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Chapter 3

Recruitment for Alzheimer disease research

Chapter 3.1

European Prevention of Alzheimer Dementia (EPAD) Registry: recruitment and pre-screening approach for a longitudinal cohort and prevention trials.

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Abstract

BACKGROUND: It is a challenge to find participants for Alzheimer Disease (AD) prevention trials within a short period of time. The European Prevention of Alzheimer Dementia (EPAD) Registry aims to facilitate recruitment by preselecting subjects from ongoing cohort studies. This paper introduces this novel approach.

METHODS: A virtual registry, with access to risk factors and biomarkers for AD through minimal datasets of ongoing cohort studies, was set up.

RESULTS: To date, ten cohorts have been included in the EPAD Registry. Around 2500 participants have been selected, using variables associated with the risk for AD. Of these, 15% were already recruited in the EPAD longitudinal cohort study, which serves as a trial readiness cohort.

DISCUSSION: This study demonstrates that a virtual registry can be used for the preselection of participants for AD studies.

1 Introduction

1.1 Finding participants for secondary prevention of Alzheimer Disease

Finding participants for Alzheimer Disease (AD) trials is challenging [1]. This is particularly the case for studies with prodromal or preclinical AD participants, because these persons may not seek care for their problems and are unaware of the presence of amyloid pathology. An increasing number of AD trials aims to delay the onset of dementia in prodromal and preclinical AD. Traditional ad-hoc recruitment strategies, such as advertising in newspapers, result in a costly, labor-intensive and long recruitment process with many screen failures. Novel pre-selection and patient recruitment strategies are warranted. Online registries or the use of existing data sources may help to facilitate recruitment [2]. EPAD Registry makes use of existing data sources for recruitment in a virtual registry in order to speed up recruitment, reduce recruitment efforts, and reduce screen failures.

1.2 EPAD Registry as part of the EPAD project

The EPAD Registry is part of the European Prevention of Alzheimer Dementia (IMI-EPAD) project. This project is meant to create a platform for AD secondary prevention trials and to improve the understanding of the development of AD, by setting up the EPAD Registry, EPAD longitudinal cohort study (EPAD-LCS) and EPAD proof-of-concept trials (EPAD-PoC) [3]. The EPAD Registry was set-up to find participants without dementia for the EPAD-LCS. In the EPAD-LCS participants undergo longitudinal assessments of cerebral spinal fluid (CSF), blood, MRI, AD risk factors and cognition. The primary outcome is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The EPAD-LCS serves as the trial readiness cohort for EPAD-PoCs. The first EPAD-PoC is planned to start in 2018.

The EPAD Registry preselects participants from ongoing cohort studies and uses data from these cohorts for prescreening. The EPAD Registry involves several steps (figure 1). First the collaboration with an ongoing cohort study representative is established. Second a minimal dataset from the ongoing cohort study is created that can be queried in a software tool, called PREPAD. Potential participants are identified and invited for the EPAD-LCS by the EPAD study team. The results of these efforts are monitored.

2 Methods

2.1 Selection of and engagement with ongoing cohort studies

Cohorts that are selected for the EPAD Registry fulfil the following criteria: they are willing to provide participants for the EPAD-LCS, include participants without dementia over the age of 50, collected data suitable for prescreening, and have consent to contact their participants about the EPAD-LCS. In return the ongoing cohort studies will receive the data collected within the EPAD project for their participants. When interest is expressed by a cohort representative, cohort characteristics are collected online either in the European Medical Information Framework (EMIF) or Dementia Platform UK (DPUK) catalogues [4, 5]. Legal contracts are developed to cover interactions between cohorts and EPAD. These contracts cover the use of the virtual registry for EPAD purposes and receiving the EPAD data of their own participants.

2.2 Minimal dataset and PREPAD query platform

Each cohort is asked to provide a minimal dataset of variables that can be used to preselect participants with an increased risk for AD. The variables comprise age, gender, education, *apolipoprotein E ε4* (*APOE ε4*) genotype, family history of dementia, diagnosis of cognitive disorder, CSF biomarkers, MRI hippocampal atrophy, memory test scores, and baseline and longitudinal minimal mental state examination (MMSE) scores. At least 4 of the above variables are required. The minimal dataset of each cohort is harmonized. Cohort specific harmonisation rules are run with every update. Cohort representatives were supported by a small EPAD Registry workgroup consisting of software developers and AD-researchers. AD-researchers used mock files from each of the cohorts to define harmonisation rules and shared those with the developers supporting the harmonisation. The minimal dataset is uploaded on a regular basis to the PREPAD software tool. PREPAD was developed to search these minimal datasets. It was adapted from an existing data discovery platform to allow for querying federated datasets and allow complex queries [6]. To ensure participants remain anonymous in the EPAD Registry, a software called 'Deridiom' was created that generates 'Derivative IDs' (derIDs). Deridiom converts cohort local identification numbers to derIDs.

Searching participants with PREPAD involves a number of steps. First an algorithm is defined that aims to identify participants, according to the needs of the EPAD-LCS and EPAD-PoC. The algorithm is tailored for each cohort allowing

selection of participants in different risk-stages for AD. An algorithm can for example be a decreased memory score and age over 65. The search results in a list of derIDs. This list is provided to a cohort representative who converts derIDs into local IDs and selects participants to invite for EPAD-LCS screening.

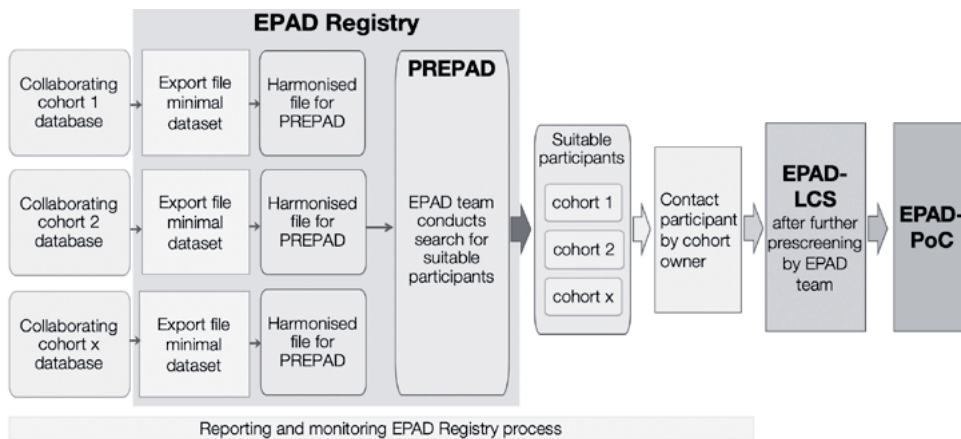


Figure 1 Schematic overview of data and participant flow in EPAD. Abbreviations: EPAD-LCS = EPAD longitudinal cohort study; EPAD-PoC = EPAD proof-of-concept trials

2.3 From EPAD Registry to EPAD-LCS and measuring recruitment rate

After participants have been selected via PREPAD, cohort representatives use local additional pre-screening information to decide whether a participant should be invited for EPAD-LCS screening. Next, a cohort representative approaches a potential participant. Dependent on local preferences and legislation, an opt-in letter is sent or a phone call is made to invite participants to one of the EPAD centres where screening activities and EPAD-LCS procedures will be conducted by the EPAD-LCS team. During the first contact by EPAD with a potential participant, usually by phone, in- and exclusion criteria are checked, such as the availability of a study partner. At each step, summary counts are collected of the number of participants in the process and predefined reasons for pre-screen failure such as contra-indication, no contact possible, in other study, unspecified reason, no interest of the participant, and prefer to invite later.

3 Results

3.1 Cohorts

Twenty cohorts representatives from 8 countries completed the first step, the questionnaire about cohort characteristics, each of them giving access to 100 to 500,000 potential participants. Ten cohorts from France, Italy, the Netherlands,

Sweden, Spain, Switzerland and the UK are currently formally signed-up to PREPAD, providing access to 17,500 potential participants aged over 50 and without dementia [7-13]. Incentives for cohorts to participate were: acquiring follow-up and biomarker measures in a subset of the cohort, scientific involvement in EPAD project, and providing clinical trial access for participants. In Table 1a the distribution according to diagnosis and age is presented. The variables available in each of the cohorts are shown in Table 1b. Memory clinic cohorts often have amyloid data available, and almost all cohorts have information on the *APOE* ε4 status. All cohorts have at least one parameter on cognitive status.

3.2 Recruitment for EPAD-LCS via EPAD Registry

As of the first of June 2017, 2433 participants of the EPAD Registry were pre-selected, of whom 75% were invited for EPAD-LCS screening by the team of the collaborating cohorts. The main reason for not contacting a participant was a known exclusion criterion. Most cohorts chose to contact participants by phone. Thus far around 15% of the subjects selected were suitable and agreed to undergo EPAD-LCS screening. This percentage may increase as more of the participants in the EPAD Registry will be considered for EPAD-LCS screening. Reasons of potential participants not entering EPAD-LCS screening are variable and partly dependent on collaborating cohort type. We will monitor uptake prospectively and report on this in detail once we have sufficient data available.

Table 1 Number of participants of existing cohorts in the EPAD Registry June 2017 by age group

Age	CN	SCI	MCI	Total
50-64	9,065	511	83	9,659
65-79	5,160	265	219	5,644
>= 80	845	9	182	1,036
All	15,070	785	484	16,339

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment, SCI, subjective cognitive impairment. NOTE. The 2433 participants already selected are not included in the table.

Table 2 Prescreening data available on participants in existing cohorts of EPAD Registry June 2017

Cohort characteristics	Population based			Memory clinic							Total
	Generation Scotland [8]	Pilot Amsterdam Registry	PREVENT [7]	ALFA [10]	GAP [13]	GEDOC [12]	ADC [9]	French Trial Registry [2]	ARWIBO [11]	Epinettes	
Country	UK	NL	UK	Spain	Spain	Sweden	NL	France	Italy	SW	NA
N over age of 50*	12,600	500	200	2,400	400	150	400	200	1,700	200	18,750
Population	Sample of general population	Online registration of volunteers	High percentage off-spring AD patients	High percentage off-spring AD patients	Advertisement recruited	Consecutive patients	Consecutive patients	Consecutive patients	Consecutive patients	Consecutive patients of a 1year period	NA
Relevant in- and exclusion criteria	Select additional family member	None	No cognitive decline due to other causes	No cognitive decline due to other causes, study partner	No cognitive decline due to other causes	No cognitive decline due to other causes	No cognitive decline due to other causes	Consent for Registration for EPAD-Registry	None	None	NA
Age ranges at inclusion	18+	18+	45-65	45-74	45-65	50+	50+	50+	50+	50+	NA
General and demographics											
Diagnosis											
CN	✓	✓	✓	✓	✓	-	-	✓	✓	✓	8
SCI	-	✓	-	✓	✓	✓	✓	✓	✓	✓	8
MCI and/or MCI due to AD	-	✓	-	-	✓	✓	✓	✓	✓	✓	7
Dementia	✓	✓	✓	-	✓	✓	-	-	✓	✓	7
Demographics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Visit dates	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10

Risk factors and biomarkers and cognitive tests											
APOE ε4	✓	s	✓	✓	✓	✓	✓	✓	-	✓	9
Family history of dementia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
CSF biomarkers	-	-	-	P	✓	✓	✓	✓	-	✓	5
Hippocampal atrophy	-	-	-	✓	✓	✓	✓	✓	-	✓	5
MMSE score	-	s	-	L	✓	✓	✓	✓	✓	✓	8
Memory test	WLM	Muistikko	Cognito	MBT	FCSRT	RAVLT	RAVLT	FCSRT	Babcock	FCSRT	10

Abbreviations: AD, Alzheimer disease; ADC, Amsterdam Dementia cohort; ALFA, for Alzheimer and Families project; APOE 34, apolipoprotein E 34; Babcock, Babcock short story memory test; CN, cognitively normal; Cognito, computerized test battery with narrative memory test and associative memory test; CSF, cerebrospinal fluid; EPAD, European Prevention of Alzheimer's Dementia; FCRST, Free Recall Selective Reminding Test (Grober-Buschke); GAP, Gipuzkoa Alzheimer Project; GEDOC, Clinical dementia research database Stockholm; Hippocampal atrophy, Medial temporal lobe score or volume corrected for intracranial volume; MBT, memory binding test; MCI, mild cognitive impairment; MMSE, minimal mental state examination; Muistikko, a web-based cognitive test battery; NL, The Netherlands; P, pending; PREVENT, cohort for mid-life biomarkers of late-onset AD; RALVT, Rey Auditory Verbal Learning Task; s, subset; SCI, subjective cognitive impairment; SW, Switzerland; UK, United Kingdom; WLM, Weschler logical memory test. NOTE. N* aged 50+, round to 50. NOTE. ✓, available; -, not available; ✓ L, 2 or more results available.

4 Discussion

The EPAD Registry provides a novel recruitment strategy. It is sufficiently flexible as we can adapt the screening algorithms to the type of data collected in a cohort and the type of participants needed for future EPAD-PoCs. The collaborating cohorts have different levels of information and draw on different populations. We chose not to define strict criteria for collaboration, but instead to use the data that are available within the cohorts. This approach leads to collaboration with more cohorts than would have been possible otherwise. However, a limitation is that risk estimates vary over cohorts. The efficacy of the approach will be monitored and reported on in the future. This includes the recruitment rate and the characteristics of population recruited, which can then be compared to other strategies. It may well be that this approach is particularly effective for specific populations of volunteers or patients. The adaptation of existing software led to a fast implementation. Plans for further development of the EPAD Registry functions entail extending PREPAD with other risk factors and inclusion of information on exclusion criteria. We also intend further automation of the harmonization process.

Our approach for recruitment and prescreening differs from those used in other studies and trials aimed at preventing disease progression in preclinical AD. Examples are the Early trial with a BACE-inhibitor from Janssen and another BACE inhibitor trial, the A4 study, that stepwise screen individuals from over 65 years old found via advertisements or a website. Additionally for the Early trial, persons between 60 and 64 that have an additional risk factor, being a positive family history for AD or being an *APOE* ϵ 4 allele carrier can be screened [14, 15]. The API-*APOE*4 trial from the Banner Institute pioneers with *APOE* genotyping as a screening method to find suitable trial participants [16]. The MOPEAD project is set up to formally test different recruitment and pre-screening strategies, including an online memory screening and recruitment via a diabetes mellitus outpatient clinic [17]. Another approach is to let potential participants register online individually. Registrants provide prescreening information, after which the platform matches them to ongoing studies. The Brain Health Registry is a leading example of this. All studies mentioned are ongoing and have not reported yet on the recruitment and the screen failure rate. When the EPAD-PoCs have started, the EPAD Registry approach can be evaluated in terms of trial participation. Combining insights from these various approaches has the potential to greatly improve our understanding of the best ways to find participants for preclinical AD trials in the near future. Our approach could be adapted for other projects in the AD field and beyond, or to find participants within projects, if a minimal dataset for prescreening is available.

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Declarations

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Prescreening for European Prevention of Alzheimer Dementia (EPAD) Trial-Ready Cohort: Impact of AD risk factors and recruitment settings

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Abstract

BACKGROUND: Recruitment is often a bottleneck in secondary prevention trials in Alzheimer disease (AD). Furthermore, screen-failure rates in these trials are typically high due to relatively low prevalence of AD pathology in individuals without dementia, especially among cognitively unimpaired. Prescreening on AD risk factors may facilitate recruitment, but the efficiency will depend on how these factors link to participation rates and AD pathology. We investigated whether common AD-related factors predict trial-ready cohort participation and amyloid status across different pre-screen settings.

METHODS: We monitored the prescreening in 4 cohorts linked to the European Prevention of Alzheimer Dementia (EPAD) Registry ($n=16,877$; mean \pm SD age=64 \pm 8 years). These included a clinical cohort, a research in-person cohort, a research online cohort, and a population-based cohort. Individuals were asked to participate in the EPAD longitudinal cohort study (EPAD-LCS), which serves as a trial-ready cohort for secondary prevention trials. Amyloid positivity was measured in cerebrospinal fluid as part of the EPAD-LCS assessment. We calculated participation rates and numbers needed-to-prescreen (NNPS) per participant that was amyloid-positive.

We tested if age, sex, education level, *APOE* status, family history for dementia, memory complaints or memory scores, previously collected in these cohorts, could predict participation and amyloid status.

RESULTS: 2,595 participants were contacted for participation in the EPAD-LCS. Participation rates varied by setting between 3% and 59%. The NNPS were 6.9 (clinical cohort), 7.5 (research in-person cohort), 8.4 (research online cohort), and 88.5 (population-based cohort). Participation in the EPAD-LCS (n=413 (16%)) was associated with lower age (odds ratio (OR) age = 0.97 [0.95-0.99]), high education (OR=1.64 [1.23-2.17]), male sex (OR=1.56 [1.19-2.04]), and positive family history of dementia (OR=1.66 [1.19-2.31]). Among participants in the EPAD-LCS, amyloid positivity (33%) was associated with higher age (OR=1.06 [1.02-1.10]) and *APOE* $\epsilon 4$ allele carriership (OR=2.99 [1.81-4.94]). These results were similar across prescreen settings.

CONCLUSIONS: Numbers needed-to-prescreen varied greatly between settings. Understanding how common AD risk factors link to study participation and amyloid positivity is informative for recruitment strategy of studies on secondary prevention of AD.

1 Background

Recruitment of participants for secondary prevention trials in Alzheimer Disease (AD) is challenging, which can cause substantial delays in study completion [1, 2]. The target population for these types of clinical trials typically comprises of individuals without signs of dementia, and with evidence of amyloid pathology [3]. Clinical trial screening of these mildly symptomatic or asymptomatic participants is accompanied by large numbers of screen failures [1]. The solution may be to introduce low-burden prescreening steps, which would limit the screening efforts to individuals with an increased prospect of enrolment into the study [4-7]. However, there is little empirical evidence on prescreening for secondary prevention trials and whether the efficacy depends on recruitment setting [8-11].

The European Prevention of Alzheimer Dementia (EPAD) Registry was set up as a virtual registry from existing cohorts [12]. The purpose was to enable recruitment and preselection of individuals for participation in the EPAD longitudinal cohort study (EPAD-LCS) [13], which also serves as a trial-ready cohort for the EPAD secondary prevention trials [14]. Data on several AD-related factors were available in these existing cohorts, including age, sex, education, *APOE* genotype, family history of dementia, subjective cognitive decline (SCD), and memory tests, as well as on common exclusion criteria. Furthermore, unlike in most trials, where a participant contacts a site following advertisements, in EPAD, researchers invited participants from the cohorts in the EPAD Registry into the EPAD-LCS. This approach allowed for investigation of how AD risk factors related to the participation rate, an important consideration for the feasibility assessment of

recruitment strategies. The recruitment settings linked to the registry include memory clinics, online and in-person brain research cohorts, and population-based cohorts, thereby offering the opportunity to compare them. We assessed participation rates across different recruitment settings, and provide a number needed-to-prescreen (NNPS) to identify one eligible and amyloid-positive individual. We also tested the AD-related factors as predictors for participation in the EPAD-LCS and for amyloid positivity.

2. Methods

2.1 Population

The analysis included participants from the first four cohorts that were linked to the EPAD Registry. The French Trial Registry in Toulouse selected patients referred by GPs and self-referral from memory clinics [15]. Inclusion criteria were: interest in clinical trials, available study partner and no obvious exclusion criteria for clinical trials. Data from 195 participants without dementia, with visits between July 2016 and February 2018, had been linked to the EPAD Registry. The ALFA Study included cognitively unimpaired individuals who expressed interest in participating in AD research and data of 2,595 participants aged over 50 years, with first visits in 2013 and 2014, were linked to the EPAD Registry [16]. Generation Scotland (GS) was a population-based study which collected data between 2006 and 2011 in Scotland on randomly drawn individuals with a relative to co-enrol [17]. Its aim was to create a resource of human biological samples and information for medical research, and data on 13,681 participants aged over 50 years, without a known diagnosis of dementia, were linked to the EPAD Registry. The pilot 'hersenenonderzoek.nl' (pilotHO.nl) was a web-based registry with the aim of recruiting people from the general public for brain research and ran from Sept 2016 to Sept 2017 when the final version of the registry was launched. This pilot registry had 412 participants, age over 50 years and without a self-reported diagnosis of dementia, linked to the EPAD Registry.

2.2 EPAD Registry selection and prescreening process

The enrolment process for the EPAD-LCS consisted of 4 steps. In step 1, participants were preselected from the 4 cohorts using algorithms in the EPAD Registry online tool [18], based on different combinations of age, sex, diagnosis of mild cognitive impairment (MCI), *APOE* genotype, SCD, memory test scores, and/or family history for dementia, available in the parent cohort (Table 1). Flexible algorithms were tailored to each of the cohorts, and adjusted if the number of individuals meeting the algorithmic criteria was low. The algorithms selected individuals older than 50 years across an AD dementia risk spectrum [13]. These included those with low and medium risk for AD to reach the recruitment targets for the study, as well as to avoid AD risk status disclosure by invitation. In step 2, the cohorts' investigators checked eligibility of selected individuals, using data from their databases. These criteria included the EPAD in-

and exclusion criteria, which involve absence of disorders that could interfere with trial participation, absence of dementia, and openness to potentially participate in intervention studies and receive disclosure [13]. In three of the cohorts, preselected individuals were then approached by telephone for participation. The population-based cohort GS sent an opt-in letter. In step 3, the EPAD sites performed a telephone screen to check eligibility amongst those who expressed interest in participating. Prescreen failures during the first 3 steps were categorized as: ‘matching an exclusion criterion’, ‘no interest in participation in the study’, ‘not returning the opt-in letter’, ‘other reason, not specified’ [12]. In step 4, participants visited a site and enrolled in the EPAD-LCS for a screening/baseline visit, after which eligibility was confirmed and amyloid status was determined [13].

2.3 Data collected as part of the EPAD-LCS

From the EPAD-LCS baseline visit we used, clinical information, i.e., the CDR sum of boxes (CDR-SOB) and Mini-Mental State Examination (MMSE); structural MR imaging visual rating scales, i.e., the medial-temporal atrophy scale (MTA) mean score and Fazekas deep score of white matter hyperintensities. From the cerebrospinal fluid (CSF) analysis, we used Elecsys $A\beta_{42}$, total tau, and phosphorylated tau values, and from the blood analyses, for some participants, *APOE* $\epsilon 4$ genotype. For a full description of the EPAD-LCS protocols, we refer to [13].

2.4 Predictors

The predictors as collected in the cohorts linked to the Registry were: age, sex, education level (low to normal or high), *APOE* genotype ($\epsilon 4$ non-carrier or carrier), presence of family history for dementia, presence of SCD, and a low score on a delayed recall memory test (z-score < -1.28, details on definitions of variables Supplement, legend Table 1). All cohorts had data available on demographics. SCD data was present in all cohorts, except GS. *APOE* genotype was available in the ALFA Study, GS, and a subset of pilotHO.nl. Family history and memory test scores were available for all participants of the ALFA Study and GS, and for the majority in the Toulouse Registry and pilotHO.nl. The definitions of the predictors were as follows: high education was 14 years or more in Toulouse Registry, the ALFA Study, and GS, and in pilotHO.nl a score of 6 or more on the Verhage scale, equivalent to college or university level [19]. Subjective cognitive decline: presence of memory complaints in the absence of impairment on cognitive tests (Toulouse Registry); a positive answer on the question whether the participant memory had complaints (ALFA study), a positive answer on the questions whether the participant memory had complaints and worries about their memory (pilotHO). Low memory delayed recall z-score < -1.28 on the FCSRT delayed recall (Toulouse), the memory binding test (ALFA study), the Wechsler logical memory - delayed recall (GS), and the Muistikko-test (pilotHO).

2.5 Outcomes

The first outcome measure was enrolment into the EPAD-LCS, indicating participation in a screening/baseline visit. The second outcome was amyloid positivity, defined as CSF A β_{42} below 1098 pg/mL [20-22], for participants who completed and passed the eligibility checks of the EPAD-LCS screening visit.

2.6 Statistical analysis

Participation rate was defined as the percentage of individuals who underwent the EPAD-LCS screening visit out of the individuals approached for participation in the EPAD-LCS. The NNPS was defined as the ratio between the number of individuals contacted for participation and the number of individuals that passed baseline visit classified as amyloid positive. The number needed-to-screen (NNS) was the ratio between the number of individuals with baseline data and the number of individuals that passed screening visit who were classified as amyloid positive. To test the association between AD risk factors (predictors) and participation into the EPAD-LCS, and among those enrolled, between AD risk factors and amyloid positivity, we applied univariate logistic mixed models with a random term for cohort and fixed term for the predictor. Age was centered at 65. Explorative analyses included analyses stratified now by cohort using univariate logistic regression models. Additionally, as a second step, all significant predictors for either of the two outcomes were combined in two final multivariate models to summarize the results. Statistical analyses were performed in R version 3.4.2, using packages 'lme4' and 'lmerTest' [23, 24].

3 Results

The four cohorts linked to the EPAD Registry included 16,877 participants. The participants were on average 64 (SD=8) years old and 39% were male, and expected amyloid positivity was calculated to be 19% based on a published meta-analysis [4] (Table 1). Figure 1 and Table 2 describe the recruitment flow of participants to enrolment and amyloid measurement in the EPAD-LCS between May 2016 and March 2018. Table 3 presents clinical, imaging and CSF markers of the EPAD-LCS baseline visit for participants recruited from each of the cohorts, stratified by amyloid status.

From the EPAD Registry, 3009 individuals were preselected for participation in the EPAD-LCS and 2,595 individuals were contacted, of whom 413 (16%) agreed to participate and were eligible for the EPAD-LCS screening visit. To prevent contacting individuals matching exclusion criteria for the EPAD-LCS, most cohorts conducted a database check. This was most efficient in the Toulouse registry (100%). Of individuals with exclusion criteria in the ALFA Study 75% (110/147), and in pilotHO.nl 55% (24/53) were found during the database check. Participation rate varied by setting; in the Toulouse Registry it was 59%, in the ALFA Study 56%, in GS 3%, and in pilotHO.nl 46%. The primary reasons for not participating were not returning the opt-in leaflet (67%), no interest (16%), and other reasons (13%). Of the 324 participants who had passed the eligibility checks during EPAD-LCS screening visit and had their amyloid

status available, 107 (33%) participants were amyloid positive. The total number of amyloid-positive individuals was similar between cohorts (Toulouse Registry n=23, ALFA Study n=36, GS n=22, pilotHO.nl n=26). However, the NNPS to find one eligible amyloid-positive participant varied; in the Toulouse Registry it was 6.9, in the ALFA Study 7.5, in GS 8.5, and in pilotHO.nl 8.4. Among individuals enrolled in the EPAD-LCS, the NNS in order to find one amyloid-positive individual passing the screening visit was between 3.0 and 3.8 in all settings (Table 2).

Table 1 Baseline available data and characteristics of cohorts

	Toulouse Registry	ALFA	Generation Scotland	pilotHO.nl
Setting	Memory clinic	In-person research cohort	Population-based	Online research cohort
N	195	2,589	13,681	412
Age, y	68 (7)	60 (6)	64 (9)	65 (9)
Male, n (%)	56 (29%)	962 (37%)	5399 (39%)	155 (38%)
Highly educated, n (%) (n= 15239) [*]	97 (60%)	1,225 (47%)	4,860 (40%)	313 (77%)
APOE ε4 genotype, n (%) (n= 16185)	NA	872 (34%)	3,695 (28%)	84 (31%)
Family history for dementia, n (%) (n= 16844)	131 (71%)	2,470 (95%)	1,386 (10%)	193 (50%)
Subjective cognitive decline, n (%) (n=3175) [^]	151 (83%)	312 (12%)	NA	81 (20%)
% low memory, n (%) (n= 16420) [§]	17 (15%)	242 (9%)	1,684 (12%)	20 (9%)
Diagnosed with MCI, n (%) [#]	13 (7%)	0	3 (0%)	4 (1%)
Estimated amyloid-positive individuals based on [4], taking into account age-bins, n (%)	~40 (22%)	~430 (17%)	~2680 (20%)	~80 (20%)

Legend: ^{*} high education: Toulouse Registry: ≥14 years; ALFA Study: ≥14 years; GS: ≥14 years; pilotHO.nl: ≥6 on the Verhage scale. [^] SCD: Toulouse Registry: physician diagnosis and MCI patients excluded; ALFA Study: memory complaints question; pilotHO.nl: questions on memory complaints with worries; [§] Low memory delayed recall z-score < -1.28: Toulouse Registry: FCSRT delayed recall, normalised by formula (score-11)/2, at raw score cut-off < 9; ALFA Study: memory binding test, normalised to sample, at raw score cut-off <18; GS: Wechsler logical memory - delayed recall was normalized, at raw score cut-off <9; pilotHO.nl: online Muistikko-test, normalized to sample, at raw score cut-off <9. [#] MCI: Toulouse Registry: physician diagnosis; pilotHO.nl: self-report.

Table 2 Recruitment flow from EPAD Registry by recruitment setting

		Cohorts				Total
		Toulouse Registry	ALFA Study	Generation Scotland	pilotHO.nl	
Setting		Memory clinic	In-person research cohort	Population-based	Online research cohort	
Step 1	Selection by PREPAD tool	169	618	1,947	275	3,009
Step 2	Not eligible	11	347	1	55	414
	• Exclusion criterion	10	110	1	29	150
	• Other	1	237	0	26	264
	Selected for step 3	158	271	1,946	220	2,595
Step 3	Not eligible	65	119	1,879	119	2,182
	• No interest	64	24	178	83	349
	• No response to letter	NA	NA	1,470	NA	1,470
	• Exclusion criterion	0	37	12	24	73
	• Other	1	58	219	12	290
	Eligible, selected for step 4	93	152	67	101	413
	• % from step 2	56%	25%	3%	37%	14%
	• % from step 3	59%	56%	3%	46%	16%
Step 4	EPAD-LCS screening visit	70	137	67	88	362
	Eligible & CSF A1-42 analyzed	64	124	61	75	324
	• CSF A1-42 < 1098 pg/mL(positivity)	23 (36%)	36 (29%)	22 (36%)	26 (35%)	107 (33%)
	Number needed-to-screen	3.0	3.8	3.0	3.4	3.4
	Number needed-to-prescreen	6.9	7.5	88.5	8.5	24.3

Legend: Number of individuals unless otherwise specified. EPAD-LCS v500 is the currently available data, quality checked at data lock. N=51 EPAD screening visit details not yet available. N=5 CSF results missing. N=32 screen failure: 11x other disease/incidental findings/CDR \geq 1, 18x procedures not possible, 3xinvestigator decision/no reason provided/no contact possible.

Table 3 Included participants in EPAD Longitudinal cohort study per recruitment setting

	Toulouse Registry		ALFA Study		Generation Scotland		pilotHO.nl	
	CSF A β +ve	CSF A β normal	CSF A β +ve	CSF A β normal	CSF A β +ve	CSF A β normal	CSF A β +ve	CSF A β normal
n	23	41	36	88	22	39	26	49
Age, y	71 (5)	67 (8) [^]	64 (6)	64 (5)	71 (3)	67 (5) [#]	68 (6)	66 (7)
Male, n (%)	4 (17%)	17 (41%)	23 (64%)	41 (47%)	14 (61%)	23 (57%)	14 (52%)	19 (37%)
MMSE (30-0)	28.0 (2.1)	28.8 (1.7)	28.6 (1.1)	28.7 (1.6)	28.1 (1.6)	28.8 (1.4)	28.4 (1.5)	29.1 (1.3)
CDR-SOB (0-18)	0.74 (0.7)	0.34 (0.5) [^]	0.10 (0.3)	0.05 (0.2)	0.15 (0.3)	0.06 (0.2)	0.06 (0.2)	0.02 (0.1)
CSF pTau ₄₂ , pg/mL	756 (195)	1613 (361) [#]	823 (191)	1696 (519) [#]	748 (251)	1769 (411) [#]	846 (217)	1788 (443) [#]
CSF pTau, pg/mL	29 (15)	18 (4.9) ^{\$}	21 (15)	17 (7)	19 (9)	21 (12)	21 (10)	17 (5)
CSF tTau, pg/mL	305 (125)	210 (53) ^{\$}	223 (132)	209 (79)	211 (81)	249 (115) [*]	240 (101)	206 (58)
MTA (0-4)	0.4 (0.5)	0.2 (0.4)	0.2 (0.4)	0.1 (0.3)	0.4 (0.6)	0.1 (0.4)	0.2 (0.4)	0.2 (0.4)
Fazekas (0-3)	1.1 (0.7)	0.8 (0.7)	1 (0.6)	0.8 (0.6)	1.1 (0.9)	0.7 (0.7) [^]	0.9 (0.8)	0.9 (0.7)

Legend: pTau = phosphorylated tau. tTau = total tau. MTA = medial temporal lobe atrophy. Mean (SD) unless otherwise specified. ^{*}one outlier at tTau 792 and p-tau 81. Undetectably low p-tau and tTau was set at the detection border of 8 and 80 respectively, abeta 1-42 was extrapolated. Raw p<0.05 = [^]; p<0.01 = ^{\$}, p<0.001 = [#].

Table 4 Univariate logistic regression for enrolment and CSF A β_{42} positivity in whole sample and stratified by recruitment setting

Total		Toulouse Registry		ALFA Study		Generation Scotland		pilotHO.nl	
Sample size	n=2,595	n=324	n=158	n=64	n=271	n=124	n=1,947	n=220	n=75
Outcome	Enrolment*	CSF A β +ve [^]	Enrolment*	CSF A β +ve [^]	Enrolment*	CSF A β +ve [^]	Enrolment*	CSF A β +ve [^]	CSF A β +ve [^]
Aged over 70 Years Old	0.97 (0.95-0.99)	1.06 (1.02-1.10)	0.99 (0.94-1.03)	1.10 (1.01-1.20)	0.99 (0.95-1.03)	1.01 (0.94-1.08)	0.97 (0.93-1.01)	0.96 (0.93-1.00)	1.03 (0.97-1.11)
Male	1.56 (1.19-2.04)	1.28 (0.81-2.04)	1.17 (0.58-2.42)	0.30 (0.08-0.96)	2.03 (1.24-3.35)	2.03 (0.92-4.60)	1.81 (1.11-3.01)	1.13 (0.66-1.94)	2.01 (0.77-5.36)
Highly Educated	1.64 (1.23-2.17)	0.89 (0.56-1.42)	1.44 (0.69-2.98)	0.72 (0.25-2.13)	1.42 (0.87-2.31)	1.10 (0.50-2.39)	2.20 (1.34-3.59)	1.33 (0.67-2.67)	0.75 (0.24-2.51)
APOE ϵ 4 Genotype	0.95 (0.70-1.28)	2.99 (1.81-4.94)	NA	6.42 (1.93-24.1)	0.68 (0.41-1.10)	1.72 (0.79-3.86)	1.37 (0.84-2.25)	0.92 (0.49-1.72)	3.34 (1.22-9.48)
Family history of Dementia	1.66 (1.19-2.31)	1.58 (0.83-3.00)	1.04 (0.50-2.15)	0.95 (0.31-2.98)	1.12 (0.38-3.23)	NA*	2.95 (1.73-4.91)	1.27 (0.73-2.22)	1.94 (0.68-6.09)
Subjective Cognitive Decline	0.86 (0.58-1.27)	1.51 (0.88-2.61)	0.29 (0.09-0.76)	2.93 (0.67-20.6)	0.79 (0.41-1.55)	1.15 (0.38-3.22)	NA	1.16 (0.62-2.15)	1.73 (0.62-4.79)
Low Memory Score	0.84 (0.60-1.17)	1.47 (0.82-2.61)	0.63 (0.21-1.87)	18.90 (2.87-377)	0.95 (0.56-1.64)	1.29 (0.55-2.96)	0.78 (0.44-1.31)	0.91 (0.29-2.83)	0.58 (0.03-4.98)

Odds ratio (95% CI); Bold is significant $p < 0.05$. * = Odds ratio for participating baseline/ screening visit after invitation; ^ = Odds ratio for amyloid positivity among those included in EPAD-LCS; # = infinite, not possible to calculate a value.

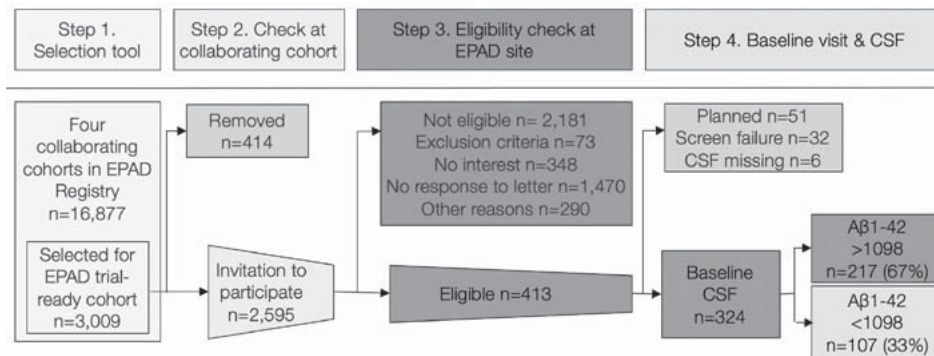


Figure 1 Prescreening to enrolment: flow from EPAD Registry to EPAD trial-ready cohort
Legend: CSF = cerebrospinal fluid; EPAD = European Prevention of Alzheimer Dementia.

3.1 Predictors for participation rate

The AD risk factors that were univariately associated with participation in the EPAD-LCS, for all cohorts combined, were lower age (odds ratio (OR): age=0.97 [0.95-0.99]), high education level (OR=1.64 [1.23-2.17]), male sex (OR=1.56 [1.19-2.04]) and family history of dementia (OR=1.66 [1.19-2.31], Table 4, for AUCs Table S2). In single cohorts, participation rates in the Toulouse Registry were predicted by SCD (OR=0.29; [0.09-0.76]), in the ALFA Study by male sex (OR=2.03 [1.24-3.35]), in GS by male sex (OR=1.81 [1.11-3.01]), high education (OR=2.20 [1.34-3.59]), and family history (OR=2.95 [1.73-4.91], and in pilotHO.nl by age (OR=0.96 [0.93-1.00]). As a next step, we combined the predictor variables age, sex, education, family history, and *APOE* in a multivariate model (Figure 2, Supplement Table S1 and S3). Study enrolment was still associated with age, sex, education and family history (n with all variables = 2322).

3.2 Predictors for amyloid positivity

Among all individuals enrolled in EPAD-LCS, amyloid positivity was univariately predicted by older age (OR= 1.06 [1.02-1.10]) and carrying an *APOE* ϵ 4 allele (OR=2.99 [1.81-4.94]) (Table 4, for AUCs Table S2). In individual cohorts, amyloid positivity in the Toulouse Registry was predicted by higher age (OR=1.10 [1.01-1.20]), gender (male OR=0.30 [0.08-0.96]), *APOE* ϵ 4 (OR=6.42 [1.93-24.1]), and low memory (OR=18.90 [2.87-377]), in the ALFA Study by none, in GS by higher age (OR=1.23 [1.08-1.45]) and *APOE* ϵ 4 (OR=7.20 [2.20-28.77]), and in pilotHO.nl by *APOE* ϵ 4 (OR=3.34 [1.22-9.48]). In the multivariate model, including predictor variables age, sex, education, family history, and *APOE*, amyloid status was predicted by age, *APOE* ϵ 4, and weakly by family history ($p=0.03$, n with all variables = 322, Figure 2, Supplement Table S1 and S3).

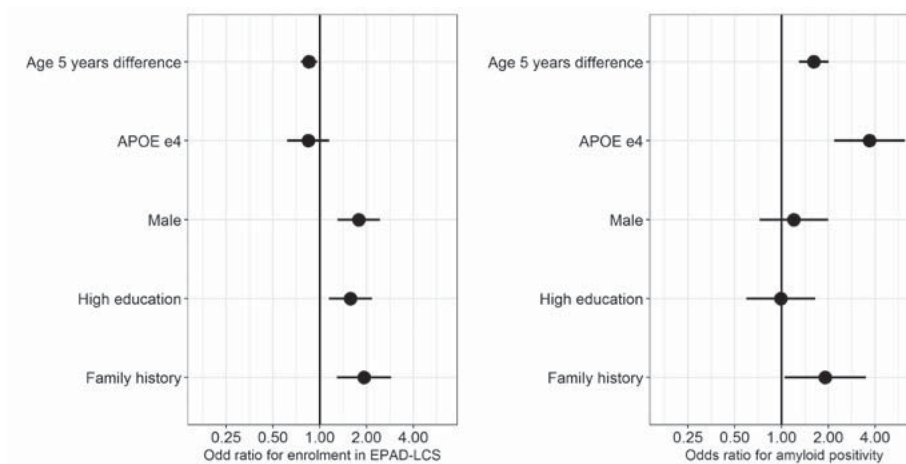


Figure 2 Multivariate model for enrolment and amyloid positivity
 Legend: EPAD-LCS = EPAD longitudinal cohort study (trial-ready cohort). *APOE* = Apolipoprotein E genotype.

4 Discussion

Across settings, participation rates varied, while predictors for participation into the trial-ready cohort and amyloid positivity were comparable. Among those contacted for participation, enrolment was higher for individuals who were younger, more educated, males or had a family history of dementia, while amyloid positivity in the trial-ready cohort was only associated with being older and carrying an *APOE* ε4 allele.

The NNPS to find one amyloid-positive eligible participant in the population-based Generation Scotland study was ten times higher than for those cohorts focused on brain disorders, which may be explained by their willingness to take part in an AD study [25]. Generation Scotland study visits have been completed, and the time between the last Generation Scotland study visit and EPAD recruitment was also longer than for the other cohorts. In addition, an opt-in letter was sent to Generation Scotland participants, while other cohorts contacted individuals by telephone, which may have lowered the response [26]. Moreover, the EPAD study site was at a travel time of 1-3 hours from the recruitment region. Finally, the cohorts from the other settings excluded persons with known exclusion criteria beforehand based on data from their cohort database, which may have decreased later stage prescreen failures. Still, the number of participants recruited of the large population-based Generation Scotland cohort were comparable to the bespoke cohorts, suggesting that there is scope and willingness within these type of cohorts to participate in dementia related intervention studies.

Lower participation at older ages, and higher participation for both highly educated participants and those with a family history of dementia is in line with studies with dementia patients and online registers [9, 10, 27-29]. Barriers for older individuals to participate may include morbidities, difficulties to travel, and not having a study partner. The higher participation rate of males was unexpected,

as many research studies have lower male than female participation [9, 10, 30, 31].

The predictors for amyloid positivity, i.e., age and *APOE*, were as expected and in line with previous studies, including an EPAD-LCS full dataset analysis [4, 6, 32, 33]. Low memory scores, in contrast, were only a significant predictor for amyloid positivity in the memory clinic cohort and the presence of SCD did not predict amyloid positivity in our sample. As low memory scores were the best predictor for amyloid positivity in the memory clinic setting, memory tests may form a useful prescreen in this situation. An explanation for the discrepancy with previously reported associations of these factors with amyloid status, could be the non-standardized test data, and could possibly show better predictive effects with the use of tailored sensitive tests and questionnaires [9, 11, 32, 34-37]

The prevalence of amyloid positivity in those enrolled in the EPAD-LCS was 33%. This prevalence was enriched around 1.5 times compared to the estimated prevalence in the whole cohorts based on a meta-analysis of prevalence in cognitively normal individuals [4]. The limited increase in prevalence of amyloid positivity could be explained by the fact that the variables available for prescreening each have a modest predictive accuracy for amyloid positivity [4, 6]. Another explanation is that low- and intermediate-risk individuals were selected from the cohorts in order to prevent risk disclosure by invitation and to have sufficient enrolment in the EPAD-LCS.

An advantage of our approach compared to other recruitment strategies such as media campaigns advertisement is that the use of existing data helped to exclude individuals with known exclusion criteria for secondary prevention trials. However, no direct comparison of efficiency relative to other prescreening strategies (e.g. advertising) could be made. A disadvantage of our approach is that consent to re-contact needs to be present in the cohorts and some costs are involved in the prescreening. In addition, cohorts become depleted, as shown for the smaller cohorts in our study. Future projects could involve direct comparisons between recruitment strategies and focus on cost and effort monitoring and comparison. Another important factor when recruiting from collaborating studies, as well as in the gathering of a 'trial ready cohort' is the aspect of time and cohort maintenance costs of both the recruitment cohorts and EPAD-LCS, but substantial. As AD is a progressive disorder, the time between testing in a parent cohort and time of selection may be important. Future work on the EPAD-LCS and similar projects needs to optimize the costs and efforts of maintaining a trial ready cohort. This should also involve monitoring the rate at which individuals become ineligible over time, for example because they develop comorbidities that are exclusion criteria.

A limitation is that the analyses were done with the risk factors available in each cohort, such that not all risk factors were available in all cohorts for all individuals. Also, the use of the available data and adaptation to local standard procedures meant that there was variability in the operationalization of variables. Secondly, algorithms for preselection in the EPAD Registry tool included predictor variables of the current study. Still, that is unlikely to influence the association between each of the risk factors and

participation rate as multivariate models yielded similar results. Additionally, cohorts were different from each other in more than one factor, such as sample size, population characteristics and communication style. Therefore differences in recruitment rate may be explained by several factors. Despite the differences, participation rate was associated with similar AD risk factors across cohorts. Finally, we have now studied the participation in a trial-ready cohort, but enrolment into an actual clinical trial might give different results, depending on study-specific in- and exclusion criteria and trial design [38]. Strengths of our study are the prospective prescreening and the large sample in which amyloid-testing was performed.

Our comparison of common AD risk factors for their association with participation rate and amyloid positivity has several implications for prescreening strategies for secondary prevention trials aimed at individuals with amyloid pathology. Age was a relatively strong predictor for amyloid positivity. However, we also showed that elderly individuals were less likely to participate in the study, which would limit the prescreening efficiency of age for amyloid positivity. Therefore, addressing barriers for older individuals to participate could increase recruitment of eligible participants [29, 39]. Carrying an *APOE* ϵ 4 allele was also a strong predictor of amyloid status but, as published before, the disadvantage is that around 40% of amyloid positive individuals are *APOE* ϵ 4 non-carriers [40]. The prevalence of *APOE* ϵ 4 positivity is around 20-30% and this may therefore not be optimal for prescreening in a small cohort. Disclosure of genotype could also be an issue [10, 41]. These limitations may be overcome by using a family history for dementia as a pre-screener. The advantage of this risk factor is the association with a greater enrolment rate, but the disadvantage is that its association with amyloid positivity is weak and the prevalence in the general population low. Subtle memory decline or concerns were not a useful prescreen for amyloid status in our study, but more specific tests or questionnaires may perform better [11, 42, 43]. A promising alternative may be blood tests for amyloid [5, 44, 45]. With a sensitive threshold, such a test has the advantage to more effectively prescreen relatively younger individuals, who often comprise a large part of a registry population and are more likely to participate, but have a low prevalence of amyloid pathology.

5 Conclusions

We found that enrolment rates show major differences between cohorts, although predictors for participation were similar. The provided NNPS to find one eligible amyloid-positive participant are indicators that future recruitment strategies can relate to. The findings highlight considerations of clinical trial investigators, balancing a gain in the ease of recruitment with potentially reducing the generalizability of the trial. Measures to increase efficiency for recruitment for secondary prevention trials may include using prospective registries with continuous enrolment of participants, adding a prescreening step with sensitive measures, such as a blood test, and addressing barriers for older and lower-educated individuals to participate.

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Declarations

Ethics approval and consent to participate: The EPAD-LCS (www.clinicaltrials.gov: NCT02804789) and the other cohorts were approved by the ethical review board in each country in which the study was performed, and all participants gave informed consent. The cohort studies had consent to contact participants for other research projects.

Consent for publication: Not applicable.

Availability of data and materials: The EPAD data used in this analysis will be made available on an open-access platform in due course. (www.ep-ad.org for updates).

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Supplemental data Chapter 3.2

Table S1 Multivariate logistic regression for enrolment and CSF A β 1-42 positivity in whole sample

Enrolment				CSF A β 1-42 positivity		
Sample size	N=2322			N=322		
Outcome	Univariate	Multivariate	Multivariate p-values	Univariate	Multivariate	Multivariate p-values
Age years	0.97 (0.95-0.99)	0.97 (0.95-0.99)	0.011	1.06 (1.02-1.10)	1.10 (1.05- 1.15)	<0.001
<i>APOE</i> ϵ 4 genotype	0.95 (0.70-1.28)	0.85 (0.62-1.15)	0.291	2.99 (1.81-4.94)	3.69 (2.18-6.24)	<0.001
Male	1.56 (1.19-2.04)	1.79 (1.31-2.45)	<0.001	1.28 (0.81-2.04)	1.20 (0.72-2.00)	0.476
Highly educated	1.64 (1.23-2.17)	1.58 (1.15-2.17)	0.005	0.89 (0.56-1.42)	0.99 (0.60-1.66)	0.977
Family history of dementia	1.66 (1.19-2.31)	1.93 (1.29-2.88)	0.001	1.58 (0.83-2.61)	1.91 (1.05-3.49)	0.034

Odds ratio (95% confidence intervals). CSF = cerebrospinal fluid. *APOE* = Apolipoprotein E gene. Shown effect sizes are: Age per 5 years older at baseline, *APOE* ϵ 4 in contrast to no *APOE* ϵ 4, male in contrast to female, highly educated in contrast to low or normal level educated, family history for dementia positive in contrast to family history for dementia reported.

Table S3 AUC on multivariate model figure 2

Cohort	Multivariate model figure 2	
	Enrolment (AUC)	Decreased CSF A β +ve [^] (AUC)
Toulouse Registry*	0.57 (0.47-0.67)	0.77 (0.65-0.89)
ALFA Study	0.62 (0.55-0.68)	0.66 (0.55-0.77)
Generation Scotland	0.70 (0.64-0.76)	0.88 (0.79-0.96)
pilotHO.nl	0.63 (0.54-0.71)	0.71 (0.58-0.84)

Models included: Multivariate AUCs calculated with pROC package in R of glm models (family=binominal, with DeLong confidence intervals). CSF = cerebrospinal fluid. Age at baseline, *APOE* ϵ 4 status, gender, highly educated in contrast to low or normal level educated, status on family history for dementia. * No *APOE* genotype included in enrolment analysis.

Table S2 AUC for binominal ROC curves of table 4

	Toulouse Registry		ALFA Study		Generation Scotland		plotHO.nl	
Sample size	n=158	n=64	n=271	n=124	n=1,947	n=61	n=220	n=75
Outcome	Enrolment*	CSF A β +ve ^	Enrolment*	CSF A β +ve ^	Enrolment*	CSF A β +ve ^	Enrolment*	CSF A β +ve ^
Age	0.54 (0.45-0.64)	0.69 (0.56-0.82)	0.49 (0.42-0.56)	0.52 (0.40-0.64)	0.55 (0.49-0.61)	0.74 (0.62-0.87)	0.58 (0.50-0.65)	0.57 (0.42-0.70)
Male or Female	0.48 (0.41-0.56)	0.62 (0.51-0.73)	0.59 (0.53-0.64)	0.59 (0.49-0.68)	0.58 (0.51-0.63)	0.54 (0.41-0.67)	0.48 (0.42-0.55)	0.60 (0.47-0.70)
Education level	0.46 (0.37-0.54)	0.54 (0.41-0.66)	0.46 (0.40-0.51)	0.51 (0.41-0.61)	0.41 (0.35-0.47)	0.56 (0.42-0.68)	0.48 (0.43-0.53)	0.53 (0.42-0.62)
APOE ϵ 4	NA	0.68 (0.56-0.79)	0.55 (0.49-0.61)	0.57 (0.47-0.66)	0.54 (0.48-0.60)	0.72 (0.60-0.83)	0.49 (0.42-0.56)	0.64 (0.52-0.75)
Yes/No Family history for Dementia	0.50 (0.42-0.57)	0.51 (0.39-0.63)	0.50 (0.47-0.52)	0.55 (0.52-0.58)	0.40 (0.36-0.46)	0.62 (0.49-0.75)	0.56 (0.41-0.54)	0.57 (0.46-0.68)
Yes/No Subjective Cognitive Decline	0.42 (0.36-0.48)	0.58 (0.48-0.67)	0.49 (0.44-0.53)	0.51 (0.44-0.58)	NA	NA	0.49 (0.43-0.54)	0.57 (0.45-0.67)
Yes/No Low Memory Score	0.54 (0.39-0.55)	0.76 (0.56-0.81)	0.50 (0.44-0.55)	0.53 (0.44-0.62)	0.47 (0.43-0.53)	0.50 (0.39-0.62)	0.50 (0.44-0.55)	0.52 (0.44-0.60)

CSF = cerebrospinal fluid. Univariate analysis AUCs calculated with pROC-package in R of glm models (family=binomial, with DeLong confidence intervals). EPAD-LCS = EPAD longitudinal cohort study (trial-ready cohort). APOE = Apolipoprotein E gene. Shown effect sizes are: Age per 5 years older at baseline, APOE ϵ 4 in contrast to no APOE ϵ 4 genotype, male in contrast to female, highly educated in contrast to low or normal level educated, family history for dementia positive in contrast to family history for dementia reported.