

Supplementary material

Is Plasma Amyloid- β 1–42/1-40 a Better Biomarker for Alzheimer’s Disease than A β X–42/X–40?

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Content:

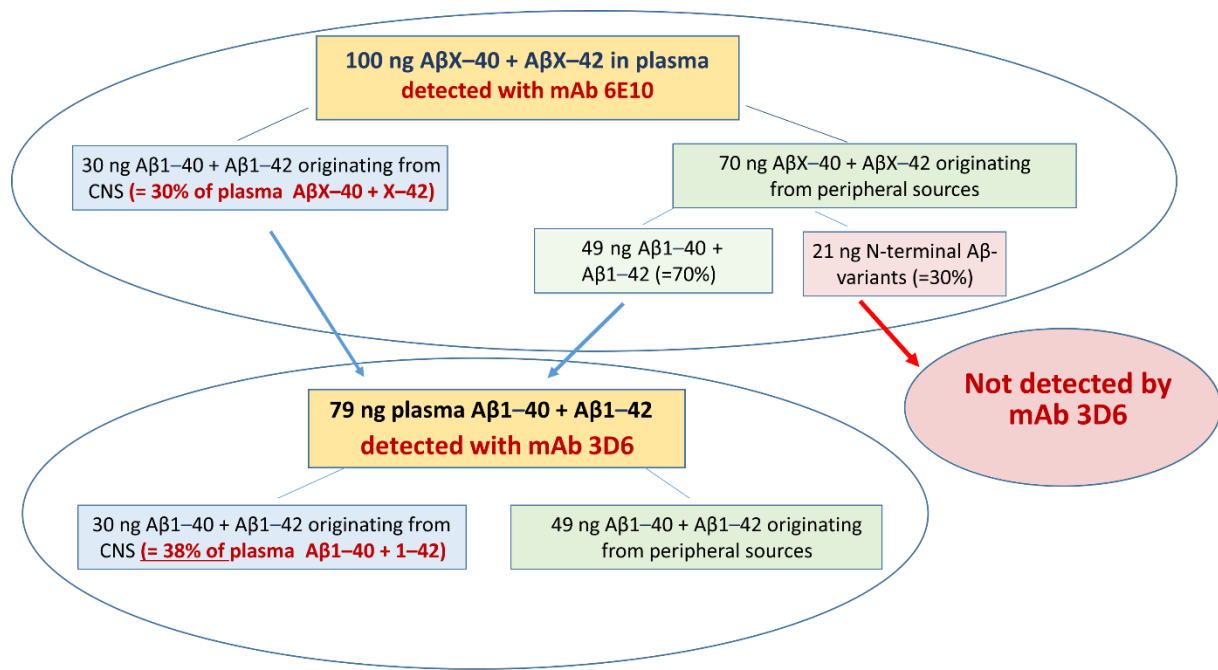
Additional file 1: Figure S1. Analysis of correlations between A β measures in cerebrospinal fluid and eluates obtained after immunoprecipitation from EDTA-blood plasma.

Additional file 1: Figure S2. Hypothetical model to explain the observed enhancement of the differences between amyloid-positive and amyloid-negative patients in plasma A β 42/40 by measuring exclusively plasma A β 1–42 and A β 1–40.

Additional file 1: Table S1. Comparison of group differences: Plasma A β X–42/X–40 vs. A β 1–42/A β 1–40.

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Additional file 1: Figure S2. Hypothetical model to explain the observed enhancement of the differences between amyloid-positive and amyloid-negative patients in plasma A β 42/40 by measuring exclusively plasma A β 1–42 and A β 1–40.



Additional file 1: Figure S2: Hypothetical model to explain the observed enhancement of the differences between amyloid-positive and amyloid-negative patients in plasma A β 42/40 by measuring exclusively plasma A β 1–42 and A β 1–40. According to our model, the molecular mechanisms causing the selective, approximately 50% reduction in CSF A β 42/40 in the presence of brain amyloid (Keshavan, Wellington et al. 2021) are restricted to the CNS. We assume that approximately 30% (in this example 30 ng of a measured total amount of 100 ng) of soluble A β in blood plasma originates from the central nervous system (CNS), most of which starting with Asp(1). Of the remaining plasma A β originating from peripheral sources, approximately 30% is estimated to have a different N-terminus. The monoclonal antibody (mAb) 6E10 detects several aminoterminal A β variants (i.e. A β X–40 and A β X–42). The measurable decrease in plasma A β 42/40 in amyloid-positive patients is proportional to the fraction of plasma A β in the assay that originates from the CNS. Measuring exclusively A β 1–40 and A β 1–42 (instead of A β X–40 and A β X–42) by employing mAb 3D6 will increase the relative fraction of A β originating from CNS from 30% (when measured with mAb 6E10) to 38% because A β peptides with other N-termini than Asp(1) are excluded from the measurements with mAb 3D6. In consequence, the measurable decrease in plasma A β 1–42/1–40 in amyloid-positive subjects is expected to be larger than that of A β X–42/X–40. The assumed 50% reduction in CSF A β 42/40

in the presence of brain amyloid is expected to be mirrored in plasma by a 15% (0.3 x 50%) reduction in A β X-42/X-40 but 19% decrease (0.38 x 50%) in A β 1-42/1-40.

Reference:

Keshavan, A., H. Wellington, Z. Chen, A. Khatun, M. Chapman, M. Hart, D. M. Cash, W. Coath, T. D. Parker, S. M. Buchanan, S. E. Keuss, M. J. Harris, H. Murray-Smith, A. Heslegrave, N. C. Fox, H. Zetterberg and J. M. Schott (2021). "Concordance of CSF measures of Alzheimer's pathology with amyloid PET status in a preclinical cohort: A comparison of Lumipulse and established immunoassays." *Alzheimers Dement (Amst)* **13**(1): e12131.

Additional file 1: Table S1. Comparison of group differences: Plasma A β X-42/X-40 vs. A β 1-42/A β 1-40.

Variable	Median difference (%) ¹	Mean difference (%) ²	Cohen's d ³
Plasma A β X-42/X-40	-15.56	-15.50	1.48
Plasma A β 1-42/1-40	-20.86	-18.34	1.73

¹ The relative median difference between amyloid-positive (A β +) and amyloid negative (A β -) groups was calculated as:

$$\text{Median difference (\%)} = 100 * \frac{\text{median (A}\beta\text{ +)} - \text{median (A}\beta\text{-)}}{\text{median(A}\beta\text{-)}}$$

² The relative mean difference between amyloid-positive (A β +) and amyloid-negative (A β -) groups was calculated as:

$$\text{Mean difference (\%)} = 100 * \frac{\text{mean (A}\beta\text{ +)} - \text{mean (A}\beta\text{-)}}{\text{mean(A}\beta\text{-)}}$$

³ Cohen's d was calculated with R package "effsize" (version 0.8.1).

A β , amyloid- β .

Additional file 1: Table S2. Classification statistics for detection of amyloid-positivity¹ for plasma A β 1–42/1–40 and A β X–42/X–40.

	Plasma A β 1–42/1–40	Plasma A β X–42/X–40
True positive	31	32
True negative	32	31
False positive	5	6
False negative	5	4
Positive predictive value	0.861	0.842
Negative predictive value	0.865	0.886
Sensitivity	0.861	0.889
Specificity	0.865	0.838
Accuracy	0.863	0.863
Area under the ROC curve (AUC)	0.884	0.875

Receiver operating characteristic (ROC) curves were evaluated at the maximum Youden point.

¹ The study participants were categorized according to the CSF A β X–42/A β X–40 ratio. Amyloid- β -positive (A β ⁺): CSF A β X–42/X–40 \leq 0.058; amyloid- β -negative (A β [–]): CSF A β X–42/X–40 $>$ 0.058

A β , amyloid- β .