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## LETTER

Plasma A $\beta$ 42/A $\beta$ 40 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.<sup>1</sup> 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.<sup>2</sup>

We also recently investigated the interest of plasma amyloid beta peptides (A $\beta$ ) in a large cohort of cognitively impaired patients, where history of kidney disease was available.<sup>3</sup> Our cohort had the further benefit of onsite measurement of blood creatinine as a proxy for and estimate of glomerular filtration rate (eGFR).<sup>4</sup> 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 A $\beta$ 40 and A $\beta$ 42 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 A $\beta$ 42/A $\beta$ 40 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.<sup>5</sup> We then split our population into categories of decreasing kidney function following the KDIGO staging system<sup>6</sup> based on eGFR (<45, 45–60, or 60–90 ml/min/1.73m<sup>2</sup>). As illustrated in Figures 1D,F, altered kidney function progressively impacted plasma A $\beta$ 40 and A $\beta$ 42 levels for all categories, but not the A $\beta$ 42/A $\beta$ 40 ratio. Correlative scatter plots for all the included subjects confirmed this association (Figures 1G,I)

The rationale for the “resistance” of the A $\beta$ 42/A $\beta$ 40 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 A $\beta$  isoforms, will be needed to confirm this hypothesis. Irrespective of the causes, our cohort reveals that computing the A $\beta$ 42/A $\beta$ 40 ratio dissects away the confounding effect of renal dysfunction. It is noteworthy that studies evaluating cerebrospinal fluid<sup>7</sup> and blood A $\beta$  rely primarily on this A $\beta$ 42/40 ratio rather than on the individual levels of A $\beta$ 40 or A $\beta$ 42. In cerebrospinal fluid, the ratio largely overrides preanalytical biases of the individual peptides since it takes into account individual variations in A $\beta$  production and amplifies the synergistic effect of A $\beta$ 40 increase<sup>8</sup> and A $\beta$ 42 decrease in AD. In blood, we propose that calculating the A $\beta$ 42/40 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.<sup>9</sup> 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<sup>2</sup> varies from 38% to 62% depending on the estimation equation used.<sup>10</sup> The independence of A $\beta$ 42/A $\beta$ 40 plasma ratio to renal dysfunction will also be useful to confirm the association between this comorbidity and prevalence of dementia.<sup>11</sup>

The fact that computing the ratio between A $\beta$ 42 and A $\beta$ 40 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.<sup>12</sup>

In conclusion, the fact that the plasma A $\beta$ 42/A $\beta$ 40 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.<sup>1</sup>

## AUTHOR CONTRIBUTIONS

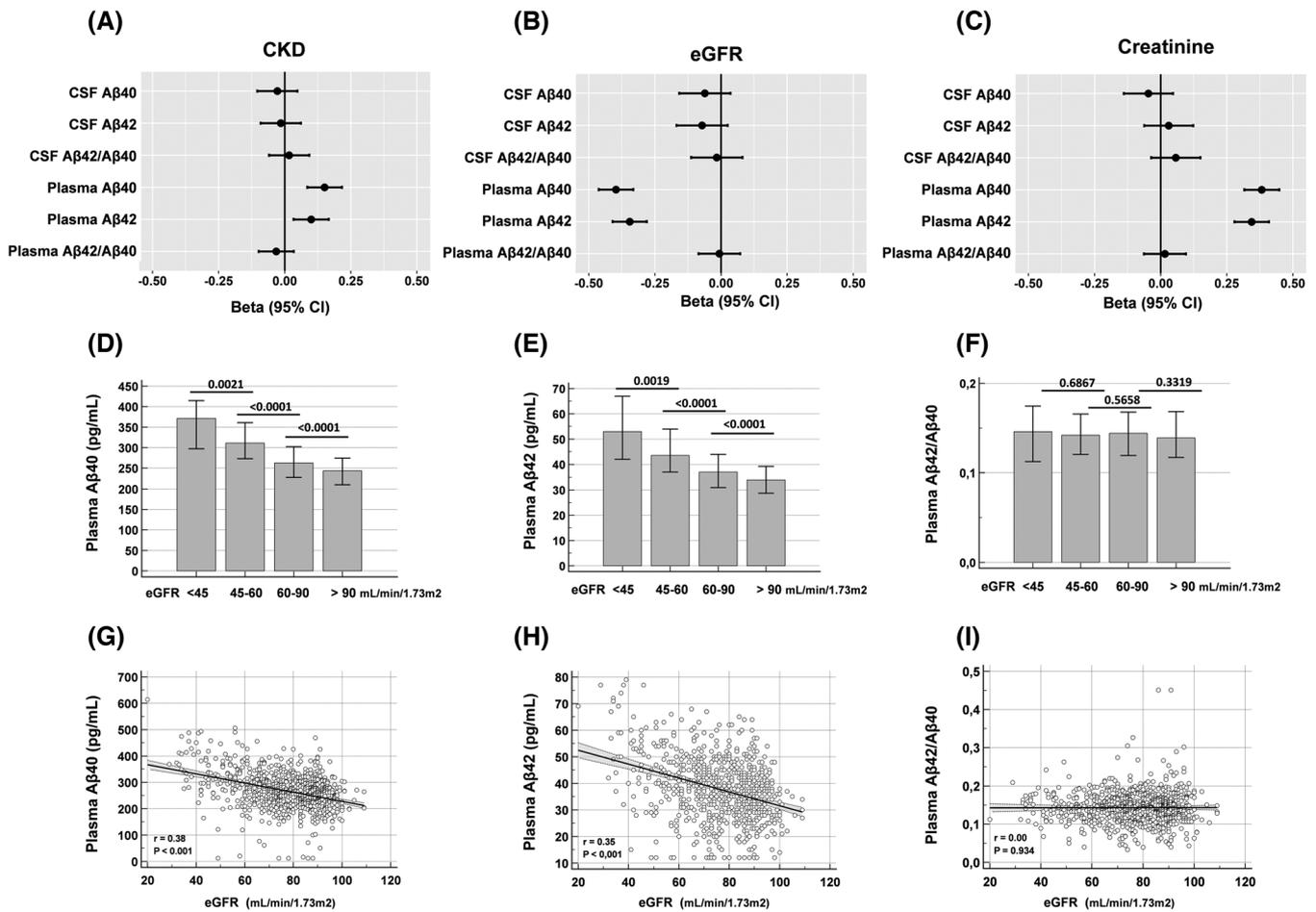
Sylvain Lehmann and Olivier Hanon contributed equally to this work.

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**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<sup>4</sup> as follows:  $eGFR = 142 \times \min(Scr/k, 1) \times \max(Scr/k, 1) - 1.2 \times 0.9938Age \times 1.012$  [if female] where *k* is 0.7 for females and 0.9 for males,  $\alpha$  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).

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#### 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 be 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.

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