Bootstrap aggregation for modelling biomarkers' change across the preclinical stage of Alzheimer's disease

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Background

Whether plasma biomarkers steadily increase during the preclinical stage of Alzheimer's disease (AD) is unknown. Herein, we aimed to determine the rate-of-change of plasma biomarkers throughout preclinical AD. This may be important to determine the optimal time window for treatment.

Methods

We included baseline and follow-up plasma biomarkers measurements (follow-up: 3.37±0.40 years) of 240 cognitively unimpaired participants of the ALFA+ cohort (mean age: 60.75±4.85 years). Plasma Aβ40, Aβ42, GFAP and NfL were measured with the Simoa N4PE Advantage Kit, and plasma p-tau231 with a Simoa-validated in-house assay.For each participant we calculated the difference between follow-up and baseline levels, and corrected for sex, time between measurements, and age. We computed z-scores from the corrected values, and we applied a bootstrapped regression approach to model the rate-of-change of each plasma biomarker as a function of baseline age or Aβ PET centiloids (CL).

Moreover, we also computed the plasma biomarkers rate-of-change in three stages of preclinical AD: (I) CSF/PET Aβ-negative group, (II) CSF Aβ-positive/PET Aβ-negative (CL < 30), and (III) CSF/PET Aβ-positive. Significance was determined if the 95% confidence interval of the rate-of-change did not overlap with zero.

Results

Significant acceleration in the rate-of-change of plasma GFAP was observed with ageing, becoming significant at 60 years. There was also a significant accelerated change of p-tau231 from 55 to 68 years. Plasma NfL was the only biomarker whose rate-of-change accelerated with Aβ accumulation, and that rate became significant at 40 CL. Consistently, we observed a significant acceleration of plasma NfL when there was overt Aβ pathology (CSF/PET Aβ-positive group). The rest of plasma biomarker rates-of-change did not significantly increase, some were even deaccelerating (plasma Aβ42/40 and p-tau231), as Aβ accumulated.

Conclusion

Plasma biomarkers rate-of-change throughout the preclinical AD continuum differ. Plasma NfL rate-of-change accelerates in the later stage of preclinical AD, when overt Aβ pathology is present. The deceleration on the rate-of-change of plasma Aβ42/40 and p-tau231 may explain why their early increase in the preclinical AD continuum tends to plateau in later stages.