The AMYPAD Prognostic and Natural History Study (PNHS): amyloid-PET predicts cognitive functioning in a pre-dementia population

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Background

The Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) PNHS study aims to determine the added value of amyloid-PET imaging in predicting changes in cognitive functioning in a population before dementia. In addition, demographics such as age, sex, APOE-ε4 carriership, and level of education are widely used predictors for cognitive decline. However, their (potentially complex) interactions in early disease stages are less understood. Previous literature underlines the importance of sensitive cognitive outcomes (1,2) and consideration of potential interaction effects, particularly for sex and education (3). A more detailed understanding of the combined predictive value of these factors is paramount to understand AD progression and to provide supporting guidelines for clinical trial design in the pre-dementia AD population.

Aim

Determine the additive value of amyloid-PET quantification in combination with established risk factors in predicting cognitive decline in all domains.

Methods (1)

The AMYPAD PNHS

The AMYPAD PNHS has build a well-phenotyped longitudinal European cohort of non-demented participants of ≥ 50 years of age from 11 parent cohorts (EPAD-LCS, ALFA+, FACEHBI, EMIF-AD (60++ and 90+), FPACK, UCL-2010-412, DELCODE, AMYPAD-DPMS, H70, and Microbiota) across 8 countries (Belgium, France, Germany, Netherlands, Spain, Sweden, Switzerland, and United Kingdom). At this moment, the clinical data and amyloid PET quantification for 1044 participants has been integrated in the AMYPAD PNHS data-platform (***top figure***).

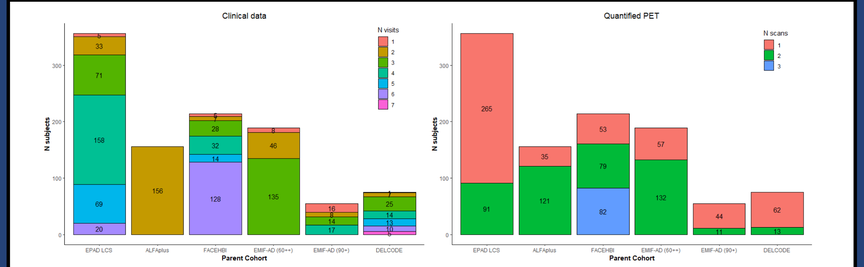
Amyloid PET-imaging

All participants were scanned with either [^{18}F]flutemetamol or [^{18}F]florbetaben. Scans were quantified as Centiloid (CL) values by IXICO, with the whole cerebellum as reference region. Based on CL, subjects were grouped into Aβ *negative* (CL≤12), *grey-zone* (12<CL≤50) or *positive* (CL>50).

Neuropsychological assessment

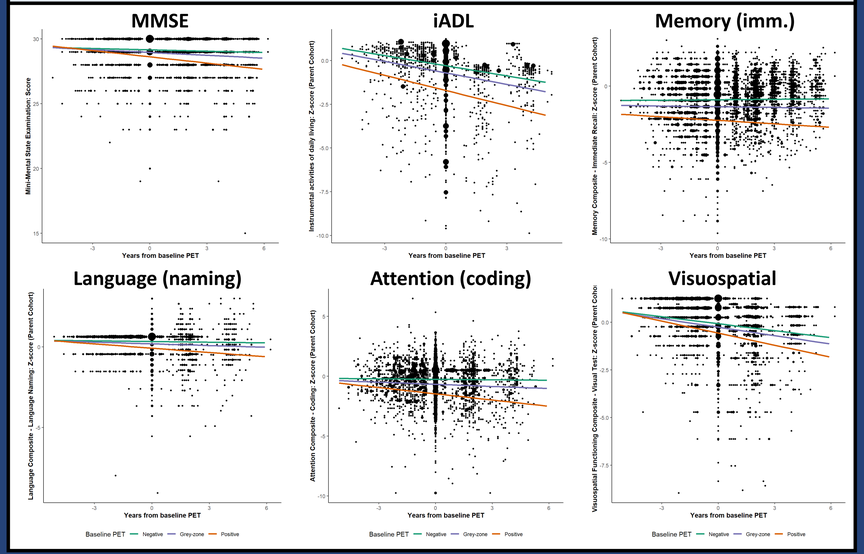
All subjects underwent standardized neuropsychological testing across cognitive domains (global, memory, language, visuospatial function, and attention). Scores were converted to Z-scores based on a cohort-specific reference-group (i.e., <65 years of age, *APOE*-ε4 non-carriers, Aβ *negative* based on CL and MMSE > 28).

The AMYPAD PNHS integrated database



	Aβ-	Aβ grey-zone	Aβ+	Total
Sample size	650	267	127	1044
Age (mean±sd)	67 ± 8	70 ± 9	76 ± 9	69 ± 9
Sex (male)	224 (39%)	110 (46%)	61 (50%)	395 (42%)
APOE-ε4 (0)	431 (75%)	136 (58%)	46 (39%)	613 (66%)
APOE-ε4 (1)	128 (22%)	90 (38%)	59 (49%)	277 (30%)
APOE-ε4 (2)	16 (3%)	9 (4%)	14 (12%)	39 (4%)
CDR (0)	511 (91%)	200 (86%)	82 (68%)	793 (86%)
CDR (0.5)	53 (9%)	33 (14%)	38 (32%)	122 (14%)

Amyloid burden predicts cognitive decline across domains



Methods (2)

Statistical analysis:

- Gaussian Mixture Modeling was applied to assess the Centiloid distribution for the Aβ *negative*, *grey-zone,* and *positive* groups (***middle figure***).
- A Linear Mixed Effects (LME) modeling framework were used with Z-score of cognitive performance as **dependent variable.** Global CL baseline (BL), time, global CL BL*time, and BL composite cognitive performance were included as **independent variables.** Age at BL, sex, years of education, BL Clinical Dementia Rating scale (CDR), and number of *APOE*-ε4 alleles were included as **covariates.**

	MMSE	iADL	Memory (imm.)	Memory (del.)	Memory (recog.)	Memory (Visual)	Language naming	Attention (coding)	Visuo-spatial
Centiloid at BL	**-0.005**	**-0.008**	**-0.007**	-0.003	**-0.005**	**-0.006**	-0.002	**-0.005**	-0.002
Visit (years)	**-0.033**	**-0.191**	0.010	**0.034**	**-0.037**	**-0.075**	-0.012	-0.010	**-0.120**
CL at BL × time	**-0.002**	-0.001	**-0.001**	-0.001	-0.001	-0.001	**-0.001**	**-0.002**	-0.001
Sex (Female)	0.074	-0.095	**0.575**	**0.300**	**0.479**	**-0.302**	**-0.195**	0.207	0.107
Age at BL	**-0.022**	**-0.088**	**-0.082**	**-0.033**	**-0.043**	**-0.047**	**-0.026**	**-0.084**	**-0.038**
Education (years)	**0.039**	0.004	**0.032**	**0.027**	**0.037**	**0.031**	**0.038**	**0.076**	**0.053**
CDR at BL (0.5)	**-0.563**	**-1.250**	**-0.949**	-0.235	**-0.730**	-0.207	-0.042	**-0.770**	**-0.275**
APOE-ε4 (1)	**-0.146**	-0.052	-0.132	0.105	-0.071	0.030	0.032	-0.108	-0.071
APOE-ε4 (2)	0.185	-0.147	**-0.476**	-0.386	-0.100	0.037	-0.191	0.166	0.059
n subjects (observations)	896 (2801)	6134 (1379)	908 (3265)	908 (3264)	731 (2769)	782 (2405)	571 (1909)	693 (2242)	643 (2153)

Table shows the β-estimates of the LME modeling framework. **Bold** font indicates significance (p<0.05). MMSE = mini mental state examination, iADL = instrumental activities of daily living, imm./del./recog. = immediate/delayed/recognition.

Results

Amyloid burden predicts cognitive decline across domains

Higher CL at baseline was associated with a decline in global functioning (MMSE, iADL), memory and attention performance. In addition, amyloid burden overt-time was predictive of a decline in MMSE, memory, language, and attention. No significant relationships were observed for executive or visuospatial function (***see Table***).

Future Steps

Next steps include:

- Stratification for baseline Centiloid groups
- Stratification for sex
- Investigate interactions between demographic factors
- Use of non-linear models

Conclusion

Amyloid-PET quantification predicts cognitive decline across multiple domains in combination with established risk factors.

Academic partners barcelonaBeta BRAIN RESEARCH CENTRE · VUmc · VU University Medical Center Amsterdam · The University of Edinburgh Centre for Dementia Prevention · Université de Genève · UCL · Hôpitaux de Toulouse · Uniklinik Köln · Karolinska Institutet · Radboud umc · IXICO · SYNAPSE · Life Molecular Imaging

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