Publishable Summary

In this deliverable, we report the final progress of the disease modeling activities of the AMYPAD Prognostic and Natural History (PNHS) study. The AMYPAD PNHS dataset is a combination of prospective and historical data from 17 European sites in Belgium, France, Germany, Spain, Sweden, Switzerland, The Netherlands, and The United Kingdom. These sites have provided information through 11 parent cohorts, including EPAD LCS, EMIF-AD (60++ and 90+), ALFA+, FACEHBI, FPACK, UCL-2010-412, Microbiota, H70, DELCODE, and AMYPAD Diagnostic and Patient Management Study (DPMS).

The integration and harmonization of all these data sources resulted in the largest European dataset phenotyping longitudinally individuals at risk of AD-related progression. At the end of the project, the data set consists of ~9700 observations from 3350 subjects, ~1600 with baseline amyloid PET, and about 940 of them having at least one follow-up scan. All this information is organized into 614 variables, grouped into 68 concepts, and 13 domains (such as demographics, family history, genetics, vital signs, medical history, neuropsychological questionnaires, lifestyle, CSF, PET, and MRI). The first stable internal (i.e., within the AMYPAD consortium) release of the dataset is expected by the end of October 2022. Nevertheless, preliminary results are already obtained using this dataset and have been presented at international scientific conferences. In short, analyses reported in this document allow for the following observations:

- In the recruitment of participants, the enrollment of healthy volunteers may benefit most from the thorough provision of information concerning the (low) risks of the amyloid PET scan whereas enrollment in clinical settings may benefit more from the implementation of engagement strategies.
- Higher baseline CL was associated with lower performance and steeper decline over time for global cognitive functioning, memory performance, and attention coding.
- Semi- and fully-quantitative PET measures seem to perform similarly in predicting cognitive decline in preclinical AD.
- Preliminary findings suggest that subjective measures of sleep-in adults with mild cognitive impairment (MCI) should be interpreted with caution and complemented with objective methods.
- MRI-derived measurements of volume and cortical thickness had limited added value to that of plasma biomarkers in the prediction of Aβ positivity.
- Preliminary results suggest that AD CSF biomarkers associate differently with cognitive performance in cognitively unimpaired women and men, which can be informing of differences in disease pathogenesis.

- The associations between amyloid-β, tau, neurodegeneration, and cognitive decline are minimally affected by (genetic) confounding.
- A continuous measure of amyloid CSF/PET imbalance might hold meaningful information on baseline characteristics and heterogeneous cognitive trajectories from the early stages of AD.
- Cross-sectional analysis showed that amyloid burden was associated with functional outcomes, measured by Clinical Dementia Rating (CDR) sum-of-boxes and the Instrumental Activity of Daily Living (IADL) scores.
- Cortical amyloid deposition, as measured with amyloid PET, is a meaningful predictor of future brain atrophy.
- There is an increase in Aβ burden in APOE ε4 carriers compared to non-carriers, but with a similar pattern of Aβ accumulation in the function of age.

The presented modeling work will provide valuable insight into the best practices for modeling amyloid PET measurements accurately in the preclinical Alzheimer's Disease population, which can support current and future clinical trial designs and possibly provide guidance on enrichment strategies. Efforts shown in this deliverable have been done in close collaboration with the WP2 team.

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