Plasma Aβ42/Aβ40 ratio is independent of renal function.

Sylvain Lehmann, Susanna Schraen, Jean-Sébastien Vidal, Bernadette Allinquant, Stephanie Bombois, Audrey Gabelle, Olivier Hanon

Received: 28 October 2022 | Revised: 17 December 2022 | Accepted: 22 December 2022

DOI: 10.1002/alz.12949

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

LETTER

Plasma Aβ42/Aβ40 ratio is independent of renal function

Letter to the Editor in response to

Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities, J.A. Syrjanen, M.R. Campbell, A. Algeciras-Schimnich, P. Vemuri, J. Graff-Radford, M.M. Machulda, G. Bu, D.S. Knopman, C.R. Jack, Jr., R.C. Petersen, M.M. Mielke, Alzheimer's & dementia: the journal of the Alzheimer's Association 18(6) (2022) 1128-1140. https://doi.org/10.1002/alz.12466

We read with great interest the recent article by Syrjanen et al., who reported the association of comorbidities with amyloid and neurodegeneration plasma biomarkers.[1] Their main conclusion was that a history of chronic kidney disease was associated with significant elevations of all Alzheimer's disease (AD) biomarkers in a large population of cognitively unimpaired participants, that is, that chronic kidney disease is a confounding factor that needs to be taken into account. This important contribution complemented their work focusing on plasma phosphorylated tau (P-Tau) levels in AD patients.[2]

We also recently investigated the interest of plasma amyloid beta peptides (Aβ) in a large cohort of cognitively impaired patients, where history of kidney disease was available.[3] Our cohort had the further benefit of onsite measurement of blood creatinine as a proxy for and estimate of glomerular filtration rate (eGFR).[4] This gave us an opportunity to test Syrjanen's findings, in another population and using biological results to estimate renal function. By having access not only to kidney disease history but also to continuous numerical values of renal function, one can expect more accurate results and more clinically relevant conclusions.

As illustrated in Figures 1A,C, plasma Aβ40 and Aβ42 levels are higher with chronic kidney disease history, as well as in high-blood-creatinine and low-eGFR subjects. Importantly, however, unlike the individual components, the plasma Aβ42/Aβ40 ratio is not associated with any of these factors and therefore is independent of impaired renal function. This was also reported recently in cohorts with longitudinal measures of kidney function.[5] We then split our population into categories of decreasing kidney function following the KDIGO staging system[6] based on eGFR (<45, 45–60, or 60–90 ml/min/1.73m^2). As illustrated in Figures 1D,F, altered kidney function progressively impacted plasma Aβ40 and Aβ42 levels for all categories, but not the Aβ42/Aβ40 ratio. Correlative scatter plots for all the included subjects confirmed this association (Figures 1G,I)

The rationale for the "resistance" of the Aβ42/Aβ40 plasma ratio to altered renal function is likely linked to the fact that the two peptides are equally affected by this comorbidity. Further work, including the study of the renal clearance of the different Aβ isoforms, will be needed to confirm this hypothesis. Irrespective of the causes, our cohort reveals that computing the Aβ42/Aβ40 ratio dissects away the confounding effect of renal dysfunction. It is noteworthy that studies evaluating cerebrospinal fluid[7] and blood Aβ rely primarily on this Aβ42/40 ratio rather than on the individual levels of Aβ40 or Aβ42. In cerebrospinal fluid, the ratio largely overrides preanalytical biases of the individual peptides since it takes into account individual variations in Aβ production and amplifies the synergistic effect of Aβ40 increase[8] and Aβ42 decrease in AD. In blood, we propose that calculating the Aβ42/40 ratio will also reduce biases linked to altered renal function, which nevertheless needs to be taken into account for other biomarkers in future large population screens.[9] It will also reduce the risk of false positives in elderly people who have a high prevalence of AD and renal dysfunction; over 70 years of age the proportion of people with a GFR < 60 ml/min/1.73 m^2 varies from 38% to 62% depending on the estimation equation used.[10] The independence of Aβ42/Aβ40 plasma ratio to renal dysfunction will also be useful to confirm the association between this comorbidity and prevalence of dementia.[11]

The fact that computing the ratio between Aβ42 and Aβ40 reduced biases is an example that could be followed for other blood biomarkers. We have in mind Tau, which exists in multiple phosphorylated and nonphosphorylated isoforms.[12]

In conclusion, the fact that the plasma Aβ42/Aβ40 ratio is independent of renal function adds greatly to its value for AD diagnosis and prognosis compared with blood P-Tau and Nfl, which are strongly affected by this comorbidity.[1]

AUTHOR CONTRIBUTIONS

Sylvain Lehmann and Olivier Hanon contributed equally to this work.

ACKNOWLEDGMENTS

We acknowledge the contribution of the BALTAZAR study group in the cohort creation and analysis. The French ministry of Health (Programme Hospitalier de Recherche Clinique), Grant/Award

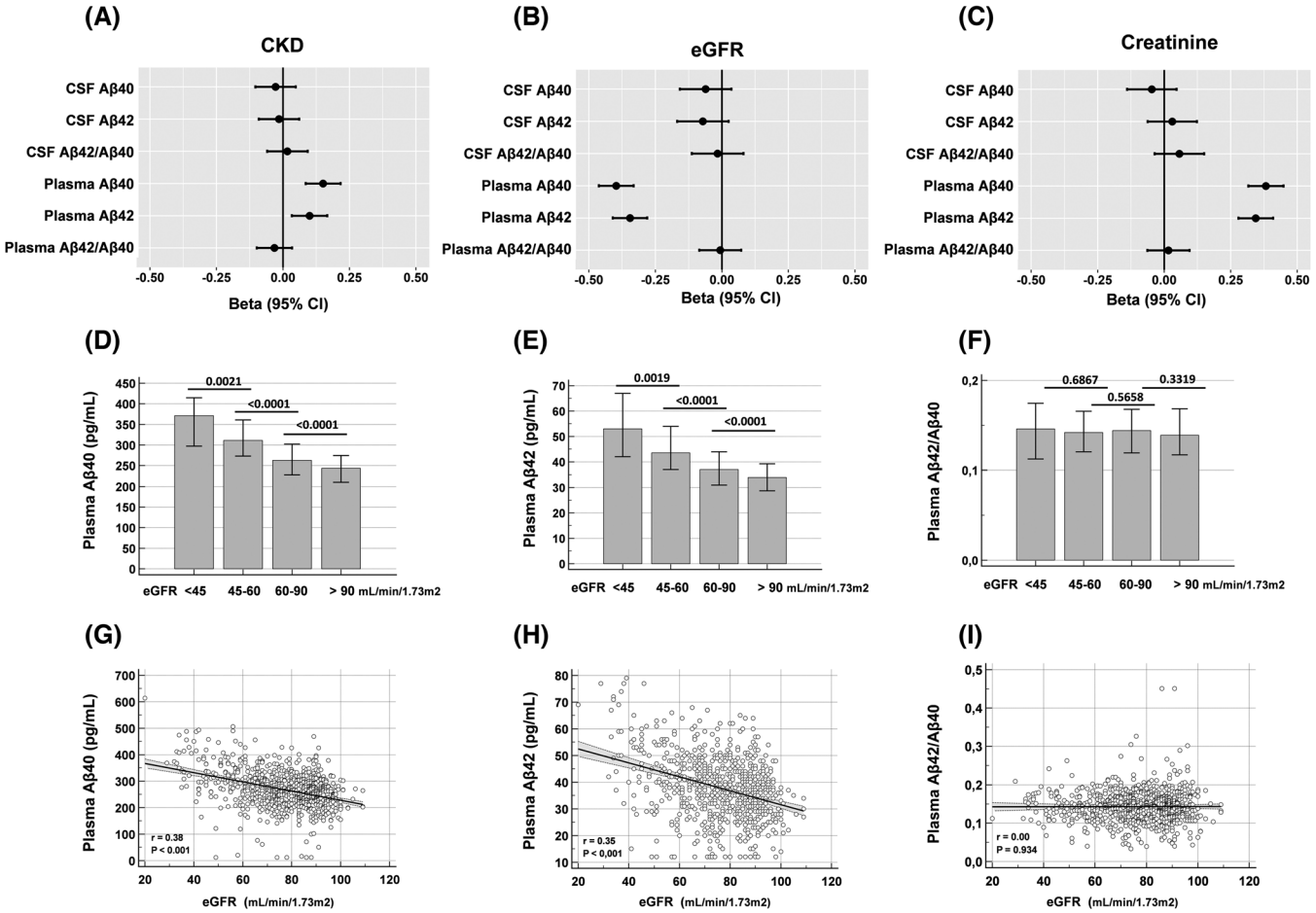

FIGURE 1 Association of plasma Aβ biomarkers with renal dysfunction. (A–C) Forest plots of linear model of plasma and cerebrospinal fluid Aβ biomarkers in BALTAZAR cohort composed of patients with mild cognitive impairment and Alzheimer's disease. (D–F) Plasma levels of Aβ40 and Aβ42 (pg/mL) and 42/40 ratio were plotted as median (25th–75th percentiles) stratified into four categories by estimated glomerular filtration rate as a proxy for compromised kidney function: moderate to severe (eGFR < 45), mild to moderate (eGFR 45–60), mildly decreased (eGFR 60–90) kidney function, and in normal kidney function (eGFR > 90) subjects. *p*-values between adjacent levels are shown. (G–H) Correlative scatter plot of Aβ biomarkers in the whole population against eGFR values showing a significant correlation (Pearson's correlation coefficient *r* with *p*-value) for Aβ40 and Aβ42 but not for the 42/40 ratio. CKD, chronic kidney disease; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate as computed using CKD Epidemiology Collaboration (CKD-EPI) equation, revised in 2021 without inclusion of race[4] as follows: $eGFR = 142 \times \min(Scr/k,1)\alpha \times \max(Scr/k,1) - 1.2 \times 0.9938^{Age} \times 1.012$ [if female] where k is 0.7 for females and 0.9 for males, α is −0.241 for females and −0.302 for males, min indicates the minimum of Scr/*k* or 1, max indicates the maximum of Scr/*k* or 1. Scr corresponds to the value of creatinine in mmol/L measured using an enzymatic assay (Roche, Cobas).

Numbers:PHRC2009/01-04,PHRC-13-0404; The Foundation Plan Alzheimer; Fondation pour la Recherche Médicale (FRM); The Gerontopôle d'Ile de France (GERONDIF). None of the funding bodies had any role in study design, in the collection, analysis, and interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Data and informed consent form are available upon request after publication (APHP, Paris). Requests will be considered by each study investigator based on the information provided by the requester regarding the study and analysis plan. If the use is appropriate, a data sharing agreement will byhhn e put in place before a fully de-identified version of the dataset, including the data dictionary used for analysis with individual participant data, is made available.

Sylvain Lehmann[1]
Susanna Schraen-Maschke[2]
Jean-Sébastien Vidal[6]
Bernadette Allinquant[3]
Stéphanie Bombois[2,4]
Audrey Gabelle[5]
Olivier Hanon[6]

[1]*LBPC-PPC, Université de Montpellier, INM INSERM, IRMB CHU de Montpellier, Montpellier, France*

[2]*Univ. Lille, Inserm, CHU Lille, UMR-S-U1172, LiCEND, Lille Neuroscience & Cognition, LabEx DISTALZ, Lille, France*

[3]*UMR-S1266, Université Paris Cité, Institute of Psychiatry and Neurosciences, Inserm, Paris, France*

[4]*Assistance Publique-Hôpitaux de Paris (AP-HP), Département de Neurologie, Centre des Maladies Cognitives et Comportementales, GH Pitié-Salpêtrière, Paris, France*

[5]*CMRR, Université de Montpellier, INM INSERM, CHU de Montpellier, Montpellier, France*

[6]*Université de Paris, EA 4468, APHP, Hopital Broca, Memory Resource and Research Centre of de Paris-Broca-Ile de France, Paris, France*

Correspondence

Sylvain Lehmann, CHU and University of Montpellier, IRMB, 80 av Fliche, 34295 Montpellier, France.

Email: s-lehmann@chu-montpellier.fr

REFERENCES

1. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimers Dement*. 2022;18(6):1128-1140.
2. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405.
3. Hanon O, Vidal JS, Lehmann S, et al. Plasma amyloid beta predicts conversion to dementia in subjects with mild cognitive impairment: the BALTAZAR study. *Alzheimers Dement*. 2022;18(12):2537-2550.
4. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737-1749.
5. Pajewski NM, Elahi FM, Tamura MK, et al. Plasma amyloid beta, neurofilament light chain, and total tau in the systolic blood pressure intervention trial (SPRINT). *Alzheimers Dement*. 2022;18(8):1472-1483.
6. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63(5):713-735.
7. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid beta (Abeta) 42/40 ratio in the diagnosis of Alzheimer's disease. *Alzheimer's res ther*. 2019;11(1):34.
8. Lehmann S, Dumurgier J, Ayrignac X, et al. Cerebrospinal fluid A beta 1-40 peptides increase in Alzheimer's disease and are highly correlated with phospho-tau in control individuals. *Alzheimer's res ther*. 2020;12(1):123.
9. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18(12):2669-2686.
10. Ebert N, Jakob O, Gaedeke J, et al. Prevalence of reduced kidney function and albuminuria in older adults: the Berlin Initiative Study. *Nephrol Dial Transplant*. 2017;32(6):997-1005.
11. Singh-Manoux A, Oumarou-Ibrahim A, Machado-Fragua MD, et al. Association between kidney function and incidence of dementia: 10-year follow-up of the Whitehall II cohort study. *Age Ageing*. 2022;51(1):afab259.
12. Barthelemy NR, Toth B, Manser PT, et al. Site-specific cerebrospinal fluid tau hyperphosphorylation in response to Alzheimer's disease brain pathology: not all tau phospho-sites are Hyperphosphorylated. *J Alzheimer's dis: JAD*. 2022;85(1):415-429.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.