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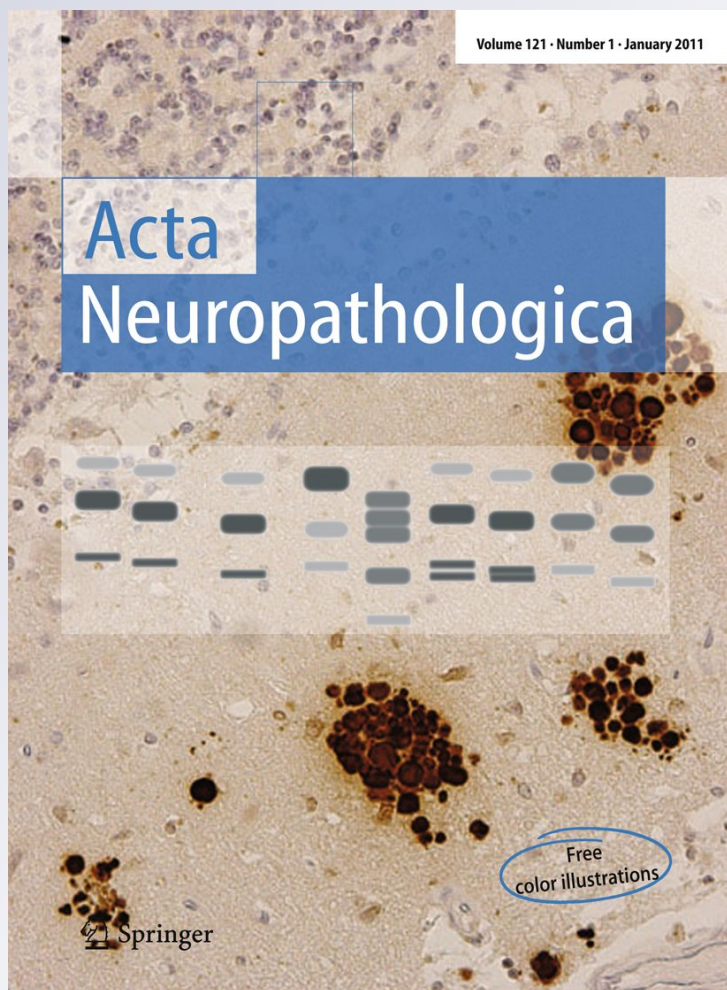
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Factors affecting A β plasma levels and their utility as biomarkers in ADNI

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Abstract Previous studies of A β plasma as a biomarker for Alzheimer's disease (AD) obtained conflicting results. We here included 715 subjects with baseline A β_{1-40} and A β_{1-42} plasma measurement (50% with 4 serial annual measurements): 205 cognitively normal controls (CN), 348 patients mild cognitive impairment (MCI) and 162 with

AD. We assessed the factors that modified their concentrations and correlated these values with PIB PET, MRI and tau and A β_{1-42} measures in cerebrospinal fluid (CSF). Association between A β and diagnosis (baseline and prospective) was assessed. A number of health conditions were associated with altered concentrations of plasma A β . The effect of age differed according to AD stage. Plasma A β_{1-42} showed mild correlation with other biomarkers of A β pathology and were associated with infarctions in MRI. Longitudinal measurements of A β_{1-40} and A β_{1-42} plasma levels showed modest value as a prognostic factor for clinical progression. Our longitudinal study of complementary measures of A β pathology (PIB, CSF and plasma A β) and other biomarkers in a cohort with an extensive neuropsychological battery is significant because it shows that plasma A β measurements have limited value for

For the Alzheimer's Disease Neuroimaging Initiative: Data used here were produced by the ADNI Biomarker Core or obtained from the ADNI database (www.loni.ucla.edu/ADNI). Many ADNI investigators contributed to ADNI but did not participate in the analysis of the data presented here or in the writing of this report. ADNI investigators are listed at www.loni.ucla.edu/ADNI/Collaboration/ADNI_Manuscript_Citations.pdf.

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disease classification and modest value as prognostic factors over the 3-year follow-up. However, with longer follow-up, within subject plasma A β measurements could be used as a simple and minimally invasive screen to identify those at increased risk for AD. Our study emphasizes the need for a better understanding of the biology and dynamics of plasma A β as well as the need for longer term studies to determine the clinical utility of measuring plasma A β .

Keywords Biomarker · Alzheimer disease · Amyloid beta-peptides · Prognosis · Diagnosis · PET · Cerebrospinal fluid

Introduction

Alzheimer's disease (AD) is neuropathologically defined by the deposition of intracellular tau aggregates, extracellular amyloid beta (A β) deposits and synapse loss. These findings, coupled with other data, led to the amyloid cascade hypothesis and thus to the development of biomarkers to measure A β pathology including A β imaging and measurements of A β peptides in cerebrospinal fluid (CSF) and plasma [22, 49]. In turn, biomarkers have advanced our understanding of the temporal profile of the pathophysiological events that occur during the progression of AD [24]. For example, measurement of CSF A β has been shown to be accurate and informative diagnostically for distinguishing cognitively normal subjects from AD subjects [49], predicting conversion of MCI subjects [10, 50] and in the differential diagnosis with frontotemporal degeneration [11]. CSF A β values also show a strong negative correlation with Pittsburgh Compound B (PIB) PET values [13, 14, 57]. But there is a compelling need for minimally invasive plasma biomarkers [1].

However, studies of plasma A β have been contradictory and cross-sectional analyses have reported higher A β_{1-42} levels [36–38], higher A β_{1-40} [36], lower levels of A β_{1-42} [31, 34] as well as lower A $\beta_{1-42/1-40}$ ratio (A β R) values [5, 31, 34] in AD patients. Further, when other studies adjusted for different factors, they only found a mild effect of baseline A β_{1-40} as a predictor for developing MCI, while the other associations with plasma A β disappeared after multivariate adjustment [17, 33, 54].

In cohort studies, baseline higher A β_{1-40} concentration [8, 52, 55], higher levels of A β_{1-42} [8, 30, 36, 37, 46], high A β R [36, 37] or low A β R [20, 28, 55, 59] were associated with risk for AD [36]. Studies that measured plasma A β concentrations at two time points in cohort studies report that a decrease of plasma A β_{1-42} [8, 37, 46–48] and a decrease of the A β R [46–48] were associated with progression to AD or with cognitive decline. Two studies measured plasma A β levels at several time intervals but did not describe the temporal profile of changes in their concentrations [32, 47, 48].

Plasma A β concentrations have also been linked to vascular brain pathology in the case of A β_{40} [21] and in longitudinal studies of plasma A β concentrations were related to progression to mixed and vascular dementia [28] and hypertension [29].

Factors that lead to the discrepancies in the literature on the diagnostic and prognostic utility of measuring plasma A β are not well understood, but could reflect many clinical and methodological factors that affect plasma levels [3, 4, 9, 37], while age may act as a confounding factor [17, 20, 33, 52] (plasma A β concentrations could have different values at different stages of disease).

To address all these conflicting results, we analyzed different factors affecting A β concentration in order to be able to adjust the statistical models used to test the considered hypotheses. The relationship of the A β burden measured by biomarkers in different biological compartments was tested. We then tested the association with cerebrovascular lesions and vascular risk factors followed by testing the utility for baseline classification. Finally, we tested the longitudinal changes of A β plasma concentrations across time at different stages of the disease and the utility of A β plasma as a prognostic factor in AD.

Materials and methods

Subjects

The ADNI is a multicenter longitudinal neuroimaging study, launched in 2004 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations. ADNI includes 819 adult subjects, 55–90 years old, who meet entry criteria for a clinical diagnosis of amnesic mild cognitive impairment (MCI), probable AD or cognitively normal (CN), who are prospectively followed, gathering clinical information, neuroimaging studies and biological samples for molecular biomarker measurement as previously described [23, 25, 39, 49] (for more details, see <http://www.adni-info.org/index> and supplementary material). We further classified subjects as stable if they did not

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change their diagnostic category from CN to MCI/AD or from MCI to AD, having a follow-up of at least 36 months. Patients who progressed were classified as CN progressors and MCI progressors.

Plasma and CSF $A\beta_{1-42}$ and $A\beta_{1-40}$

Plasma concentrations of $A\beta_{1-42}$ and $A\beta_{1-40}$ were measured using Module A of the INNO-BIA plasma $A\beta$ forms immunoassay kit (Innogenetics, Ghent, Belgium, for research use-only reagents) on the Luminex 100 immunoassay platform and IS v.2.3 software (Luminex, Austin, TX, USA) using a fully automated sample preparation approach and lowest calibrator concentrations of 3.75 pg/mL and 1.25 pg/mL for $A\beta_{1-40}$ and $A\beta_{1-42}$, respectively (Figurski et al., manuscript in preparation) and other operating conditions as previously described [5, 27]. The same reagents were used for all samples. The inter-assay %CV obtained from daily measurement of aliquots prepared from two human subject plasma samples was 4.1% ($n = 75$) and 5.2% ($n = 42$) for $A\beta_{1-42}$ and 7.0 and 5.5% for $A\beta_{1-40}$. After each of 75 analytical runs, 2–3 samples were randomly selected for re-testing of a second never previously thawed aliquot. The average %CV obtained for 195 test–retest pairs was: 4.5%CV for $A\beta_{1-42}$ and 7.2%CV for $A\beta_{1-40}$. The qualification of this assay has been described in studies by Vanderstichele, Shaw and colleagues and the data are available at <http://www.adni-info.org/index>.

Details of the CSF collection, measurements and the formula to classify subjects by normal and pathological CSF signature can be found in Shaw et al. [49].

Pittsburgh Compound B PET imaging

ADNI PIB PET studies were performed at 14 different sites, where the production and radiolabeling of PIB were performed as outlined previously by Mathis et al. [35]. The ADNI PIB PET images undergo several quality control and standardization steps. Regional assessment of the PIB-PET data involves sampling 13 different brain areas using an automated region of interest (ROI) template method and standardized uptake value ratios were calculated as reviewed in Jagust et al. [25], using a cerebellar gray matter reference region. A PIB retention summary measure was formed by combining anterior cingulate cortex, lateral temporal cortex, precuneus, parietal and frontal cortex ROI values for each subject.

MRI and white matter hyperintensity volume

Acquisition of 1.5-T MRI data at each performance site followed a previously described standardized protocol that was rigorously validated across sites [23]. Then, for each fast-spin echo scan, the proton density and T2 images were

linearly combined to form a “pseudo-T1”, which was aligned to the T1 scan and non-brain tissues were removed from the T1 scan. White matter hyperintensities (WMH) were detected in minimum deformation template space at each voxel based on corresponding PD, T1, and T2 intensities, the prior probability of WMH, and the conditional probability of WMH based on the presence of WMH at neighboring voxels. The resulting map of WMH voxels across the brain is summarized by an estimate of total WMH volume (WMHV) [7]. Infarctions were ascertained through qualitative review by experts in Helen Wills Institute on the PD/T2 images.

Cognitive testing

Neuropsychological evaluation and criteria for the clinical diagnosis of MCI and AD have been described [39]. Briefly, the battery consists of global assessment scales (ADAS-Cog [44], MMSE [16]) and a neuropsychological battery that assesses different cognitive domains: story A from the Logical Memory Test [56], Rey Auditory Verbal Learning Test [43], the Boston Naming Test [26], Category Fluency Test [6], Trail Making Test [41], Digit Symbol Substitution Test [56] and Digit Span Test [19, 56].

Measures of cognitive reserve

The errors in the American National Adult Reading test (e-AMNART) [45] were used as an estimate of cognitive reserve, which has shown to have greater variation than education [42]. However, AMNART scores are affected with the progression of cognitive decline [53], therefore a correction of the score was used linearly regressing e-AMNART (re-AMNART) on MMSE score [2].

Statistics

To study the effect of different factors on plasma $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_R$, continuous variables were classified in quartiles except bilirubin, creatinine and liver enzyme levels, which were classified according to the laboratory reference levels as normal or abnormal. For comparisons of normally distributed numerical variables, a *t* test or ANOVA was used. In the absence of a normal distribution, log transformation was applied (individual $A\beta$ measures were normally distributed but the ratio was log transformed), but if this failed to normalize the data, the non-parametric Kruskal–Wallis test was applied. Variables with a *p* value lower than 0.20 were selected to enter a forward stepwise selection multivariate regression model. For correlations between biomarker levels Pearson *r* coefficients were calculated (r_p), but in the presence of bivariate outliers in the relplot representation [18] a percentage bend

correlation (r_{PB}) was used. For dependent categorical variables binary logistic regression models were applied. ROC curves and their respective area under the curve (AUC) were estimated using values predicted by the logistic regression. To assess MCI conversion to AD, Cox proportional hazards models were used. For repeated measures analysis of quantitative variables, mixed-effect models were applied. The obtained p values were corrected for multiple comparisons using Bonferroni's method.

Z-scores were obtained calculating an α -winsorized mean and standard deviation (SD) ($\alpha = 0.10$). We obtained an averaged z-score for five cognitive domains (learning and delayed verbal memory, language, executive function and processing) using the baseline scores of the 167 subjects who continued to be classified as CN at the third year follow-up, and a global composite cognitive measure was obtained averaging these domains. The mean and SD for A β plasma levels were obtained using the baseline values of CN subjects with normal CSF signature. A change in A β measures was classified as a decrease or increase if at 36 months there was a decrease greater than 0.5 SD or an increase greater than 0.5 SD. Statistical analyses were performed using SPSS 19.0 and R 2.12.1 [40, 58].

Results

We included 715 subjects who had a baseline A β measurement, whose follow-up information is presented in Fig. 1 and whose characteristics are summarized in Table 1.

Factors affecting A β plasma concentration

Increased concentrations of baseline plasma A β_{1-42} and A β_{1-40} were associated with increasing age, low levels of total proteins, decreasing platelet count, impaired kidney function and with gender (males > females), while A β_{1-40} levels decreased with increasing cholesterol levels. A β_{1-42} decreased with increasing copies of APOE4 allele. However, A β_{1-42} /A β_{1-40} ratio values were only affected by glucose (Table 2).

Age, platelet count, total protein and creatinine concentration were independent predictors for A β_{1-40} and A β_{1-42} and explained 12.1 and 12.9% of the variability of their respective concentrations. These variables were included in the multivariate models to adjust for possible confounders.

A β levels measured in plasma and CSF and the PIB A β burden in brain

Correlation between A β_{1-40} and A β_{1-42} plasma concentrations was 0.834 ($p < 0.001$), while the correlation between

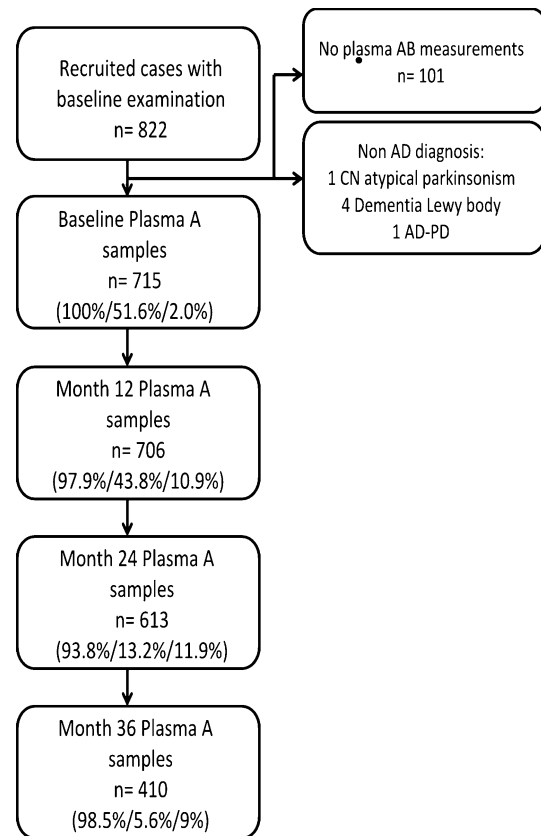


Fig. 1 Flow chart with follow-up data of the cohort. The percentages in brackets represent proportion of subjects with plasma A β , CSF A β and PIB measures at each follow-up, respectively. A β amyloid beta, AD Alzheimer's disease, CN cognitively normal, PD Parkinson's disease

A β_{1-42} in plasma and CSF in the 368 available subjects was low ($r_{PB} = 0.155$, $p = 0.017$). Adjusting for factors affecting A β_{1-42} plasma levels did not improve the ability to predict CSF A β_{1-42} values. There was a mild inverse correlation between A β_{1-42} plasma and CSF tau ($r_{PB} = -0.143$, $p = 0.037$) and p -tau_{p181} ($r_{PB} = -0.171$, $p = 0.006$) (Supplementary Fig. 1). Similar results were obtained for the following groups: CN and MCI with normal CSF and MCI stable, MCI progressors and AD with pathological CSF.

Ninety-five subjects had at least one PIB and plasma A β measures and 44 subjects had A β_{1-42} CSF and PIB measures obtained at the same follow-up visit. Mean PIB values showed a high inverse correlation with CSF A β_{1-42} levels ($r_P = -0.759$, $p < 0.001$), a mild inverse correlation with A β_{1-42} plasma levels ($r_{PB} = -0.234$, $p = 0.044$) and no correlation with plasma A β_{1-40} (Fig. 2).

A β plasma levels, vascular risk factors and WMHV

There was no correlation between WMHV and plasma A β_{1-42} ($r_{PB} = 0.069$, $p = 0.17$) and A β_{1-40} ($r_{PB} = 0.083$, $p = 0.82$). We adjusted in a multiple regression model with

Table 1 Demographics, baseline cognitive measurements and blood analytes

	CN stable (n = 187)	CN progression (n = 10)	CN dropouts (n = 8)	MCI stable (n = 162)	MCI progression (n = 145)	MCI dropouts (n = 41)	AD (n = 162)	p value
Age (years)	75.80 (5.02)	78.40 (4.06)	75.63 (4.41)	74.69 (7.57)	74.61 (7.20)	76.63 (7.26)	75.27 (7.60)	0.866 ^a 0.106 ^b
Gender (% male)	52.4	50.0	50.0	68.5	62.1	61.0	53.1	0.265 ^c 0.723 ^d
Ethnicity (% caucasian)	92.0	90.0	75.0	91.4	90.3	90.2	93.8	
Education (years)	16.08 (2.81)	16.10 (3.00)	16.38 (2.07)	15.98 (2.86)	15.65 (2.96)	15.22 (3.45)	14.83 (3.06)	0.973 ^a 0.249 ^b
e-AMNART	9.04 (8.18)	8.70 (4.90)	15.12 (9.58)	13.05 (10.28)	13.76 (9.56)	14.76 (10.58)	14.76 (10.58)	0.990 ^c 0.004 ^d
MMSE	29.17 (0.99)	29.10 (0.74)	28.25 (1.67)	27.52 (1.71)	26.72 (1.70)	26.59 (1.73)	23.44 (1.99)	0.033 ^a 0.787 ^b 0.026 ^c <0.003 ^d
ADAS-Cog	5.74 (2.75)	8.17 (3.43)	8.75 (4.38)	9.57 (4.19)	13.14 (4.11)	12.03 (4.03)	18.31 (6.03)	0.106 ^a 0.060 ^b 0.127 ^c <0.001 ^d
BMI (kg/m ²)	26.73 (4.34)	29.61 (5.07)	25.14 (3.81)	26.38 (3.95)	25.84 (4.13)	25.82 (3.54)	25.67 (3.79)	0.049 ^a 0.084 ^b 0.003 ^c <0.001 ^d
Creatinine (mg/dL)	0.96 (0.23)	1.04 (0.34)	0.98 (0.21)	1.00 (0.25)	1.03 (0.27)	0.93 (0.24)	1.03 (0.264)	0.276 ^a 0.650 ^b 0.410 ^c 0.030 ^d
Cholesterol (mg/dL)	192.72	176.22 (35.61)	194.40 (23.46)	195.31 (38.95)	196.86 (38.45)	201.93 (34.04)	203.29 (42.26)	0.794 ^a 0.052 ^b 0.399 ^c 0.540 ^d
								0.758 ^a 0.362 ^b 0.430 ^c 0.154 ^d

Table 1 continued

	CN stable (n = 187)	CN progression (n = 10)	CN dropouts (n = 8)	MCI stable (n = 162)	MCI progression (n = 145)	MCI dropouts (n = 41)	AD (n = 162)	p value
Platelets (cells/mm ³)	234,950 (61,850)	231,000 (56,460)	250,250 (40,294)	227,900 (49,44)	245,110 (70,523)	241,720 (71,178)	241,070 (64,549)	0.356 ^a 0.719 ^b 0.648 ^c 0.030 ^d
WMH (Volume %)	2.65 (2.60)	2.21 (1.67)	2.87 (0.98)	2.33 (1.87)	2.80 (2.93)	3.22 (2.63)	3.35 (3.27)	0.419 ^a 0.094 ^b 0.883 ^c 0.006 ^d
Plasma Aβ40 (pg/ml)	152.52 (49.45)	145.53 (52.76)	133.09 (25.50)	153.70 (54.42)	150.65 (57.15)	143.35 (35.65)	152.46 (46.80)	0.281 ^a 0.162 ^b 0.301 ^c 0.590 ^d
Plasma Aβ42 (pg/ml)	38.14 (12.33)	32.12 (10.78)	36.56 (9.29)	36.89 (12.85)	35.72 (11.39)	35.46 (9.45)	36.41 (10.40)	0.773 ^a 0.657 ^b 0.179 ^c 0.597 ^d
Plasma Aβ42/40 ratio	0.27 (0.08)	0.23 (0.07)	0.27 (0.03)	0.26 (0.11)	0.26 (0.11)	0.25 (0.05)	0.25 (0.06)	0.547 ^a 0.964 ^b 0.462 ^c 0.971 ^d
CSF Aβ42 (pg/ml)	207.38 (53.73)	172.67 (56.88)	263.50 (7.78)	175.92 (61.64)	146.68 (40.04)	180.32 (47.81)	143.97 (42.02)	0.175 ^a 0.036 ^b 0.490 ^c 0.001 ^d
CSF TTTau (pg/ml)	69.51 (28.74)	63.83 (31.20)	65.00 (19.80)	84.40 (46.57)	113.72 (11.40)	84.45 (57.03)	119.66 (60.20)	0.974 ^a 0.748 ^b 0.593 ^c <0.001 ^d

Aβ amyloid beta, ADAS-Cog Alzheimer's Disease Assessment Scale-cognitive subscale, BMI body mass index, CSF cerebrospinal fluid, e-AMNART errors in the American National Adult Reading test, MMSE mini-mental state examination, TTTAU total tau, WMH White matter hyperintensity

- ^a p value for comparison between CN who had follow-up for at least 24 months and CN dropouts
- ^b p value for comparison between MCI who had follow-up for at least 24 months and MCI dropouts
- ^c p value for comparison between CN stables who had follow-up for at least 24 months and CN progressors
- ^d p value for comparison between MCI stables who had follow-up for at least 24 months and MCI progressors

a two-category variable that divided the population into CN and MCI subjects with normal CSF tau and A β signature and MCI and AD with the pathological CSF tau and A β

Table 2 Factors affecting plasma AB measurements

Factor	A β_{1-40} <i>p</i>	A β_{1-42} <i>p</i>	A β_R <i>p</i>
Platelets	0.001	0.006	0.419
Gender	0.004	0.003	0.228
Ethnic	0.558	0.595	0.954
Hematocrit	0.573	0.256	0.509
Red blood cells	0.402	0.633	0.372
White Blood cells	0.510	0.885	0.314
Glucose	0.053	0.159	0.030
Creatin kinase	0.747	0.251	0.560
Cholesterol	0.127	0.025	0.911
Bilirubin	0.832	0.558	0.244
DirectBil	0.637	0.567	0.332
GGT	0.477	0.394	0.469
Creatinine	<0.0001	<0.0001	0.059
GPT	0.673	0.473	0.300
Total protein	0.012	<0.0001	0.652
Albumin	0.307	0.155	0.851
Calcium	0.819	0.861	0.641
Triglycerides	0.445	0.866	0.187
APOE4 ^a	0.093	0.006	0.169
Age	<0.0001	<0.0001	0.419
BMI	0.859	0.239	0.492

p values are not corrected for multiple comparisons (see methods)

BMI body mass index, GGT gamma glutamyl transpeptidase, GPT alanine transaminase

^a Adjusted for baseline diagnosis

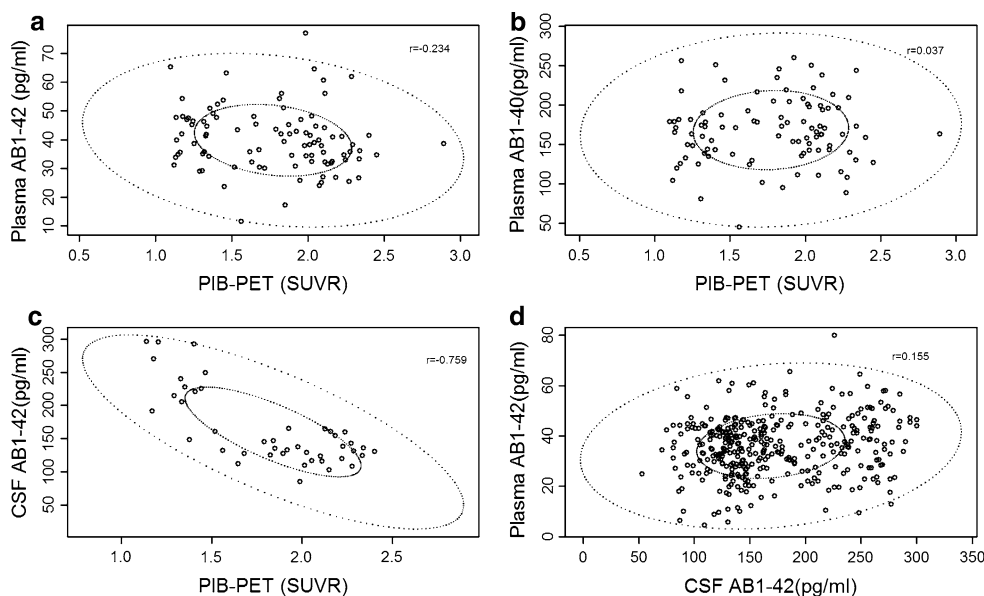
signature and the factors that affected plasma levels. In this model, the partial correlation value of A β_{1-42} was 0.129 with a *p* value of 0.058 while there was no interaction between the diagnostic groups and plasma A β_{1-42} .

Subjects with infarctions revealed by MRI had higher plasma A β_{1-42} levels [*p* = 0.024, mean A β_{1-42} difference 7.10 pg/ml (95%CI 1.90–12.29)] in the model adjusted for factors that affected plasma A β_{1-42} concentration. There was no correlation between the three plasma A β measurements and the studied vascular risk factors (BMI, systolic and diastolic blood pressure). Plasma A β_{1-42} levels, adjusted for age and BMI, predicted if a subject was or was not hypertensive (*p* = 0.03), however the AUC of the model was 0.639.

Baseline plasma A β levels, changes in cognitive status and CSF tau and A β levels

There were no differences in plasma A β measures comparing CN stable, MCI stable, MCI progressors and AD. We then compared in a two factor ANOVA, adjusting for age groups (split by median age, 75 years) and the following diagnostic categories based on CSF signature: CN stable with normal CSF (*n* = 71), MCI stable with normal (*n* = 42) and pathological CSF (*n* = 32), and MCI progressors (*n* = 58) and AD cases with pathological CSF (*n* = 86). In this model, there were no differences based on diagnostic categories (*p* = 0.333) but the term for age (*p* = 0.003) as well as the interaction between diagnostic category and age (*p* = 0.018) was significant in the ANOVA studying A β_{1-42} (Fig. 3). The latter was only significant in the groups with pathological CSF signature. The results for A β_{1-40} were similar, with an interaction between age and diagnostic group (*p* = 0.015), that was

Fig. 2 Relplots of the biomarker data (The *small ellipse* represents the bivariate interquartile range and the *outer ellipse* delimits the data points not classified as outliers). **a** PIB PET and plasma A β_{1-42} . **b** PIB PET and plasma A β_{1-40} . **c** PIB PET and cerebrospinal A β_{1-42} . **d** Plasma A β_{1-42} and cerebrospinal A β_{1-42} . A β amyloid beta, PIB-PET Pittsburgh Compound B positron emission tomography, SUVR standardized uptake value ratio



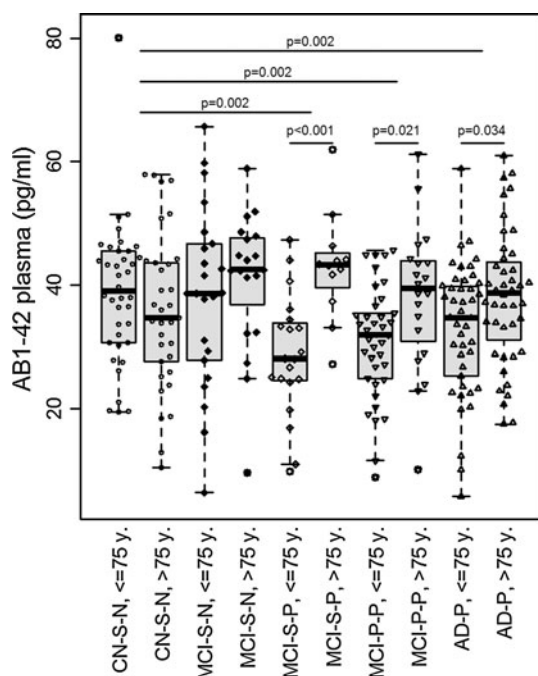


Fig. 3 Amyloid beta ($A\beta$)₁₋₄₂ levels in the different cognitive groups stratified by CSF signature and age. $A\beta$ ₁₋₄₂ levels in cognitively normal (CN) stable, mild cognitive impairment (MCI) stable and progressors and Alzheimer's disease (AD) subjects, stratified by normal and pathological cerebrospinal fluid signature (CSF). There was an interaction between age and diagnostic group in the three groups with pathological CSF signature: MCI stables ($p < 0.001$), MCI progressors ($p = 0.021$) and AD ($p = 0.034$). Only the groups with younger subjects and pathological CSF had a difference in $A\beta$ ₁₋₄₂ levels than the pooled cognitively normals with normal CSF signature

only significant in both MCI groups with a pathological CSF signature. When studying $A\beta$ R, there was neither a difference between the diagnostic groups ($p = 0.234$), nor an interaction between the diagnostic groups and age groups ($p = 0.249$).

Longitudinal analysis of $A\beta$ plasma levels

For the analysis of the temporal profile of changes in $A\beta$ plasma levels, we studied the following groups: CN stable subjects with normal CSF ($n = 71$), MCI stable subjects ($n = 31$) and MCI progressors with pathological CSF ($n = 35$). In the mixed-effect models studying $A\beta$ ₁₋₄₀ and $A\beta$ ₁₋₄₂ plasma measures there was a statistically significant effect of time, with values increasing in the successive follow-ups and a difference between groups in the $A\beta$ ₁₋₄₂ model (Fig. 4). The $A\beta$ R decreased along time and there was no difference between diagnostic groups. AD subjects could only be studied up to 2-year follow-up. There was no difference between baseline and 24-month follow-up in the AD group.

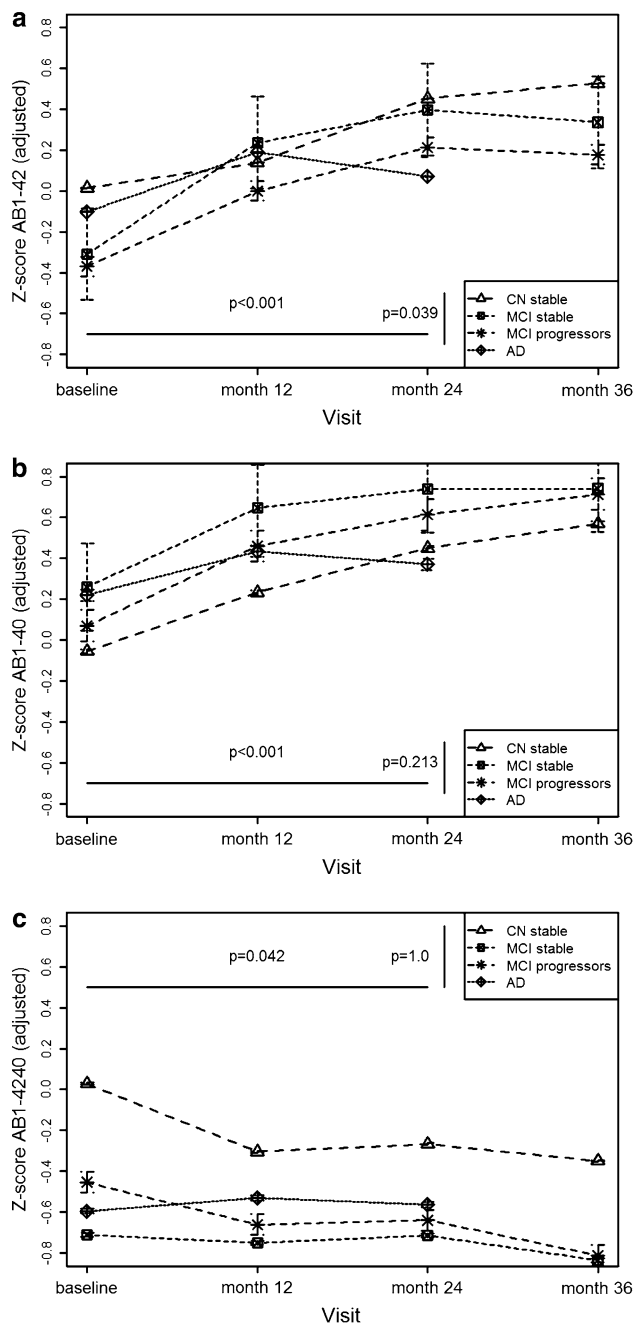


Fig. 4 Amyloid beta ($A\beta$) plasma biomarker changes along time in cognitive normal subjects with normal cerebrospinal fluid (CSF), mild cognitive impairment stable and progressor subjects with pathological CSF and Alzheimer's disease (AD) subjects with pathological CSF with 95% CI based on SE. All the models were adjusted for age and took into consideration the interaction between age and diagnostic category. **a** $A\beta$ ₁₋₄₂ along time: There is an increase in the concentration across time ($p < 0.001$), except in AD cases ($p = 0.067$), and mild cognitive impairment (MCI) progressors have lower levels than MCI stables and cognitive normals (CN) ($p = 0.039$). **b** $A\beta$ ₁₋₄₀ along time: There is an increase in the concentration across time ($p < 0.001$), except in AD cases ($p = 0.372$), and no difference between diagnostic groups ($p = 0.213$). **c** $A\beta$ R along time: There was a decrease of the ratio across time ($p = 0.042$) except in AD cases ($p = 0.902$), but no difference between diagnostic groups ($p = 1.0$). $A\beta$ amyloid beta

Utility of A β plasma measure to predict cognitive decline

We calculated tertiles of baseline A β plasma measures in the CN group. None of the three plasma A β measurements classified according to the previously described tertiles showed an increased risk for conversion from MCI to AD in the adjusted Cox proportional hazards models ($p_{A\beta_{1-40}} = 0.633$, $p_{A\beta_{1-42}} = 1.0$, $p_{A\beta_R} = 1.0$). On the other hand, a pathological CSF signature heralded a higher risk of conversion [HR 2.12 (95%CI 1.20–3.75)], as previously reported. The percentage of dropouts with a follow-up of 36 months was 23.6%. Results were similar with a follow-up of 24 months and 13.8% of dropouts.

We further studied the cognitive evolution of our sample in a mixed-effect model that included age at baseline, re-AMNART, the different annual visits, A β tertiles at baseline and the following diagnostic categories: CN stable with normal CSF and MCI stable and MCI progressors with a pathological CSF signature. None of the A β plasma measures had a statistical effect on change in the composite cognitive measure. However, there was a significant interaction between re-AMNART and A β_{1-42} tertiles (Fig. 5). When analyzing the different cognitive domains, the interaction was present in the language and executive domains (Table 3). Subjects with highest re-AMNART and in the lowest A β_{42} tertile had worse cognitive performance than those in the highest A β_{42} tertile and highest re-AMNART. The interaction was not significant when using the years of education. But education did not predict cognitive scores in two of the models and the association was milder in the model with general cognition ($p = 0.031$).

We then studied the previous statistically significant models in the whole sample without classifying subjects according to their CSF signature. There was no effect on A β_{1-42} tertiles or an interaction of A β_{1-42} tertiles and re-AMNART in any of the models.

Finally, in a mixed-effect model with CN stable ($n = 168$) and all MCI ($n = 276$) subjects, there was no interaction between re-AMNART and the A β categories, but patients who had an increase in A β_R ($p = 0.027$) or a decrease of A β_{1-40} ($p = 0.045$) had worse performance on the composite cognitive measure, without a significant effect of the change of A β_{1-42} ($p = 0.778$; Fig. 5).

Discussion

In our study we confirmed the poor performance of measuring plasma A β levels for classification at different stages of AD in cross-sectional analyses, but we found a different trends in the repeated plasma measurements with levels being stable in the AD group. Thus, it is possible that

longitudinal measures of plasma A β could be informative as a biomarker for the response to A β therapies or as an indicator of increased risk for conversion from normal or MCI to AD. We also quantified systemic factors that account for 12–13% of the variability of plasma levels. Finally, we confirmed the interaction between cognitive reserve and A β plasma measurements, finding an effect in the executive and language domains, and described a new association with infarctions.

The results of this study show that patients with infarctions documented by MRI have higher A β_{1-42} levels than subjects without such lesions, and there was a trend for an association between WMHV and A β_{1-42} plasma. In addition to the well-described association between renal function and plasma A β [3, 36], we also found that total proteins and platelets affected plasma A β levels as suggested earlier for blood levels [9]. Plasma A β_{1-42} and A β_{1-40} concentrations were associated with aging, but this association was only present in MCI subjects with a pathological CSF signature who showed increasing levels with increasing age. When repeated measures of plasma A β_{1-40} and A β_{1-42} were analyzed, there was an increase in both biomarker concentrations with time in the three studied groups although levels were lower in MCI patients with a pathological CSF signature. A β_R decreased with time and the ratio was lower in MCI patients with pathological CSF. Concentration did not change in the AD group which would favor the hypothesis that levels stay stable or decrease in advanced stages of the disease. We found that in early stages a decrease in A β_{1-40} and an increase in A β_R were associated with a worse cognitive performance. Subjects with lower cognitive reserve, who had lower A β_{1-42} plasma concentrations at baseline scored worse on cognitive testing, indicating that they may only exert a mild effect that is counteracted by cognitive reserve as reported recently [59]. In our study, we had a cognitive battery which allowed us to study different domains, finding that the effects were driven by the executive and language domain. Results for years of education were negative. We think that this is due to the skewed representation of mainly highly educated subjects that precludes a wide range and normal distribution of values. A β plasma levels had a better correlation with A β amyloid brain deposits than with CSF A β values across all the studied groups, thereby confirming previous results [12, 13, 34]. We did not find a significant association between vascular risk factors and A β plasma levels.

Our results are consistent with the idea that the conflicting results of previous studies can, in part, be caused by age and disease stage effects on plasma A β concentrations as these factors differed across the studies. Our data also underline the importance of having well-defined subjects and the use of biomarkers that recognize the underlying

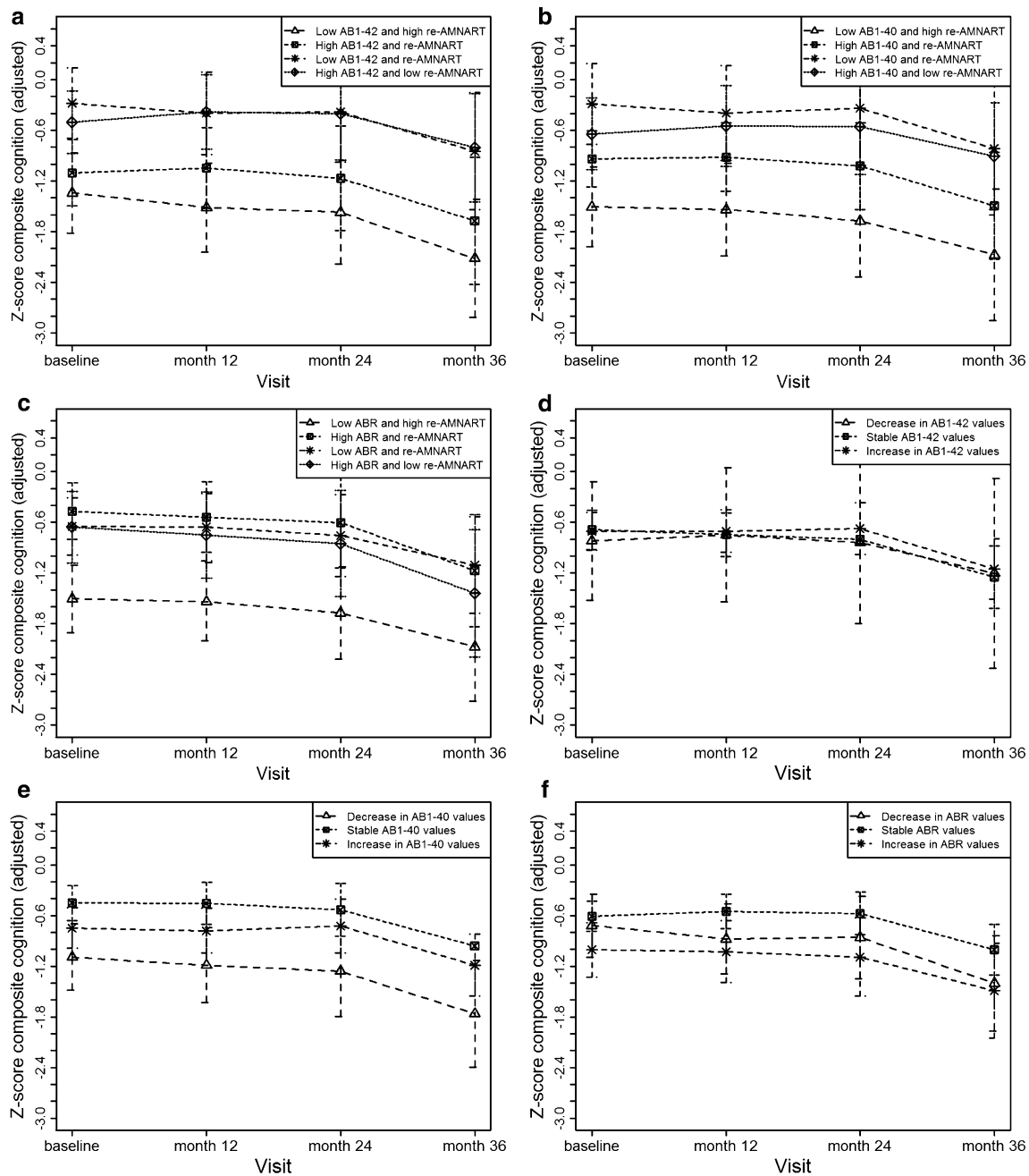


Fig. 5 Changes in global cognitive score according to errors in the in American National Adult Reading test and amyloid beta ($A\beta$) measures, with 95% CI based on SE. **a** $A\beta_{1-40}$ baseline level tertiles. **b** $A\beta_{1-42}$ baseline level tertiles. **c** A β R baseline level tertiles.

d Change in $A\beta_{1-40}$ measures at 36 months. **e** Change in $A\beta_{1-42}$ measures at 36 months. **f** Change in A β R measures at 36 months. A β amyloid beta

pathology in AD (i.e. CSF tau and $A\beta$ biomarkers) to evaluate the utility of other potential AD biomarkers (i.e. plasma $A\beta$) in the absence of neuropathological diagnosis. Our results show that given our current understanding $A\beta$ plasma levels, they are not useful for cross-sectional classification purposes in agreement with a recent meta-analysis [51]. Although our study did not find a prognostic utility studies with longer follow-up periods and their joined

results have shown predictive value [15, 46, 51]. Thus, it is plausible that measures of plasma $A\beta$ within subjects over periods of greater duration could become simple and minimally invasive screens to identify individuals at increased risk for AD dementia. Notably, our study provides insight into factors that affect $A\beta$ plasma levels and better understanding of these factors will be critical if we are to be able to exploit measures of plasma $A\beta$ as a

Table 3 Mixed effect models for cognitive outcome measures

Outcome and baseline BM	Age	Tertile A β	Diagnostic evolution	Visit	re-AMNART	Interaction re-AMNART and Tertile A β	Interaction diagnostic evolution and visit	Interaction tertile A β and visit
GC (A β_{1-42})	0.264	0.501	<0.0001	<0.0001	0.005	0.001	<0.0001	0.346
GC (A β_{1-40})	0.207	0.891	<0.0001	<0.0001	0.006	0.314	<0.0001	0.348
GC (A β_R)	0.078	0.753	<0.0001	<0.0001	0.075	0.753	<0.0001	0.467
Language (A β_{1-42})	0.380	0.263	<0.0001	<0.0001	0.005	0.0002	<0.0001	0.778
Executive (A β_{1-42})	0.161	0.163	<0.0001	<0.0001	0.003	0.013	<0.0001	0.129
Outcome and change in BM	Age	Change A β	Diagnostic evolution	Visit	re-AMNART	Interaction re-AMNART and Change A β	Interaction diagnostic evolution and Visit	Interaction change A β and visit
GC (A β_{1-42})	0.043	0.676	<0.0001	<0.0001	0.246	0.987	<0.0001	0.577
GC (A β_{1-40})	0.017	0.054	<0.0001	<0.0001	0.087	0.044	<0.0001	0.874
GC (A β_R)	0.070	0.044	<0.0001	<0.0001	0.042	0.065	<0.0001	0.505

p values are not corrected for multiple comparisons

GC global cognitive Z score, A β amyloid beta, *re-AMNART* regressed errors on the American National Adult Reading test

screening assay along the lines described above. Indeed plasma A β levels increase with aging, but changes in plasma A β are more stable as AD progresses to more advanced stages of disease.

One of the major strengths of our study is that it combines imaging, CSF and plasma A β data from the same cohort, i.e. ADNI subjects, and our study included an analysis of the data according to underlying AD neuropathology (assessed with CSF tau and A β signature of AD) with a comprehensive neuropsychological battery to assess the effects of plasma levels of A β on different cognitive domains.

Our study also has some weaknesses. The inclusion criteria excluded subjects with important vascular pathology, so our results on vascular risk factors and vascular dementia are to be taken cautiously. The selection criteria used in the ADNI study were designed to enroll late MCI subjects, and this has been confirmed by the high progression rate to AD, and therefore we may not have captured important plasma A β changes that could have occurred in earlier stages of the disease. Last, the follow-up and biomarker sampling were not complete in AD cases and we did not have available data for the whole cohort which decreases the statistical power. These weaknesses notwithstanding, our study advances understanding of the significance of plasma A β measurements in normal aging, MCI and AD.

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Conflict of interest J.Q.T., V.M.Y.L., A.W.T., S.X.X., E.T., M.F., M.W., C.J., P.A., W.J. and J.B.T. have no conflicts of interest. L.S. belongs to the advisory board of Innogenetics Technical. H.V. works at INNX-Fujirebio.

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