse performance.

Key: Aβ, amyloid beta; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; pTau181, tau phosphorylated at threonine 181; RAVLT, Dutch version of the Rey Auditory Verbal Learning Test; tTau, total tau; TMT, Trail Making Test; VAT, Visual Association Task.

* P < 0.05FDR.

### Table 2

|                   | CSF Aβ42 |                       | CSF tTau |                       | CSF pTau181 |                       |
|-------------------|----------|------------------------|----------|------------------------|-------------|------------------------|
|                   | Baseline, | Annual change,          | Baseline, | Annual change,          | Baseline,   | Annual change,          |
|                   | sβ ± SE  | sβ ± SE                | sβ ± SE  | sβ ± SE                | sβ ± SE     | sβ ± SE                |
| Global cognition  |          |                        |          |                        |             |                        |
| MMSE              | 0.05 ± 06| 0.08 ± 0.03*            | 0.04 ± 06| -0.13 ± 0.03*          | 0.04 ± 06   | -0.08 ± 0.03*          |
| Attention         |          |                        |          |                        |             |                        |
| Digit span forward| 0.03 ± 06| 0.03 ± 0.01*            | 0.12 ± 06| -0.02 ± 0.01           | 0.07 ± 06   | 0.01 ± 0.01            |
| TMT A             | 0.02 ± 06| 0.08 ± 0.02*            | 0.12 ± 06| -0.09 ± 0.02*          | 0.11 ± 06   | -0.06 ± 0.02*          |
| Stroop word naming| 0.01 ± 07| 0.06 ± 0.02*            | 0.03 ± 07| -0.05 ± 0.02*          | 0.02 ± 07   | -0.03 ± 0.02*          |
| Stroop color naming| 0.03 ± 07| 0.06 ± 0.02*            | 0.05 ± 07| -0.06 ± 0.02*          | 0.00 ± 07   | -0.03 ± 0.02*          |
| Memory            |          |                        |          |                        |             |                        |
| RAVLT immediate recall| 0.08 ± 06| 0.08 ± 0.03*            | 0.05 ± 07| -0.13 ± 0.02*          | 0.05 ± 06   | -0.10 ± 0.02*          |
| RAVLT delayed recall| 0.08 ± 06| 0.09 ± 0.02*            | -0.02 ± 07| -0.12 ± 0.02*         | 0.04 ± 07   | -0.10 ± 0.02*          |
| RAVLT recognition | -0.03 ± 07| 0.11 ± 0.03*            | 0.06 ± 07| -0.16 ± 0.03*          | 0.05 ± 07   | -0.14 ± 0.03*          |
| VAT A             | 0.00 ± 07| 0.27 ± 0.06*            | 0.01 ± 07| -0.25 ± 0.06*          | -0.02 ± 07  | -0.19 ± 0.06*          |
| Language          |          |                        |          |                        |             |                        |
| VAT naming        | -0.15 ± 08| 0.08 ± 0.03*            | 0.02 ± 08| -0.02 ± 0.03           | 0.02 ± 08   | -0.03 ± 0.03           |
| Category fluency activities | 0.03 ± 06| 0.04 ± 0.02*            | 0.12 ± 06| -0.06 ± 0.02*          | 0.12 ± 06   | -0.06 ± 0.02*          |
| Executive functioning |        |                        |          |                        |             |                        |
| Digit span backward| 0.01 ± 06| 0.05 ± 0.01*            | 0.11 ± 06| -0.03 ± 0.01           | 0.08 ± 06   | -0.02 ± 0.01           |
| TMT B             | 0.07 ± 05| 0.05 ± 0.02*            | 0.03 ± 06| -0.06 ± 0.02*          | 0.05 ± 05   | -0.04 ± 0.02*          |
| Stroop color word naming | 0.04 ± 06| 0.05 ± 0.03            | 0.11 ± 07| -0.11 ± 0.03*          | 0.07 ± 06   | -0.08 ± 0.03*          |
| Letter fluency    | -0.02 ± 06| 0.04 ± 0.01*            | 0.20 ± 0.07| -0.05 ± 0.01*         | 0.19 ± 06   | -0.04 ± 0.01*          |

Data are presented as standardized β ± SE. Linear mixed models including terms for the CSF marker under investigation, time, interaction of CSF marker*time, neuropsychological tests and covariates age, gender, and education were applied to assess associations between baseline CSF markers and baseline and longitudinal neuropsychological test scores. The interaction term CSF marker*time represents the estimated annual change in test performance. CSF markers and neuropsychological test scores were standardized by transformation into Z-scores before analysis to make effect sizes comparable. 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.
Data are presented as standardized β ± SE. Linear mixed models including terms for the plasma marker under investigation, time, interaction of plasma marker * time, neuropsychological tests and covariates age, gender, and education were applied to assess associations between baseline plasma markers and baseline and longitudinal neuropsychological test scores. The interaction term plasma marker * time represents the estimated annual change in test performance. Plasma markers and neuropsychological test scores were standardized by transformation into z-scores before analysis to make effect sizes comparable. 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.

Key: Aβ, amyloid beta; MMSE, Mini-Mental State Examination; RAVLT, Dutch version of the Rey Auditory Verbal Learning Test; tTau, total Tau; TMT, Trail Making Test; VAT, Visual Association Task.

* P < 0.05FDR.

### Table 3
Baseline and longitudinal associations of plasma markers and neuropsychological test performance

|                        | Plasma Aβ42/Aβ40 ratio | Plasma tTau |
|------------------------|------------------------|-------------|
|                        | Baseline, β ± SE       | Annual change, β ± SE | Baseline, β ± SE | Annual change, β ± SE |
| Global cognition       |                        |                     |                |
| MMSE                   | 0.07 ± 0.06            | 0.07 ± 0.04         | −0.07 ± 0.06    | 0.06 ± 0.04 |
| Attention              |                        |                     |                |
| Digit span forward     | 0.04 ± 0.06            | 0.00 ± 0.01         | −0.02 ± 0.06    | 0.01 ± 0.01 |
| TMT A                  | −0.11 ± 0.06           | 0.05 ± 0.03         | −0.04 ± 0.06    | 0.03 ± 0.02 |
| Stroop word naming     | −0.03 ± 0.07           | 0.08 ± 0.02*        | −0.06 ± 0.06    | 0.02 ± 0.02 |
| Stroop color naming    | −0.01 ± 0.07           | 0.06 ± 0.03*        | −0.01 ± 0.06    | 0.01 ± 0.03 |
| Memory                 |                        |                     |                |
| RAVLT immediate recall | 0.01 ± 0.06            | 0.09 ± 0.03*        | −0.06 ± 0.06    | 0.04 ± 0.03 |
| RAVLT delayed recall   | 0.08 ± 0.07            | 0.07 ± 0.03*        | 0.01 ± 0.06     | 0.01 ± 0.03 |
| RAVLT recognition      | −0.03 ± 0.07           | 0.09 ± 0.03*        | −0.04 ± 0.06    | 0.02 ± 0.03 |
| VAT A                  | −0.04 ± 0.07           | 0.19 ± 0.06*        | 0.03 ± 0.07     | 0.01 ± 0.06 |
| Language               |                        |                     |                |
| VAT naming             | −0.08 ± 0.08           | 0.06 ± 0.03         | −0.06 ± 0.08    | 0.02 ± 0.03 |
| Category fluency animals | 0.04 ± 0.06          | 0.02 ± 0.02         | −0.03 ± 0.06    | 0.02 ± 0.02 |
| Executive functioning  |                        |                     |                |
| Digit span backward    | −0.03 ± 0.06           | 0.04 ± 0.02         | −0.02 ± 0.05    | 0.03 ± 0.01 |
| TMT B                  | −0.05 ± 0.06           | 0.05 ± 0.02*        | 0.03 ± 0.05     | 0.01 ± 0.02 |
| Stroop color word naming | −0.02 ± 0.06         | 0.03 ± 0.03         | 0.04 ± 0.06     | 0.05 ± 0.03 |
| Letter fluency         | −0.10 ± 0.07           | 0.03 ± 0.02         | 0.00 ± 0.06     | −0.00 ± 0.02 |

word color naming, RAVLT immediate recall, delayed recall and recognition, VAT A, category fluency animals and MMSE). Finally, we applied the LMMs with z-transformed CCI as a dependent variable. The models for plasma were repeated excluding individuals that did not receive a follow-up MMSE or follow-up neuropsychological evaluation. This sensitivity analysis showed comparable results in terms of effect sizes and significant relationships (data not shown).

Finally, we constructed coefficient plots from the effect sizes (β) with their 95% confidence interval for visualization of the effect sizes of the plasma and CSF amyloid-associated cognitive decline. In addition, we constructed spaghetti plots by plotting the raw neuropsychological test scores over time. Tertiles of the baseline plasma and CSF amyloid markers were constructed, and the spaghetti plots were color coded according to these tertiles. We superimposed the average slopes with 95% confidence interval for each plasma or CSF amyloid tertile.

### 3. Results

At baseline, our study population of 241 SCD subjects was on average 61 ± 9 years old, 97 (40%) participants were female, and MMSE was on average 28 ± 2. By design, average baseline neuropsychological test scores were all within normal limits (Table 1). In general, the study population showed stable performance over time on most neuropsychological tests. We observed a general decline on VAT A (β ± SE, −0.20 ± 0.06; memory) and category fluency animals (β, −0.06 ± 0.02; language) and an improvement on letter fluency (β, 0.05 ± 0.01; executive functioning) (all: P < 0.05FDR).

We applied LMMs corrected for age, gender, and education to assess associations of the CSF markers with neuropsychological test performance (Table 2). There were no associations between baseline CSF biomarkers and baseline neuropsychological test performance, except for a contraintuitive positive association between CSF tTau and letter fluency test performance. In contrast, lower baseline CSF Aβ42 and higher CSF ttau and CSF pTau levels were associated with steeper decline on performance on the largest part of the administered tests covering MMSE and all major cognitive domains attention, memory, language, and executive functioning (Table 2).

Subsequently, we applied LMMs corrected for age, gender, and education to assess associations of the plasma markers with neuropsychological test performance (Table 3). In line with CSF results, we observed no associations between baseline plasma Aβ42/Aβ40 ratio or ttau and baseline performance on any of the neuropsychological tests. Lower baseline plasma Aβ42/Aβ40 ratio was associated with steeper rate of decline on tests related to memory (RAVLT immediate recall: β 0.09 ± 0.03, RAVLT delayed recall: β 0.07 ± 0.03, RAVLT recognition: β 0.09 ± 0.03, VAT A: β 0.19 ± 0.06; all P < 0.05FDR), attention (Stroop word naming: β 0.08 ± 0.02, Stroop color naming: β 0.06 ± 0.03; all P < 0.05FDR), and executive functioning (TMT B: β 0.05 ± 0.02; P < 0.05FDR), but not language. Baseline plasma ttau concentrations were not associated with decline on any of the neuropsychological tests.

To visualize effect sizes for associations of both CSF and plasma Aβ with rate of cognitive decline, we constructed a coefficient plot (Fig. 1), illustrating that the coefficients for plasma Aβ42/Aβ40 ratio mirrored those of CSF Aβ42. Finally, we constructed spaghetti plots for representative tests to visualize the raw neuropsychological trajectories of cognitive decline in relation to tertiles of baseline CSF or plasma amyloid biomarker concentration (Fig. 2).

Neither plasma nor CSF biomarkers were associated with baseline CCI (plasma Aβ42/Aβ40: β −0.04 ± 0.19, plasma ttau: β −0.04 ± 0.13, CSF Aβ42: β −0.14 ± 0.17, CSF pTau: β 0.06 ± 0.15, CSF ttau: β 0.05 ± 0.16) nor with longitudinal CCI (plasma Aβ42/Aβ40: β 0.04 ± 0.06, plasma ttau: β 0.10 ± 0.04, CSF Aβ42: β 0.05 ± 0.04, CSF ptau: β −0.03 ± 0.05).
4. Discussion

We found that low plasma amyloid at baseline is related to a steeper rate of subsequent cognitive decline in the domains of memory, attention, and executive functioning in cognitively normal individuals with SCD. In line with these observations, CSF amyloid was related to rate of cognitive decline in these domains as well, with effect sizes in the same order of magnitude. By contrast, despite clear associations between CSF tTau and pTau and subsequent cognitive decline, plasma tTau concentrations were not associated with any measure of cognitive decline.

Plasma amyloid and its relation with cognitive functioning has hardly been studied yet. We observed no cross-sectional associations between plasma amyloid and neuropsychological test performance, comparable to what we observed for CSF amyloid. Longitudinally, however, we observed clear associations between plasma amyloid and rate of cognitive decline. Interestingly, the effect sizes of these associations of plasma amyloid with rate of cognitive decline were in the same order of magnitude as the effect sizes of CSF amyloid, although standard errors for plasma amyloid were clearly larger, indicating that the plasma biomarker measurements are influenced more by noise. The few recent cross-sectional studies were in agreement with ours in reporting absence of relationships between CSF or PET amyloid and a few cognitive tests in cognitively normal individuals (Aizenstein et al., 2008; Landau et al., 2012; Lim et al., 2012; van Harten et al., 2013b). Summarized in a recent meta-analysis, it was concluded that cross-sectional associations between CSF or PET amyloid and cognition in cognitively normal individuals are visible in the memory, attention, and executive functioning domains, but the effect sizes of these associations are small (Baker et al., 2017). This is in line with the notion that amyloid accumulation in the brain precedes the onset of clinical symptoms by many years (Bateman et al., 2012; Dubois et al., 2016; Jack et al., 2018) and amyloid fluids levels plateau early in the disease course (Palmqvist et al., 2019a). Longitudinally, the relationship between CSF and PET amyloid and cognitive decline over time is much more evident, with multiple studies robustly showing that amyloid pathology is a predictor of cognitive decline over time (Baker et al., 2017; Donohue et al., 2014, 2017; Doraiswamy et al., 2014; Landau et al., 2012; Lim et al., 2014; Mielke et al., 2016; Roberts et al., 2018; Timmers et al., 2019; van Harten et al., 2013a). Our current CSF findings in controls, SCD, MCI, and AD dementia (Iulita et al., 2019). Although these longitudinal studies did not solely focus on cognitively normal individuals as we did, their findings are in support of our findings by showing that having lower amyloid concentration in the blood is not a harmless sign but does reflect ongoing Alzheimer’s pathological changes. The body of evidence on CSF and PET amyloid in relation to cognition is much larger. From those studies we have learned that, cross-sectionally, results vary among studies where some did observe associations between CSF or PET amyloid and a few cognitive tests in cognitively normal individuals (Donohue et al., 2014; Doraiswamy et al., 2014; Jansen et al., 2018; Mielke et al., 2016; Petersen et al., 2016; Sperling et al., 2013; Timmers et al., 2019), while others did not (Aizenstein et al., 2008; Landau et al., 2012; Lim et al., 2012; van Harten et al., 2013b).
Fig. 2. Spaghetti plots visualizing raw neuropsychological test performance over time. Raw neuropsychological test performance over time was labeled for baseline CSF Aβ42 tertiles (left) or baseline plasma Aβ42/Aβ40 tertiles (right) with superimposed average neuropsychological trajectory with 95% confidence intervals for each CSF or plasma Aβ tertile. CSF Aβ42 tertiles were: low < 892, medium 892–1160, high > 1160 pg/mL. Plasma Aβ42/Aβ40 tertiles were: low < 44.6, medium 44.6–51, high > 51. Legend: Red = Lowest tertile; Green = medium tertile; Blue = highest tertile. Abbreviation: Aβ, amyloid beta.
an SCD cohort confirm these results, and we extended on these findings by showing that a blood-based measure of amyloid as well is associated with future decline in memory, executive functioning, and attention. Further investigating these observed relationships in different, independent cohorts, might help in defining clinical cut points for screening of individuals with SCD for their risk of future cognitive decline.

Regarding the tau biomarkers, we did not observe any associations for plasma tTau and cognition, whereas CSF tTau and pTau were associated with rate of decline in test performance on the largest part of the administered neuropsychological tests covering all major cognitive domains. This contrast in findings between plasma and CSF clearly implicates that the current method used to measure plasma tTau is not yet sensitive enough to pick up subtle differences in cognitively normal individuals. In agreement with this notion, a large overlap in plasma tTau values were reported when comparing levels between healthy controls and patients with AD dementia (Mattsson et al., 2016; Mielke et al., 2018; Muller et al., 2017; Zetterberg et al., 2018), implicating that plasma tTau does not seem clinically useful as a biomarker for AD pathological processes as of yet. As an alternative, new methods for plasma pTau181 and pTau271 measurement are currently emerging, showing much promise for use of pTau instead of tTau as a plasma biomarker for AD pathological processes (Mielke et al., 2018).

In a smaller subset, we had information on severity of SCD measured by the CCI questionnaire. We did not observe any associations between plasma or CSF markers and CCI, while a few previous studies have shown that subjective complaints are higher with higher brain amyloid burden (Amariglio et al., 2012; Buckley et al., 2017; Miebach et al., 2019; Shokouhi et al., 2019; Valech et al., 2018) and/or higher tau burden (Buckley et al., 2017; Shokouhi et al., 2019; Swinford et al., 2018). Differences with our findings are probably attributable to methodological aspects: participants of these cross-sectional CSF and PET studies were generally older, and different questionnaires to measure SCD were used (e.g., self-reported ECog, different SCD-composite scores calculated from questionnaires or through interviews). The CCI label describes a highly heterogeneous group of individuals, who are at increased risk to progress to dementia (Buckley et al., 2016; Ronnlund et al., 2015), especially when they visit a memory clinic with their complaints (van Harten et al., 2013b; Vogel et al., 2017) and/or higher tau burden (Buckley et al., 2017; Shokouhi et al., 2019; Swinford et al., 2018). Differences with our findings are probably attributable to methodological aspects: participants of these cross-sectional CSF and PET studies were generally older, and different questionnaires to measure SCD were used (e.g., self-reported ECog, different SCD-composite scores calculated from questionnaires or through interviews). The CCI label describes a highly heterogeneous group of individuals, who are at increased risk to progress to dementia (Buckley et al., 2016; Ronnlund et al., 2015), especially when they visit a memory clinic with their complaints (van Harten et al., 2013b; Vogel et al., 2017). Easy accessible biological markers are thus wanted and might provide diagnostic and prognostic tools to differentiate those SCD individuals that are at a preclinical AD stage (i.e., NIA-AA stage 2 of the AD continuum) and experience subthreshold clinical Alzheimer’s symptoms from those individuals that have another cause of cognitive worries, for example, caused by feelings of unhappiness, anxiety, disturbed sleep, or experience of stress (Comijs et al., 2002; Jessen et al., 2014).

Among the strengths of the present study is that we investigated a wide portfolio of neuropsychological tests, administered longitudinally. Especially in longitudinal studies, the use of cognitive domains generates noise when specific cognitive tests are missing in some, but not all visits. By using raw data in an LMM statistical framework, we were able to incorporate all data points available, thus maximizing statistical power. Another strength of our study is that we used a highly sensitive and automated platform for the analysis of the plasma samples, which enables future implementation in routine clinical practice. In addition, we were able to compare our plasma amyloid results with the CSF amyloid results in paired samples. Finally, in this study, a large memory clinic population with cognitive complaints but no objective cognitive deficits was selected, making this study highly clinically relevant. These are the subjects that will benefit from easy and adequate screening and monitoring of their experienced cognitive complaints. Optimally, one would want to differentiate these individuals at the earliest steps of a diagnostic process, to reassure those that are unlikely to progress, and to provide diagnostic care and monitoring for individuals at increased risk of decline.

Among the limitation of the study is that the current findings cannot be directly extrapolated to the general population or to individuals further along the Alzheimer’s continuum because of our focus on SCD. Also, a clinical sample was investigated in the present study with inherent variability in follow-up time and intervals. A possible other limitation of the study is that some, but not all, of the neuropsychological tests suffer from ceiling effects, resulting in a restricted range in test scores and potentially underestimating or overestimating the plasma amyloid-associated annual decline. Independent of plasma amyloid, our cohort demonstrated an average decline on one of the memory tests and one of the language tests, while an increase was observed on one of the tests assessing executive functioning. General decline might be caused by aging effects (Harrington et al., 2017) and general improvement by alleviation of depressive symptoms (Shinada et al., 2014) or learning effects which can happen in the absence of Alzheimer’s pathology (Duff et al., 2011; Hassenstab et al., 2015; Machulda et al., 2013; Sierra-Rio et al., 2016). Future work should focus on validating the results in an external population, preferably in both memory clinic and community-based populations with and without SCD and perhaps over the complete Alzheimer’s continuum.

To conclude, we showed that lower plasma amyloid is associated with steeper rate of cognitive decline, particularly in tests related to memory, attention, and executive functions. These results were supported by comparable associations of the CSF amyloid. Our results suggest that, in cognitively normal individuals, a lower amyloid concentration in blood is not a harmless sign but reflects ongoing Alzheimer’s pathological changes.

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Azzenza, J.H., Nebers, R.D., Saxton, J.A., Price, J.C., Mathis, C.A., Tsopelas, N.D., Zullo, S.K., James, J.A., Snitz, B.E., Hoek, C.W., Bi, W., CP, 2018. Lopesoti, B.J., DeKosky, S.T., Hallgran, E.M., Kunk, W.E. 2008. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch. Neurol. 65, 1509–1517.

Albani, M., Marazzoni, M., Ferrari, C., Fusco, F., Boeri, L., Raimondi, I., Jovicich, J., Babiloni, C., Sorace, A., Lizio, R., Galluzzo, S., Cavaleri, L. Didic, M., Schonknecht, P., Molinouelo, JL, Nobili, F., Parnetti, L., Payoux, P., Bocchio, L., Salvatore, M., Rossini, PM., Tolacli, M., Visser, F.J., Richardson, J.C., Wiltfang, J., Ford, G., Titone, O., Tachezy, I., Frisoni, G.B., CP, 2018. Plaques Abeta42 as biomarker of prodromal Alzheimer’s disease progression in patients with amnestic mild cognitive impairment: evidence from the PharmaCog/ADNI study. J. Neurosci. 38, 1487–1498.

Amiraglio, R.E., Becker, J.A., Carmasson, J., Wadsdow, L.P., Nouriss, S., Liu, M.A.J., Eide, J.C., Cicidic, C., Pepin, L.C., Sperling, R.A., Johnson, K.A., Rentz, D.M., 2017. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. Neurology 90, 250–258.

Andreason, U., Perrett-Laudet, A., van Waalwijk van Dooorn, J.L., Bennoon, K., Chaisserini, D., Engelborghs, S., Fladby, T., Genc, S., Kruse, N., Kupjerich, H.B., Kulc, L., Lewczuk, P., Mollenhauer, B., Mroczko, B., Parnetti, L., vannamechene, G., Verbeek, J.M., Winsbald, B., Zetterberg, H., Koel-Simmenkel, I., Teunissen, C.E. 2015. A practical guide to immunoassay method validation. Front Neurol. 6, 179.

Baker, J.E., Lim, YY, Pietrzak, R.H., Hassesten, J., Snyder, P.J., Masters, CL, Maruff, P., 2012. Cognitive impairment and decline in cognitively normal older adults with high amyloid-beta: a meta-analysis. Alzheimers Dis. (Amst.) 10S, 1–8.

Bateman, R.J., Xiong, C., Benzinger, T.L., Fagan, A.M., Goate, A., Fox, N.C., Marcus, D.S., Chatterjee, P., Elmi, M., Goozee, K., Shah, T., Sohrabi, H.R., Dias, C.B., Pedrini, S., Baker, J.E., Lim, Y.Y., Pietrzak, R.H., Hassenstab, J., Snyder, P.J., Masters, C.L., Maruff, P., 2017. Cognitive impairment and decline in cognitively normal older adults with tauopathy independent of global amyloid and subsequent cognitive decline among cognitively normal persons. JAMA Neurol. 74, 965–1163.

Buckley, R.F., Hanseeuw, B., Schultz, AL, Fox, N.C., Marcus, D.S., Jack Jr., C.R., Proceedings of the Meeting of the International Working Group, G., the Alzheimer’s Association on The Preclinical State of, A.D., July, Wash, 2002. Memory complaints; 106

References

932

939.

221

1652.

f

1264.
Investigators, A., 2016. Plasma tau in Alzheimer disease. Neurology 87, 7377–7373.

Miebach, L., Wolfsgruber, S., Polcher, A., Peters, O., Menne, F., Luther, K., Incesoy, E., Ercolani, A., Priller, J., Spruth, E., Altenstein, S., Buerger, K., Catak, C., Janowitz, D., Perrenzczky, R., Utecht, J., Laske, C., Buchmann, M., Schneider, A., Fleisskas, B., Kalbhen, F., Heneka, M.T., Brosseron, F., Spottke, A., Roy, N., Teipel, S.J., Lilienfeld, T., Wiltfang, S., Schwaiger, A., Meibert, D., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Mielke, M.M., Hagen, C.E., Xu, J., Chai, X., Vemuri, P., Lowe, V.J., Airey, D.C., Knopman, D.S., Roberts, R.O., Matcha, M.M., Jack Jr., C.R., Petersen, R.C., Czech, P., Nasreddine, Z.S., 2014. Amyloid-beta kinetics in cognitively normal people from the community. JAMA Neurol. 73, 85–97.

Mielke, M.M., Matcha, M.M., Hagen, C.E., Christiansen, T.J., Roberts, R.O., Knopman, D.S., Vemuri, P., Lowe, V.J., Kremen, W.K., Jack Jr., C.R., Petersen, R.C., 2016. Influence of amyloid and APOE on cognitive performance in a late middle-aged cohort. Alzheimers Dement 12, 281–291.

Mulder, C., Verwey, N.A., van der Flier, W.M., Bouwman, F.H., Kok, A., van Elk, E.J.K., Scheltens, P., Blankenstein, M.A., 2010. Amyloid-beta(1–42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. Clin. Chem. 56, 248–253.

Muller, S., Preiss, O., Olopof, J.C., Yanez, A.V.C., Joos, T.O., Boecker, H., Duzel, E., Falkai, P., Priller, J., Buerger, K., Catak, C., Janowitz, D., Heneka, M.T., Brosseron, F., Nestle, F., Peters, O., Menne, F., Schwaiger, A., Spotte, A., Fleisskas, B., Kilbhen, F., Teipel, S., Wagner, M., Wiltfang, J., Jessen, F., Laske, C., 2017.tau plasma levels in subjective cognitive decline: results from the DELCODE study. Sci. Rep. 7, 9529.

Nakamura, A., Kaneko, N., Hamagami, V.L., Kata, T., Doeeke, J., Dore, V., Fowler, C., Li, Q.X., Martins, R., Rowe, C., Comita, T., Matsuoka, K., Ishii, K., Ishii, K., Arahata, Y., Iwamoto, S., Ito, K., Tanaka, K., Masters, C.L., Yanagisawa, K., 2019. High performance plasma amyloid-beta biomarkers for Alzheimer's disease.

Nature 554, 245–254.

Palmqvist, S., Insel, P.S., Storup, M., Janelidze, S., Zetterberg, H., Brix, B., Eichenlaub, U., Dage, J.L., Chai, X., Blennow, K., Mattsson, N., Hansson, O., 2019. High performance plasma amyloid-beta biomarkers for Alzheimer's disease. ACS Chem. Neurol. 5, 9.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bartz, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bars, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bartz, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bartz, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Petersen, R.C., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bartz, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bartz, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bartz, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Roberts, R.O., Mielke, M.M., Lowe, V.J., Wiltfang, S., Bartz, E., Dobisch, E., Dobisch, E., Meibert, C., Ramirez, A., Jessen, F., Wagner, M., 2019. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimers Res. Ther. 11, 66.