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

David Vállez García[1], Lyduine E Collij[1], Sophie E Mastenbroek[1], Isadora Lopes Alves[2], Juan Domingo Gispert[3], Frank Jessen[4], Pieter Jelle Visser[1], Anouk den Braber[1], Craig W Ritchie[5], Mercè Boada[6], Marta Marquié[6], Rik Vandenberghe[7], Emma Lucket[7], Michael Schöll[8], Giovanni B Frisoni[9], Bernard J Hanseeuw[10], Lisa Quenon[10], Christopher Buckley[11], Andrew W Stephens[12], Lisa Ford[13], Mark E Schmidt[13], Jean Georges[14], Anja Mett[11], Rossella Gismondi[12], Robin Wolz[15], Sylke Grootoonk[15], Richard Manber[15], Mahnaz Shekari[3], Gill Farrar[11] and Frederik Barkhof[1], *on behalf of the AMYPAD Consortium*

(1)Amsterdam UMC location VUmc, Amsterdam, Netherlands; (2)Brain Research Center, Amsterdam, Netherlands; (3)BarcelonaBeta Brain Research Center (BBRC), Barcelona, Spain; (4)German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; (5)University of Edinburgh, Edinburgh, United Kingdom; (6)Ace Alzheimer Center Barcelona, Barcelona, Spain; (7)University Hospital Leuven, Leuven, Belgium, (8)University of Gothenburg, Gothenburg, Sweden, (9)Geneva University Hospital, Geneva, Switzerland; (10)Cliniques Universitaires Saint-Luc, Brussels, Belgium; (11)GE Healthcare, Amersham, United Kingdom; (12)Life Molecular Imaging, Berlin, Germany; (13)Janssen Pharmaceutica, New Jersey, USA; (14)Alzheimer Europe, Luxembourg; (15)IXICO Plc, London, United Kingdom

Background

The prevention of symptomatic Alzheimer's disease (AD) is a major endeavor currently in the field, with the prevalence of subjects on the AD continuum (i.e., presence of amyloid-β [Aβ] pathology) being much higher than previously estimated. However, the knowledge on the extent to which Aβ pathology and its interaction with common risk factors (such as age, sex, APOE-ε4 carriership, or education) are related to disease progression is still limited, especially in the early stages.

In this context, the AMYPAD Prognostic and Natural History Study (PNHS) aims to evaluate the value of amyloid-PET for predicting AD-related disease progression in a population before the onset of dementia.

Aim of the study

Determine the added value of amyloid-PET quantification <u>in combination</u> with established risk factors in predicting cognitive decline across different cognitive domains

Methods (1)

The AMYPAD PNHS

A total of 1423 non-demented subjects were included from the well-phenotyped longitudinal AMYPAD PNHS dataset (version 202306, doi:10.5281/zenodo.8017084). This pan-European dataset integrates data from 17 sites across 11 Parent Cohorts (EPAD LCS, ALFA+, FACEHBI, EMIF-AD (60++ and 90+), FPACK, UCL-2010-412, DELCODE, AMYPAD-DPMS, and Microbiota) [***top figure***].

Amyloid PET-imaging

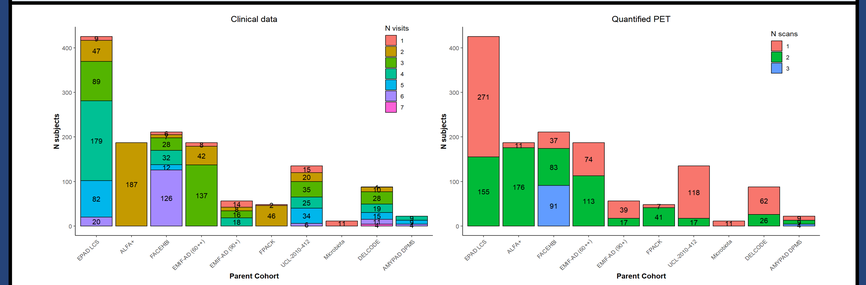
All participants were scanned at baseline with either [^{18}F]flutemetamol or [^{18}F]florbetaben amyloid-PET scans. After quality control, the scans were harmonized and quantified by IXICO using the Centiloid (CL) method, with the whole cerebellum as the reference region.

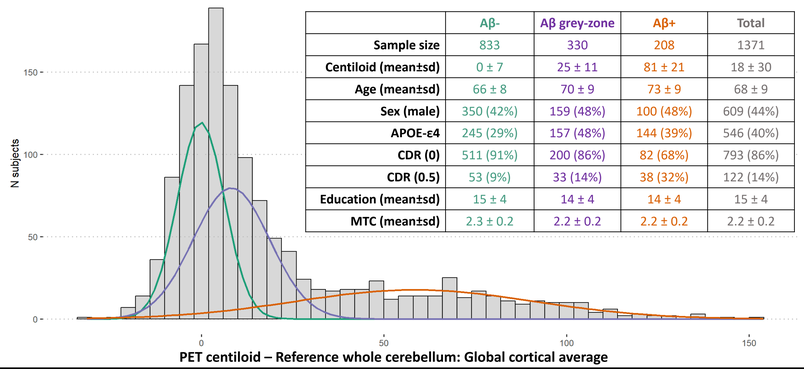
Neuropsychological assessment

All subjects underwent standardized neuropsychological testing across different cognitive domains: mini-mental state examination (MMSE), memory, attention, language fluency, visuospatial, and executive functions. The scores, except for MMSE, were standardized to *z-scores* based on cohort-specific reference-groups (i.e., <70 years of age, *APOE*-ε4 non-carriers, Aβ *negative* [CL < 12], cognitive normal [Clinical Dementia Rating Scale; CDR = 0], and MMSE > 28).

Finally, a modified Preclinical Alzheimer Cognitive Composite (mPCC) was calculated using the MMSE, delayed recall, and digit span forward questionnaires.

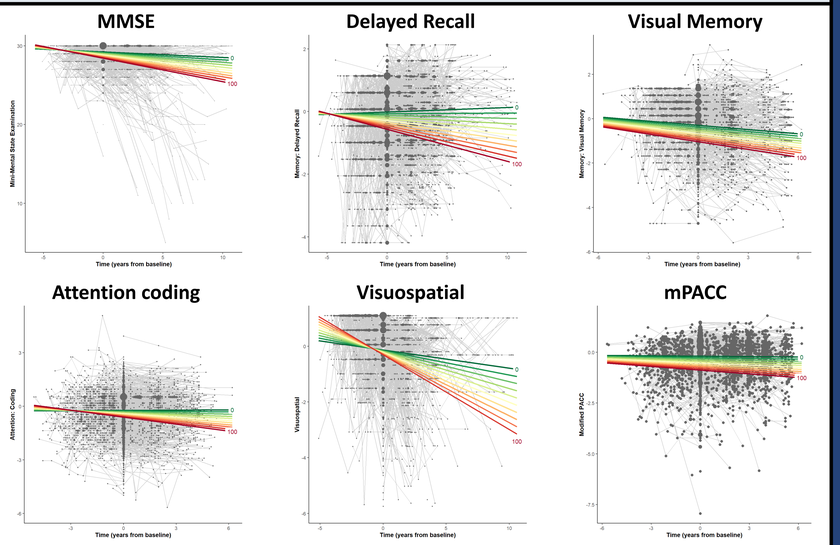
The AMYPAD PNHS database





	Aβ-	Aβ grey-zone	Aβ+	Total
Sample size	833	330	208	1371
Centiloid (mean±sd)	0 ± 7	25 ± 11	81 ± 21	18 ± 30
Age (mean±sd)	66 ± 8	70 ± 9	73 ± 9	68 ± 9
Sex (male)	350 (42%)	159 (48%)	100 (48%)	609 (44%)
APOE-ε4	245 (29%)	157 (48%)	144 (39%)	546 (40%)
CDR (0)	511 (91%)	200 (86%)	82 (68%)	793 (86%)
CDR (0.5)	53 (9%)	33 (14%)	38 (32%)	122 (14%)
Education (mean±sd)	15 ± 4	14 ± 4	14 ± 4	15 ± 4
MTC (mean±sd)	2.3 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2

Amyloid burden predicts cognitive decline across domains



The size of the dots represents the count on overlapping points, with subjects connected between visits by grey lines. Representative regression lines were included to the figures as an example of a reference subject only varying on its Centiloid value at baseline (female, 68 years age, APOE-ε4 non-carrier, CDR = 0, and 15 years of education).

Methods (2)

Statistical analysis:

- The Linear Mixed Effects (LME) modeling framework was used to assess the predictive value of baseline CL and its interaction with time (**predictors**) across the different cognitive domains (**outcomes**).
- Years from baseline, age, sex, years of education, cognitive dementia rating (CDR), APOE-ε4, and MTC (mediotemporal cortical volume, relative to whole brain)) were used as **covariates** in the model.

Results

Amyloid burden predicts cognitive decline across domains

- Baseline CL and its interaction with time were predictive of MMSE, memory, attention, and mPACC scores.
- In addition, the interaction of baseline CL with time, but not its main effect, was predictive of visuospatial function.
- Age, sex, education, and CDR were significant contributors to nearly all models. Contrarily, APOE-ε4 was found as non-significant in most of the models.

See figure and table below for details

	Mini-Mental State Examination	Memory: Immediate Recall	Memory: Delayed Recall	Memory: Visual Memory	Language: Fluency	Attention: Digit Span Forward	Attention: Coding	Executive: TMT B/A	Visuospatial	Modified PACC
Centiloid	-0.008	-0.006	-0.006	-0.007	-0.001	-0.001	-0.004	-0.004	-0.002	-0.007
Time	-0.069	-0.009	0.014	-0.063	-0.036	-0.008	0.005	0.054	-0.065	-0.007
Age	-0.024	-0.064	-0.031	-0.038	-0.047	-0.009	-0.059	0.014	-0.031	-0.025
Education	0.051	0.046	0.034	0.041	0.050	0.035	0.067	-0.049	0.059	0.037
MTC	0.368	0.676	0.854	1.440	0.593	-0.231	0.199	-1.276	0.154	0.403
CDR [0.5]	-1.377	-0.593	-0.767	-0.568	-0.343	-0.278	-0.488	0.208	0.036	-0.933
Sex [Female]	0.067	0.410	0.459	-0.220	0.215	-0.181	0.167	-0.408	-0.028	0.105
APOE-ε4 carrier	-0.093	-0.065	0.032	0.021	-0.060	-0.041	-0.165	0.474	0.005	-0.038
Centiloid × Time	-0.001	-0.001	-0.002	-0.001	-0.000	0.000	-0.001	0.000	-0.003	-0.001
(Centiloid × Time) × CDR [0.5]	-0.011	-0.001	-0.001	-0.001	-0.001	-0.000	-0.001	0.002	-0.001	-0.002
(Centiloid × Time) × Sex [Male] × APOE-ε4 non-carrier	-0.002	0.001	0.002	0.002	-0.000	-0.000	0.001	-0.002	-0.003	0.000
(Centiloid × Time) × Sex [Female] × APOE-ε4 non-carrier	-0.002	-0.000	0.000	0.001	-0.001	-0.001	-0.000	0.001	0.000	0.001
(Centiloid × Time) × Sex [Male] × APOE-ε4 carrier	0.000	-0.000	0.001	-0.000	-0.001	-0.001	0.001	-0.003	0.002	0.000

Table shows the β-estimates of the LME analysis. A **coloured** background indicates statistical significance (p<0.05)

Conclusion

Higher baseline CL was associated with lower cognitive performance in most of the explored domains, suggesting that emerging cerebral amyloid accumulation in non-demented individuals is predictive of overall cognitive function

Future Steps

- ❖ Explore other confounding factors
- ❖ Use of longitudinal PET outcomes
- ❖ Use of other biomarkers of AD disease

Academic partners · **SMEs** · **Industrial partners** · **Patient Organization**

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CONTACT
d.vallezgarcia@amsterdamumc.nl
l.collij@amsterdamumc.nl
www.amypad.eu