Received: 16 September 2021 | Revised: 11 March 2022 | Accepted: 29 April 2022

DOI: 10.1002/alz.12696

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Description of a European memory clinic cohort undergoing amyloid-PET: The AMYPAD Diagnostic and Patient Management Study

Daniele Altomare[1,2] | Lyduine Collij[3] | Camilla Caprioglio[1,2] | Philip Scheltens[4] | Bart N.M. van Berckel[3] | Isadora Lopes Alves[3] | Johannes Berkhof[5] | Yvonne de Gier[3] | Valentina Garibotto[6,7] | Christian Moro[1,2] | Léa Poitrine[1,2] | Julien Delrieu[8,9] | Pierre Payoux[10,11] | Laure Saint-Aubert[10,12] | José Luis Molinuevo[13,14] | Oriol Grau-Rivera[13,15,16] | Juan-Domingo Gispert[13,15,17] | Carolina Minguillón[13,15,16] | Karine Fauria[13,16] | Marta Felez Sanchez[13] | Andreea Rădoi[13] | Alexander Drzezga[18,19,20] | Frank Jessen[21] | Claus Escher[21] | Philip Zeyen[21] | Agneta Nordberg[22,23] | Irina Savitcheva[24] | Vesna Jelic[25] | Zuzana Walker[26,27] | Ho-Yun Lee[27] | Lean Lee[26] | Jean-François Demonet[28] | Sonia Plaza Wuthrich[28] | Rossella Gismondi[29] | Gill Farrar[30] | Frederik Barkhof[3,31] | Andrew W. Stephens[29] | Giovanni B. Frisoni[1,2] | on behalf of the AMYPAD Consortium

[1]Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva, Geneva, Switzerland

[2]Geneva Memory Center, Geneva University Hospitals, Geneva, Switzerland

[3]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers (UMC) – Location VUmc, Amsterdam, The Netherlands

[4]Alzheimer Center, Department of Neurology, Amsterdam University Medical Centers (UMC) – Location VUmc, Amsterdam, The Netherlands

[5]Department of Epidemiology and Data Science, Amsterdam University Medical Centers (UMC) – Location VUmc, Amsterdam, The Netherlands

[6]Laboratory of Neuroimaging and Innovative Molecular Tracers (NIMTlab), Geneva University Neurocenter and Faculty of Medicine, University of Geneva, Geneva, Switzerland

[7]Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospitals, Geneva, Switzerland

[8]Gérontopôle, Department of Geriatrics, Toulouse University Hospital, Toulouse, France

[9]Maintain Aging Research team, CERPOP, Inserm, Université Paul Sabatier, Toulouse, France

[10]Department of Nuclear Medicine, Toulouse University Hospital, Toulouse, France

[11]Toulouse NeuroImaging Center (ToNIC), Inserm, Université Paul Sabatier, Toulouse, France

[12]Toulouse NeuroImaging Center (ToNIC), Université de Toulouse, Inserm, Université Paul Sabatier, Toulouse, France

[13]Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain

[14]H. Lundbeck A/S, Copenhagen, Denmark

[15]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

[16]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain

[17]Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina, (CIBER-BBN), Barcelona, Spain

[18]Department of Nuclear Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Germany

[19]German Center for Neurodegenerative Diseases (DZNE), Bonn-Cologne, Germany

[20]Institute of Neuroscience and Medicine (INM-2), Molecular Organization of the Brain, Forschungszentrum Jülich, Germany

[21]Department of Psychiatry, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[22]Department of Neurobiology, Care Sciences and Society, Center of Alzheimer Research, Karolinska Institutet, Stockholm, Sweden

[23]Theme Aging, Karolinska University Hospital, Stockholm, Sweden

[24]Medical Radiation Physics and Nuclear Medicine, Section for Nuclear Medicine, Karolinska University Hospital, Stockholm, Sweden

[25]Cognitive Disorders Clinic, Theme Inflammation and Aging, Karolinska University Hospital-Huddinge, Stockholm, Sweden

[26]Division of Psychiatry, University College London, London, UK

[27]St. Margaret's Hospital, Essex Partnership University NHS Foundation Trust, Essex, UK

[28]Leenaards Memory Center, Lausanne University Hospital (CHUV), Lausanne, Switzerland

[29]Life Molecular Imaging, Berlin, Germany

[30]GE Healthcare, Amersham, UK

[31]Institutes of Neurology and Healthcare Engineering, UCL, London, UK

Correspondence
Daniele Altomare, Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva, Geneva, Switzerland; and Geneva Memory Center, Geneva University Hospitals, Geneva, Switzerland, Rue Gabrielle-Perret-Gentil 6, Geneva 1205, Switzerland.
Email: Daniele.Altomare@unige.ch

Funding information
The AMYPAD project is funded by the EU-EFPIA Innovative Medicines Initiatives 2 Joint Undertaking (IMI 2 JU), Grant/Award Number: 115952

Abstract

Introduction: AMYPAD Diagnostic and Patient Management Study (DPMS) aims to investigate the clinical utility and cost-effectiveness of amyloid-PET in Europe. Here we present participants' baseline features and discuss the representativeness of the cohort.

Methods: Participants with subjective cognitive decline plus (SCD+), mild cognitive impairment (MCI), or dementia were recruited in eight European memory clinics from April 16, 2018, to October 30, 2020, and randomized into three arms: ARM1, early amyloid-PET; ARM2, late amyloid-PET; and ARM3, free-choice.

Results: A total of 840 participants (244 SCD+, 341 MCI, and 255 dementia) were enrolled. Sociodemographic/clinical features did not differ significantly among recruiting memory clinics or with previously reported cohorts. The randomization assigned 35% of participants to ARM1, 32% to ARM2, and 33% to ARM3; cognitive stages were distributed equally across the arms.

Discussion: The features of AMYPAD-DPMS participants are as expected for a memory clinic population. This ensures the generalizability of future study results.

KEYWORDS
amyloid, Alzheimer's, dementia, memory clinic population, mild cognitive impairment, PET, subjective cognitive decline

1 | BACKGROUND

Amyloid deposition in the brain is one of the core and earliest neuropathological hallmarks of Alzheimer's disease (AD).[1] It can be assessed in vivo using positron emission tomography (PET) imaging.[2] Although several studies provided evidence of the diagnostic value of amyloid-PET in patients with suspected neurodegenerative diseases,[3–10] definitive evidence of its clinical utility in a memory clinic population is still lacking.[11] As a consequence, amyloid-PET is currently not (or only partially) reimbursed by health care payers. The AMYPAD Diagnostic and Patient Management Study (DPMS) is the largest European, multicenter, prospective, and randomized controlled study implementing amyloid-PET in clinical practice, and it aims to fill this gap by providing unique evidence on the clinical utility and cost-effectiveness of amyloid-PET in Europe.

The rationale and study design of AMYPAD-DPMS have been described in detail in a previous publication.[12] The study enrolled 840 participants with a balanced representation of cognitive stage groups with variable severity ranging from subjective cognitive decline plus (SCD+, a condition of self-experienced cognitive decline in absence of objectively confirmed cognitive impairment featuring increased likelihood of preclinical AD[13]) to mild cognitive impairment (MCI) and dementia. These participants underwent amyloid-PET scans (using 18F-Flutemetamol or 18F-Florbetaben as PET tracers) according to

their randomization into one of the three study-arms: ARM1, early amyloid-PET; ARM2, late amyloid-PET; or ARM3, free-choice amyloid-PET. The data collected during this study will constitute the largest and one of the best phenotyped memory clinic samples in Europe. This extensive database will be analyzed by different research groups within and outside the AMYPAD Consortium to answer a variety of research questions. It is therefore essential that the AMYPAD-DPMS sample is representative of a larger memory clinic population, ensuring the reliability and generalizability of its scientific outcomes.

The aim of this article is to discuss the implemented enrollment strategies and describe the baseline features of the AMYPAD-DPMS participants in order to assess whether our sample is representative of a wider memory clinic population and to ensure that the future study results will be reliable and generalizable.

RESEARCH IN CONTEXT

1. **Systematic Review**: Amyloid-PET (positron emission tomography) is currently not (or only partially) reimbursed by health care payers due to the lack of definitive evidence on its clinical utility and cost-effectiveness. The aim of AMYPAD Diagnostic and Patient Management Study (DPMS), the largest European study implementing amyloid-PET in clinical practice, is to fill this evidence gap. As a first step, we assessed whether the AMYPAD-DPMS sample is representative of a wider memory clinic population.
2. **Interpretation**: Our findings support the representativeness of the study sample to a wider European memory clinic population, indicating that the upcoming results of AMYPAD-DPMS will be generalizable.
3. **Future Directions**: The AMYPAD-DPMS data set will be analyzed by a number of research groups within and outside of the AMYPAD consortium in order to assess the clinical utility and cost-effectiveness of amyloid-PET, and to answer pre-specified and post hoc research questions.

2 | METHODS

2.1 | Participants

Inclusion and exclusion criteria have been described previously.[12] Briefly, the main inclusion criteria were: age between 60 and 85 for SCD+ and between 50 and 85 for MCI and dementia patients; the patient must have had a cognitive complaint considered by the managing physician to be possibly due to AD; the patient must have been entering a diagnostic workup including recent (not older than 12 months) magnetic resonance imaging (MRI) and/or computed tomography (CT) scan; and the managing physician must have felt that knowledge of the patient's brain amyloid status may increase diagnostic confidence and alter diagnosis and/or management. The main exclusion criterium was: the patient had a previous amyloid-PET and/or had other AD biomarker workup before screening. Although other inclusion/exclusion criteria of MCI and dementia were based on their respective clinical diagnostic criteria,[14,15] those of the SCD+ were based on a modified version of the SCD-I Working group criteria,[13] of which the most relevant features are age between 60 and 85 years, perceived decline in memory over time, SCD onset within the previous 5 years and duration >6 months, Mini-Mental State Examination (MMSE) score between 27 and 30, exclusion of MCI, explicit concerns (worries) about the cognitive symptoms, and active seeking of consultation.

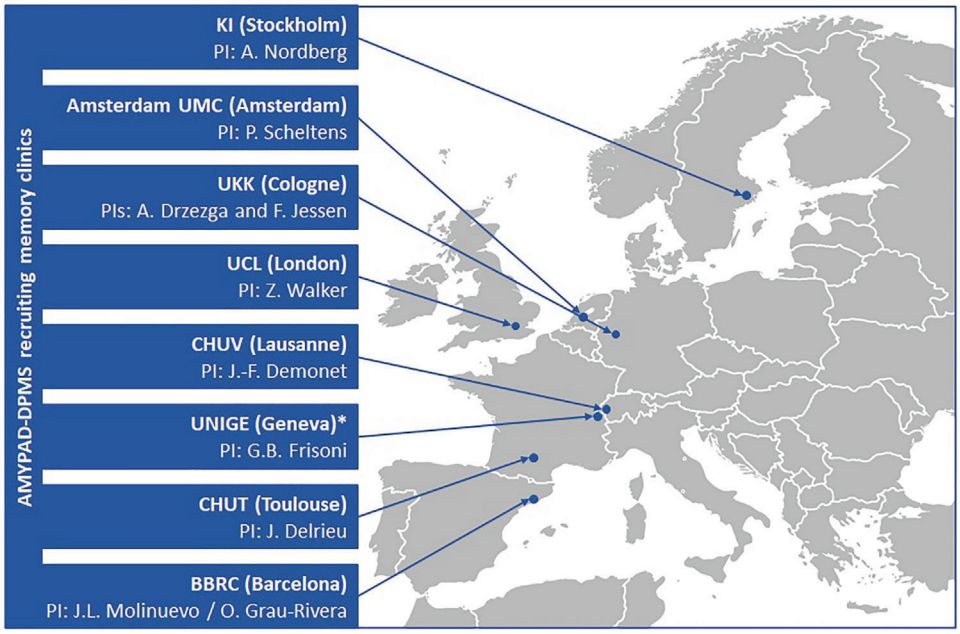
The assignment of cognitive stage (i.e., SCD+, MCI, and dementia) was based on local diagnostic workup and procedures. Indeed, the clinical and neuropsychological assessments were not standardized across recruiting memory clinics consistently with the AMYPAD-DPMS purpose of interfering as little as possible with the local practices and recruit participants representative of the clinical routine.

2.2 | Recruiting memory clinics

The eight recruiting memory clinics (Figure 1) were: (1) University and University Hospital of Geneva (UNIGE; Geneva, Switzerland), (2) Amsterdam University Medical Centers, location VUmc (Amsterdam UMC; Amsterdam, The Netherlands), (3) Centre Hospitalier Universitaire de Toulouse (CHUT; Toulouse, France), (4) Barcelonaβeta Brain Research Center (BBRC; Barcelona, Spain), (5) University of Cologne and Deutsches Zentrum für Neurodegenerative Erkrankungen (UKK; Cologne, Germany), (6) University College London (UCL; London, UK), (7) Karolinska Institutet and Karolinska University Hospital (KI; Stockholm, Sweden), and (8) Centre Hospitalier Universitaire Vaudois (CHUV; Lausanne, Switzerland). CHUV replaced the University of Edinburgh, which originally was one of the eight recruiting memory clinics but was unable to start recruitment due to scanning restrictions.

2.3 | Clinical assessment

A number of variables have been collected systematically during the study. Generic descriptive variables were collected only during the baseline visit. Global cognition (i.e., MMSE), and levels of anxiety and depression (i.e., Hospital Anxiety and Depression Scale [HADS]) were collected at baseline and after 6 and 13 months. Prescription of cognition specific and other medications was recorded at baseline and after 3, 6, and 13 months. Finally, cognitive stage (i.e., SCD+, MCI, or dementia), etiological diagnosis (i.e., AD, non-AD, or undetermined), diagnostic confidence (50%-100% visual numeric scale), use of medical resources, and patient management were collected for each patient at baseline and after 3, 6, and 13 months (and 18 months, only for ARM1, not mandatory).



* Sponsor of the study. PI, Principal Investigator; UNIGE, University and University Hospital of Geneva; Amsterdam UMC, Amsterdam University Medical Centers, location VUmc; CHUT, Centre Hospitalier Universitaire de Toulouse; BBRC, Barcelonaβeta Brain Research Center; UKK, University of Cologne and DZNE; UCL, University College London; KI, Karolinska Institutet and Karolinska University Hospital; CHUV, Centre Hospitalier Universitaire Vaudois

FIGURE 1 AMYPAD-DPMS recruiting memory clinics

Tools for assessing participants' generic health status and quality of life were: 5-level EuroQol 5 Dimensions (EQ-5D-5L),[16,17] ICEpop CAPability measure for Older people (ICECAP-O),[18,19] and Brief COPE[20–22] (see Supplementary Material for a detailed description of these tools); and were administered at baseline and after 6 and 13 months.

Finally, we retrospectively collected apolipoprotein E (*APOE*) genotype and CSF biomarker results, when available, even if they were not part of the study procedures. CSF biomarker results were based on local essays and cutoffs; no standardization was performed.

2.4 | Recruitment strategies

AMYPAD-DPMS enrollment was competitive. To maximize the recruitment strategies and represent non-academic memory clinics, three sites (Amsterdam UMC, CHUT, and UCL) extended the recruitment to external partnering sites. External sites affiliated with Amsterdam UMC were Medisch Centrum Alkmaar/Noordwest Ziekenhuisgroep (n = 21 participants enrolled), Reinier de Graaf groep (n = 5), Tergooi Ziekenhuis (n = 5), Antonius Ziekenhuis (n = 3), OLVG (n = 2), Diakonessen Ziekenhuis (n = 1), and Elisabeth Ziekenhuis (n = 1); those affiliated with CHUT were Geriatrics departments of Lavaur (n = 26) and Castres (n = 19) hospitals, and neurology department of Toulouse University Hospital (n = 6); finally, all UCL participants (n = 64) were recruited from the affiliated Essex Partnership University NHS Foundation Trust. Other sites used local networks to include additional departments of their institution in the study (UNIGE, Amsterdam UMC, UKK, UCL) by collaborating with neurology, geriatrics, or psychiatry specialists.

Naturally, participating memory clinics have different patient flows and were expected to start recruitment at different time points due to local circumstances. To avoid an excessive overrepresentation of clinics with an early start of recruitment or of some cognitive stage groups (i.e., SCD+, MCI, and dementia), a maximum number of 80 participants per cognitive stage group per memory clinic was set. After reaching this threshold, the memory clinic in question was asked to stop the enrollment of that specific cognitive stage group and focus on the remaining ones.

2.5 | Representativeness

To ensure that our sample is representative of a European memory clinic population, a minimum target of 30 patients per cognitive stage groups per recruiting memory clinic was set based on the recommendation from our biostatistician (HB).

Moreover, we assessed if there are substantial differences in participants' features among the eight recruiting memory clinics for each cognitive stage group (i.e., SCD+, MCI, and dementia). Indeed, relevant differences would increase the risk of bias when pooling participants coming from different centers and analyzing them as a uniform sample. For this purpose, we reported all comparisons in the

Supplementary Material, but focused on only some key variables (i.e., age, gender, education, and global cognition) for the purposes of a summary.

Finally, to ensure that the AMYPAD-DPMS participants are representative of a wider memory clinic population, their baseline features were compared to those of similar clinical samples. For this purpose, we selected the most relevant studies on the clinical utility of amyloid-PET reporting the features of each cognitive stage group individually. The selected studies were the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study involving MCI and dementia[23]; the Alzheimer's biomarkes in daily practice (ABIDE) study involving SCD (not SCD+), MCI, and dementia[9]; the Swedish Flutemetamol Study involving SCD (not SCD+) and MCI patients with unclear diagnosis[10]; the Dutch Flutemetamol Study involving early-onset dementia[5]; and the NEUUS in AD study involving complex dementia cases.[6]

2.6 | Randomization

To test the primary end point of AMYPAD-DPMS, participants were randomized to three study arms: ARM1, early amyloid-PET (i.e., within 1 month from baseline); ARM2, late amyloid-PET (i.e., after 8 ± 2 months from baseline); or ARM3, free-choice amyloid-PET (i.e., if and when the physician chooses to prescribe it). This was accomplished using the minimization method,[24] which takes into account relevant covariates, that is, site, age at screening, and education. Here we tested whether the randomized procedure was successful by comparing the sociodemographic and clinical features of the three study arms as well as the proportions of participants randomized to the three study arms, and of each cognitive stage group within the three arms.

2.7 | Statistical methods

Continuous variables are described as median and interquartile range (IQR), and categorical variables as percentages (raw numbers), unless otherwise specified. Differences among the three cognitive stage groups, the three study arms, and the eight recruiting memory clinics were assessed using Kruskal-Wallis rank sum test for continuous variables, or test for equality of proportions for categorical variables. Significance was set at $P < .05$ and post hoc pairwise comparisons (Dunn's all-pairs rank comparison test for continuous variables, or pairwise comparisons for proportions) were adjusted using Bonferroni correction. The comparison between our participants and other similar clinical samples was only qualitative.

All statistical analyses were performed with R, version 4.1.2 (R Foundation for statistical computing, https://www.r-project.org/).

3 | RESULTS

3.1 | Enrollment strategies and achievements

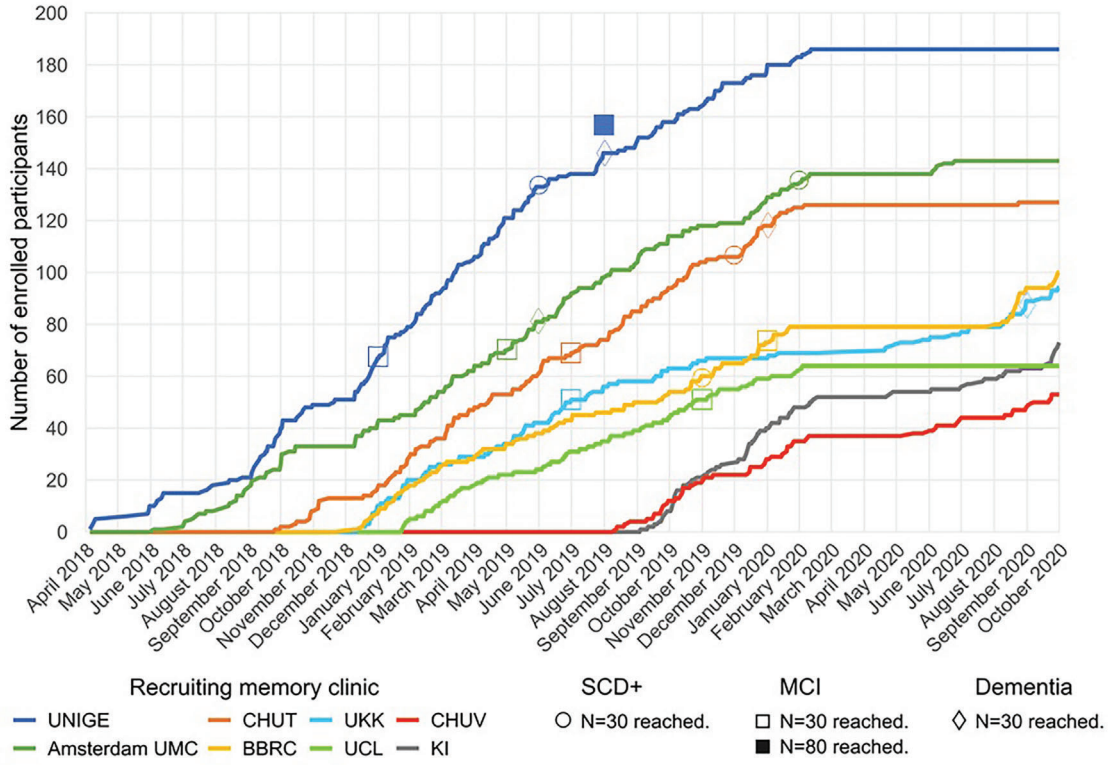
Figure 2 illustrates how the enrollment developed throughout the study. UNIGE was the first memory clinic to start enrollment, on April 16, 2018, after the initial approval of the study by the local ethics committee. Due to local circumstances, the additional seven memory clinic openings have been spread between June 2018 (Amsterdam UMC) and September 2019 (KI) (Figure 2).

Because MCI participants reached their target sample size ($n = 300$) far before enrollment closure, in November 2019, we allowed for a limited over-recruitment of these participants across the whole study, so that more memory clinics could reach the minimum sample size ($n = 30$). Once this target was reached, all memory clinics with ≥30 MCI patients were asked to stop enrollment of this subpopulation and focus on the two other cognitive stage groups. This strategy was successful, as the inclusion of MCI participants slowed down and the recruitment of SCD+ and dementia participants increased (while the overall recruitment remained stable). The maximum sample size ($n = 80$) was reached only by UNIGE for MCI participants (Figure 2).

3.2 | Baseline features across cognitive stage groups

A total of 844 participants were screened and 840 were enrolled (i.e., 4 were screening failures, meeting the exclusion criteria) from eight European memory clinics, representing 93% of the originally planned sample size ($n = 900$). At baseline, 244 had a cognitive stage of SCD+ (representing 81% of the originally planned sample size, $n = 300$), 341 MCI (114%), and 255 dementia (85%). Of these 840 enrolled participants, eight were withdrawn from the study before undergoing the baseline visit. Nevertheless, the data of these eight participants were analyzed (when available) according to the intention-to-treat principle.

Table 1 illustrates the baseline features of the AMYPAD-DPMS participants. Age was directly proportional to cognitive stage severity (SCD+: 69 ± 9, MCI: 72 ± 11, and dementia: 75 ± 10; $P < .001$), even though the minimum age to enter the study was higher for SCD+ (60 years) than MCI and dementia (50 years). Conversely, formal education (SCD+: 14 ± 6 years, MCI: 12 ± 5, and dementia: 12 ± 6; $P < .001$) and global cognition (MMSE score; SCD+: 29 ± 2, MCI: 26 ± 4, dementia: 22 ± 6; $P < .001$) were inversely proportional to cognitive stage severity. Dementia and MCI participants presented higher levels of depression (HADS Depression; dementia: 5 ± 5, $P = .015$; and MCI: 4 ± 5, $P = .010$) than those with SCD+ (SCD+: 3 ± 4). Moreover, we observed a higher prevalence of hypertension in dementia (61%) as compared to SCD+ (41%, $P < .001$) despite higher body mass index (BMI) in SCD+ (26 ± 5) as compared to dementia (25 ± 6, $P = .011$). SCD+ participants reported head injury more frequently (16%) than those with MCI (9%, $P = .047$). The frequency of reported vitamin deficiency was higher in MCI (16%) as compared to SCD+ (7%, $P = .006$). Notably, a considerable proportion of patients with dementia (7%) were still working at the time of study enrollment, but this proportion was significantly lower than that for SCD+ (20%, $P < .001$). Finally, dementia patients were more frequently taking one or more cognition-specific medications (24%) and involved in one or more patient-management activities (21%) than those with MCI (6%, $P < .001$; and 12%, $P = .017$) or SCD+ (5%, $P < .001$; and 12%, $P = .016$).



UNIGE, University and University Hospital of Geneva; Amsterdam UMC, Amsterdam University Medical Centers, location VUmc; CHUT, Centre Hospitalier Universitaire de Toulouse; BBRC, Barcelonaβeta Brain Research Center; UKK, University of Cologne and DZNE; UCL, University College London; KI, Karolinska Institutet and Karolinska University Hospital; CHUV, Centre Hospitalier Universitaire Vaudois. Across recruiting memory clinics, 22% (186/840) of participants were enrolled at UNIGE, 17% (143/840) at Amsterdam UMC, 15% (127/840) at CHUT, 12% (100/840) at BBRC, 11% (94/840) at UKK, 9% (73/840) at KI, 8% (64/840) at UCL, 6% (53/840) at CHUV. N = 30 corresponds to the minimum number of participants per cognitive stage group per memory clinic set during the study. N = 80 corresponds to the maximum number of participants per cognitive stage group per memory clinic set during the study

FIGURE 2 Enrollment and achievements throughout the study disaggregating by recruiting memory clinic

At baseline, prior to amyloid-PET, the prevalence of a presumed etiological diagnosis of AD was directly proportional to cognitive stage severity (SCD+: 7%, MCI: 44%, and dementia: 67%; $P < 0.001$), whereas the prevalence of non-AD (SCD+: 27%, MCI: 15%, and dementia: 8%; $P < .001$) and the prevalence of undetermined diagnoses (SCD+: 66%, MCI: 40%, and dementia: 24%; $P < .001$) were inversely proportional to cognitive stage severity (Table 2).

Regarding patients' health and quality of life (assessed by EQ-5D-5L), dementia patients reported a higher impact on their usual activities and felt more anxious or depressed than patients with SCD+ and MCI, and it had a higher impact on mobility and self-care than MCI; despite patients with SCD+ experiencing more pain or discomfort, their global perceived health was greater than that of MCI and dementia patients. Moreover, SCD+ and MCI perceived less love and friendship than dementia participants, whereas the perceived independence was inversely proportional to cognitive stage severity (assessed by ICECAP-O). Finally, SCD+ participants showed overall better coping strategies than MCI and dementia (assessed by Brief COPE) (Table 3).

APOE genotype and CSF biomarker results were available for a subset of participants. *APOE* genotype was available for 163 participants (51 SCD+, 65 MCI, and 47 dementia) from UNIGE ($n = 53$), Amsterdam UMC ($n = 69$), and KI ($n = 41$). The *APOE* ε4 allele was observed in 41% (21/51) of SCD+, 55% (36/65) of MCI, and 64% (30/47) of dementia participants ($P = .074$). CSF biomarker results were available for 114 participants (33 SCD+, 46 MCI, and 35 dementia) from UNIGE ($n = 43$), Amsterdam UMC ($n = 27$), KI ($n = 39$), and CHUT ($n = 5$). One MCI patient (from Amsterdam UMC) had an "unclear" CSF amyloid beta (Aβ)42 value, and was therefore excluded when we assessed this variable. The prevalence of CSF Aβ42 positivity was significantly higher in dementia (57%, 20/35) as compared to SCD+ (21%, 7/33; $P = .016$) and MCI (22%, 10/45; $P = .009$), whereas no other significant differences were observed across cognitive stage groups in the other CSF biomarkers (CSF phosphorylated tau [p-tau]: 30% (10/33) in SCD+, 54% (25/46) in MCI, and 49% (17/35) in dementia, $P = .097$; CSF total tau [t-tau]: 33% (11/33) in SCD+, 54% (25/46) in MCI, and 49% (17/35) in dementia, $P = .174$).

3.3 | Representativeness

The pre-defined minimum sample size ($n = 30$) of MCI was reached by six of eight sites, whereas that of SCD+ and dementia was reached by only four of eight sites (Figure 2).

TABLE 1 Sociodemographic and clinical features of AMYPAD-DPMS randomized participants disaggregating by baseline cognitive stage

Baseline features	SCD ± *n* = 244	MCI *n* = 341	Dementia *n* = 255	*P*
Sociodemographic				
Age, years	69 (9)[c]	72 (11)[b]	75 (10)[a]	<**.001**
Gender, male	57% (139)	55% (188)	49% (125)	.168
Education, years	14 (6)[a]	12 (5)[b]	12 (6)[c]	<**.001**
Ethnicity (White)	99% (217) [25]	97% (295) [36]	97% (230) [17]	.172
Mental status				
MMSE	29 (2)[a] [2]	26 (4)[b] [6]	22 (6)c [7]	<**.001**
History of anxiety	22% (54)	22% (75)	16% (41)	.140
HADS Anxiety	6 (5) [5]	6 (6) [6]	6 (6) [12]	.406
History of depression	31% (75)	30% (102)	28% (71)	.762
Depression in last 5 years	25% (47) [57]	30% (73) [96]	26% (51) [61]	.519
HADS Depression	3 (4)b [5]	4 (5)[a] [6]	5 (5)[a] [12]	**.005**
Dementia risk factors				
Hypertension	41% (83)[b] [41]	49% (129) [80]	61% (112)[a] [71]	<**.001**
Body mass index, kg/m^2	26 (5)[a] [6]	26 (5) [3]	25 (6)b [13]	**.013**
Reported cardiovascular events	41% (100)	35% (120)	42% (108)	.158
Reported head injury	16% (40)[a]	9% (32)b	13% (33)	**.040**
Smoking	12% (29)	11% (38)	10% (26)	.833
Alcohol abuse	5% (13)	3% (11)	4% (10)	.442
Vitamin deficiency	7% (17)[b]	16% (54)[a]	13% (34)	**.005**
Self-sufficiency				
Disabilities	6% (15)	7% (24)	9% (23)	.449
Participants living in institution	0% (0)	0% (1)	2% (6)	**.006***
Still working	20% (50)[a]	13% (45)	7% (19)b	<**.001**
Drugs and patient management				
Cognition-specific medications, ≥1	5% (11)b	6% (20)b	24% (62)[a]	<**.001**
Other medications, *n*	3 (5)	3 (3)	3 (4)	.703
Patient management, ≥1 activity	12% (28)[b] [1]	12% (42)[b] [2]	21% (53)[a] [5]	**.003**

Abbreviations: BMI; body max index (defined as the body mass divided by the square of the body height, and is expressed in units of kg/m^2); HADS, Hospital Anxiety and Depression score; MMSE, Mini Mental State Examination.
Hypertension was defined as systolic ≥140 or diastolic ≥90 mm Hg. Alcohol abuse was defined as more than 21 units per week. Patient management activities include, for example, memo techniques, physical activity, psychotherapy, speech therapy.
Values are medians (interquartile ranges) for continuous variables, or percentages (raw numbers) for categorical variables.
Statistical analyses: Kruskal-Wallis rank-sum test for continuous variables, or test for equality of proportions for categorical variables. If significant, post hoc analyses consist of pairwise comparisons using Dunn's all-pairs rank comparison test for continuous variables, or pairwise comparisons for proportions; in both cases, *P*-values were adjusted for multiple comparisons using Bonferroni correction.
Post hoc comparisons: a > b > c, i.e. values marked with "a" are greater than those marked with "b", and values marked with "b" are greater than those marked with "c".
*No pairwise comparison survived the Bonferroni correction.
[Number in square brackets]: number of missing data.

3.3.1 | Between-site differences

The eight recruiting memory clinics included participants with variable features. Age varied between 65 ± 9 and 73 ± 9 in SCD+, 69 ± 16 and 76 ± 11 in MCI, and 62 ± 12 and 80 ± 5 in dementia. The proportion of male participants varied between 41% and 79% in SCD+, 36% and 70% in MCI, and 31% and 75% in dementia. Years of education ranged between 12 ± 6 and 16 ± 6 in SCD+, 10 ± 5 and 13 ± 6 in MCI, and 6 ± 2 and 12 ± 6 in dementia. MMSE scores ranged between 28 ± 2 and 30 ± 2 in SCD+, 24 ± 5 and 28 ± 4 in MCI, and 20 ± 10 and 25 ± 3 in dementia. Further information on other variables is reported in Tables S1-S6.

TABLE 2 Etiological diagnoses of the 832 AMYPAD-DPMS participants who underwent the baseline visit disaggregating by baseline cognitive stage

Baseline etiological diagnoses		SCD± *n* = 243	MCI *n* = 339	Dementia *n* = 250	*P*
AD (total)		7% (18)[c]	44% (150)[b]	67% (168)[a]	<.001
	AD	6% (14)	39% (131)	53% (133)	
	AD mixed	2% (4)	6% (19)	14% (35)	
Non-AD (total)		27% (65)[a]	15% (52)[b]	8% (21)[c]	<.001
	CVD	2% (4)	5% (18)	4% (9)	
	DLB	0% (0)	1% (2)	2% (5)	
	FTLD	1% (2)	1% (2)	1% (2)	
	Psychiatric disease	9% (22)	3% (10)	0% (1)	
	Aging	9% (21)	0% (0)	0% (0)	
	Other	7% (16)	6% (20)	2% (4)	
Undetermined		66% (160)[a]	40% (137)[b]	24% (61)[c]	<.001

Abbreviations: AD, Alzheimer's disease; CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration.
Psychiatric diseases include, for example, anxiety and depression. Aging indicates that the cause of cognitive complain is due to age-related physiological mechanisms. Other causes include, for example, corticobasal degeneration, alcohol abuse, sleep disorder, normal pressure hydrocephalus, and suspected non-Alzheimer's pathology.
Values are percentages (raw numbers). Statistical analyses: test for equality of proportions for categorical variables. If significant, post hoc analyses consist of pairwise comparisons for proportions; *P*-values were adjusted for multiple comparisons using Bonferroni correction.
Post hoc comparisons: a > b > c, i.e. values marked with "a" are greater than those marked with "b", and values marked with "b" are greater than those marked with "c".

3.3.2 | Qualitative comparison between AMYPAD-DPMS and other studies

Values are shown as mean ± SD for the ABIDE, Swedish Flutemetamol Study, Dutch Flutemetamol Study, and NEUUS in AD studies; and median (lower and upper quartiles) for the IDEAS study.

SCD+ participants enrolled in the present study were older (69 ± 9 years) than SCD participants involved in the ABIDE study (61 ± 8 years) but similar to those involved in the Swedish Flutemetamol Study (68 ± 8), whereas global cognition was similar between the three studies (MMSE score; AMYPAD-DPMS: 29 ± 2; ABIDE: 28 ± 7; Swedish Flutemetamol Study: 29 ± 1) (Table 4). Our MCI participants were older (72 ± 11 years) than those involved in ABIDE (67 ± 8 years) and in the Swedish Flutemetamol Study (64 ± 9) but comparable to those involved in IDEAS (75, 70–79 years), whereas global cognition was consistent across the four studies (MMSE score; AMYPAD-DPMS: 26 ± 4; ABIDE: 27 ± 2; IDEAS: 27, 25–29; Swedish Flutemetamol Study: 26 ± 4) (Table 4). Finally, dementia participants enrolled in the present study were older (75 ± 10 years) than those involved in ABIDE (66 ± 8 years) and in the Dutch Flutemetamol Study (62 ± 6 years) and comparable to those involved in IDEAS (77, 72–81 years) and NEUUS in AD (71 ± 10 years), with consistent global cognition across studies (MMSE score; AMYPAD-DPMS: 22 ± 6; ABIDE: 23 ± 4; IDEAS: 22, 18–25; DFS: 23 ± 4; NEUUS in AD: 22 ± 5) (Table 4).

3.4 | Randomization

The randomization procedure assigned 35% (291/840) of the enrolled participants to ARM1 (85 SCD+, 118 MCI, and 88 dementia), 32% (271/840) to ARM2 (79 SCD+, 106 MCI, 86 dementia), and 33% (278/840) to ARM3 (80 SCD+, 117 MCI, and 81 dementia). The proportions of participants randomized into the three study arms (P = .576) as well as the proportions of each cognitive stage group within the three arms (SCD+: P = .993, MCI: P = .778, dementia: P = .802) were not different. Table S7 shows how participants were randomized across sites by cognitive stage.

Of the 23 assessed variables, only one showed a statistically significant difference among the three study arms (HADS Anxiety, 5 ± 5 in ARM1 vs. 6 ± 6 in ARM2, P = .010) (Table S8).

4 | DISCUSSION

AMYPAD-DPMS is the largest study assessing the clinical utility and cost-effectiveness of amyloid-PET in Europe through a randomized design. To ensure the reliability and generalizability of its scientific outcomes, we assessed whether the AMYPAD-DPMS sample is representative of a general memory clinic population.

A total of 840 participants were enrolled, representing 93% (840/900) of the originally planned sample size, with a modest over recruitment of MCI (n = 341) and under recruitment of SCD+ (n = 244) and dementia (n = 255). We observed that the baseline sociodemographic and clinical features of the AMYPAD-DPMS participants are as expected for a memory clinic population. Indeed, their features are consistent with the baseline cognitive stage groups, and worsen with advancing cognitive stage severity.

In AMYPAD-DPMS, recruitment was not uniform across recruiting memory clinics due to an asynchronous beginning of recruitment

TABLE 3 Global health status and quality of life of AMYPAD-DPMS participants disaggregating by baseline cognitive stage

Global health status and quality of life		SCD± $n = 244$	MCI $n = 341$	Dementia $n = 255$	*P*
EQ-5D-5L	Mobility	1 (1) [4]	1 (1)[b] [5]	1 (1)[a] [10]	**.013**
	Self-care	1 (0) [4]	1 (0)[b] [4]	1 (0)[a] [12]	**<.001**
	Usual activities	1 (1)[b] [4]	1 (1)[b] [4]	1 (1)[a] [12]	**<.001**
	Pain or discomfort	2 (2)[a] [4]	2 (2)[b] [4]	2 (2)[b] [11]	**.004**
	Anxiety or depression	2 (1)[b] [4]	2 (1)[b] [4]	2 (2)[a] [11]	**.008**
	Health today	80 (20)[a] [5]	80 (21)[b] [5]	70 (25)[b] [10]	**<.001**
ICECAP-O	Attachment – Love and friendship	3 (1)[b] [4]	4 (1)[b] [4]	4 (1)[a] [13]	**<.001**
	Security – Thinking about the future without concern	3 (1) [3]	3 (1) [4]	3 (1.5) [12]	.565
	Role – Doing things that make you feel better	3 (1) [3]	3 (1) [5]	3 (1) [13]	.808
	Enjoyment – Enjoyment and pleasure	3 (0) [3]	3 (1) [4]	3 (1) [14]	.667
	Control – Independence	4 (1)[a] [3]	3 (1)[b] [4]	3 (2)[c] [13]	**<.001**
Brief COPE	Coping style: Approach	31 (8) [65]	29 (8) [57]	30 (10) [54]	**.044***
	Coping style: Avoidant	25 (9) [67]	25 (8) [60]	25 (7) [52]	.139
	Active coping	5 (3)[a] [10]	5 (2)[b] [15]	5 (3)[b] [24]	**<.001**
	Planning	5 (3)[a] [12]	5 (2) [17]	5 (2)[b] [25]	**.008**
	Positive reframing	5 (2)[a] [62]	4 (3)[b] [49]	4 (3) [43]	**.028**
	Acceptance	6 (3)[a] [11]	6 (2) [16]	5.5 (3)[b] [25]	**.002**
	Humor	4 (2) [12]	4 (2) [13]	4 (3) [23]	.650
	Religion	2 (2) [10]	2 (2) [14]	2 (3) [26]	.135
	Using emotional support	4 (3) [10]	4 (3) [14]	5 (4) [25]	.174
	Using instrumental support	6 (3) [62]	5 (2) [48]	5 (3) [41]	.176
	Self-Distraction	5 (2) [11]	5 (3) [14]	5 (2.2) [23]	.387
	Denial	3 (3) [9]	4 (3) [16]	4 (2) [26]	.062
	Venting	4 (2) [11]	4 (2) [16]	4 (2) [23]	.125
	Substance use	2 (2) [9]	2 (2) [15]	2 (2) [29]	.987
	Behavioral disengagement	3 (2) [11]	3 (2) [18]	3 (2) [25]	.664
	Self-Blame	5 (3)[a] [64]	5 (3) [47]	4 (3)[b] [36]	**.001**

Values are medians (interquartile ranges). Statistical analyses: Kruskal-Wallis rank-sum test for continuous variables. If significant, post hoc analyses consist of pairwise comparisons using Dunn's all-pairs rank comparison test; *P*-values were adjusted for multiple comparisons using Bonferroni correction.
Post hoc comparisons: a > b > c, i.e. values marked with "a" are greater than those marked with "b", and values marked with "b" are greater than those marked with "c".
*No pairwise comparison survived the Bonferroni correction.
[Number in square brackets]: number of missing data.

and to local specificities and clinical routines (e.g., BBRC in Spain usually does not see dementia patients in the clinical routine as it mainly focuses on AD prevention; i.e., on non-demented patients). The pre-defined minimum sample size was reached in six of eight recruiting memory clinics for MCI, and in four memory clinics for SCD+ and dementia. Recruitment in the final year (2020) was considerably slower compared to previous years, as recruiting memory clinics had to stop their research activities due to the coronavirus disease 2019 (COVID-19) pandemic. We can speculate that, under normal circumstances, the minimum sample size would have been reached by most recruiting memory clinics. Even though the collected data ensure an overall good representativeness of the involved memory clinics, it might not be always possible to generalize the study results to all European countries; this is one of the main limitations of the study. We will investigate if and how it is possible to extend the generalizability of the study results to countries that did not reach the minimum sample size for a certain cognitive stage group as well as to other European countries. For example, analyses might be adjusted by including the recruiting memory clinic variable as a covariate or by using national dementia registries (where available), external benchmarks, or indices (e.g., the purchasing power parity index for health-economics analyses). It is notable that the involvement of 11 non-academic memory clinics is a

TABLE 4 Comparisons of the AMYPAD-DPMS cohort with other cohorts

	SCD			MCI				Dementia				
Baseline features	**AMYPAD-DPMS** $n = 244$	**ABIDE (2016)** $n = 159$	**SFS (2019)** $n = 5$	**AMYPAD-DPMS** $n = 341$	**ABIDE (2016)** $n = 114$	**IDEAS (2019)** $n = 6905$	**SFS (2019)** $n = 131$	**AMYPAD-DPMS** $n = 255$	**ABIDE (2016)** $n = 234$	**IDEAS (2019)** $n = 4504$	**DFS (2017)** $n = 211$	**NEUUS in AD (2018)** $n = 205$
Age, years	69 (9)	61 (8)	68 (8)	72 (11)	67 (8)	75 (70-79)	64 (9)	75 (10)	66 (8)	77 (72-81)	62 (6)	71 (10)
Gender, males	57% (139)	62% (98)	40% (2)	55% (188)	64% (73)	50% (3480)	42% (55)	49% (125)	58% (135)	47% (2125)	55% (116)	50% (103)
Education, years	14 (6)	5.4 (1.4)	NA	12 (5)	5.4 (1.2)	High school graduate: 26% (1824).	NA	12 (6)	5.0 (1.1)	High school graduate: 43% (1917).	NA	None: 0% (2).
						Some college: 25% (1763).				Some college: 21% (933).		Primary school: 17% (34).
						Bachelor's degree: 26% (1777).				Bachelor's degree: 21% (927).		High school up to 15 years old: 26% (53).
						Postgraduate degree: 22% (1541).				Postgraduate degree: 16% (727).		High school up to 18 years old: 24% (49).
												College: 33% (67)
Ethnicity (white)	99% (217) [25]	NA	NA	97% (295) [36]	NA	90% (6212)	NA	97% (230) [17]	NA	85% (3828)	NA	NA
MMSE	29 (2) [2]	28 (7)	29 (1)	26 (4) [6]	27 (2)	27 (25-29)	26 (4)	22 (6) [7]	23 (4)	22 (18-25)	23 (4)	22 (5)
Cognition-specific medications, ≥1	5% (11)	NA	NA	6% (20)	NA	34% (2384)	NA	24% (62)	NA	59% (2671)	NA	NA

Abbreviations: DFS, Dutch Flutemetamol Study; NA, Not Available; SFS, Swedish Flutemetamol Study.

For the ABIDE study, values are means (SDs) or percentages (raw numbers) for categorical variables; education was measured using the Verhage system,[26] a standardized index ranging from 1 (not completed primary school) to 7 (academic degree).

For the IDEAS study, values are median (lower and upper quartiles) or percentage (raw number) for categorical variables.

For SFS, DFS, and NEUUS in AD, values are mean (SD) or percentage (raw number) for categorical variables.

big strength of AMYPAD-DPMS and will allow testing of the difference in the use of amyloid-PET between academic and non-academic settings. Moreover, even if we observed some unavoidable variability and differences among recruiting memory clinics, possibly due to site-specific data collection procedures or culture, these are not substantial and do not prevent pooling together data collected from different memory clinics or countries.

A qualitative comparison revealed that the features of our sample are consistent with those of similar clinical samples. Specifically, the AMYPAD-DPMS SCD+, MCI, and dementia participants showed global cognition comparable to that of similar samples involved in the ABIDE, IDEAS, Swedish Flutemetamol Study, Dutch Flutemetamol Study, and NEUUS in AD studies. The age of the AMYPAD-DPMS participants was comparable to that of the IDEAS participants, but it was higher than that of the ABIDE, Dutch Flutemetamol Study, and Swedish Flutemetamol Study (only for MCI) participants. This observation might be explained partly by previous findings suggesting that patients seen at Amsterdam UMC (where ABIDE and the Dutch Flutemetamol Study took place) are usually younger than in other similar samples.[25]

It is important to note that the randomization procedure was successful, resulting in three study arms matched for the main sociodemographic and clinical features.

The findings reported here support the representativeness of the study sample to a wider European memory clinic population, suggesting that the upcoming results of AMYPAD-DPMS will be generalizable.

ACKNOWLEDGMENTS

This communication reflects the views of the authors and neither the Innovative Medicines Initiative (IMI) nor the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) are liable for any use that may be made of the information contained herein. The Geneva Memory Center is funded by the following private donors under the supervision of the Private Foundation of Geneva University Hospitals: A.P.R.A. - Association Suisse pour la Recherche sur la Maladie d'Alzheimer, Genève; Fondation Segré, Genève; Ivan Pictet, Genève; Fondazione Agusta, Lugano; Fondation Chmielewski, Genève. Competitive research projects have been funded by: H2020, Human Brain Project, Innovative Medicines Initiative (IMI), IMI2, Swiss National Science Foundation, VELUX Foundation. External sites affiliated with CHUT: Françoise Desclaux (Geriatrics department of Lavaur), Marie-Noelle Cufi (Geriatrics department of Lavaur), and Jérémie Pariente (department of Neurology of Toulouse University Hospital, Inserm Toulouse NeuroImaging Center, Université Paul Sabatier, Centre d'Investigation Clinique de Toulouse CIC 1436). The BBRC's memory center received funding from the Barcelona City Council (agreement # 20XC0354) and Biogen. Daniele Altomare received funding from the Fondation Recherche Alzheimer and the Swiss National Science Foundation (project CRSK-3_196354/1). Camilla Caprioglio was supported by EU-EFPIA Innovative Medicines Initiatives 2 Joint Undertaking (IMI 2 JU) Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD, grant agreement number: 115952). Johannes Berkhof is a recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106), and received funding from the EU (AMYPAD, RISCC), ZonMW (HPV compare), WHO, IARC, and RIVM. Valentina Garibotto was supported by the Swiss National Science Foundation (projects 320030_169876, 320030_185028 and IZSEZ0_188355), by the Velux Foundation (project 1123), by the Schmidheiny foundation, and by the Aetas foundation. Oriol Grau-Rivera received funding from Alzheimer's Association (2019-AARF-644568) and Instituto de Salud Carlos III (PI19/00117). Juan Domingo Gispert is supported by the Spanish Ministry of Science and Innovation (RYC-2013-13054) and received funding from the EU-EFPIA Innovative Medicines Initiatives 2 Joint Undertaking (IMI 2 JU) Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD, grant agreement number: 115952). Alexander Drzezga received funding by Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD, grant agreement number: 115952), DFG (Deutsche Forschungsgemeinschaft), BMBF (Bundesministerium für Bildung und Forschung), EFRE/Leitmarkt (Europäischen Fonds für regionale Entwicklung), University of Cologne, Forschungszentrum Jülich. Novartis clinical trial. Claus Escher received funding from the EU-EFPIA Innovative Medicines Initiatives 2 Joint Undertaking (IMI 2 JU) European Prevention of Alzheimer's Dementia consortium (EPAD, grant agreement number: 115736) and Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD, grant agreement number: 115952). Frank Jessen received funding from BMBF, DFG, H2020, and IMI. Agneta Nordberg received funding from Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD, grant agreement number: 115952), Swedish Foundation for Strategic Research (RB12-01929), Swedish Research Council (2017-06086, 2017-02965, 2020-019909, CIMED, Swedish Brain Foundation, Swedish Alzheimer foundation, Recherche Sur Alzheimer Fondation, France, and Michael J Fox Foundation (MJFF-019728). Zuzana Walker received funding from HTA-NIHR, Lewy body Society, and ARUK. Jean-François Demonet received funding from Biogen "EMBARK" study, Empiris foundation, Solis foundation, OM Pharma, and Leenaards foundation. Frederik Barkhof is supported by the NIHR Biomedical Research Centre at University College London Hospitals. Giovanni B. Frisoni received funding from the EU-EFPIA Innovative Medicines Initiatives 2 Joint Undertaking (IMI 2 JU) European Prevention of Alzheimer's Dementia consortium (EPAD, grant agreement number: 115736) and Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD, grant agreement number: 115952); the Swiss National Science Foundation (COSCODE, grant number: 320030_182772); A.P.R.A. - Association Suisse pour la Recherche sur la Maladie d'Alzheimer, Genève; Fondation Segré, Genève; Ivan Pictet, Genève; Fondazione Agusta, Lugano; Fondation Chmielewski, Genève; and VELUX Foundation.

Open access funding provided by Universite de Geneve.

CONFLICTS OF INTEREST

Philip Scheltens provides consultancy (via the University) for AC Immune, Alzheon, Brainstorm Cell, ImmunoBrain Checkpoint, Novartis, and Novo Nordisk. Within his university affiliation he is principal investigator of studies with AC Immune, FUJI-film/Toyama, IONIS,

UCB, and Vivoryon. He is also an employee of Life Sciences Partners Amsterdam. Valentina Garibotto received financial support for research and/or speaker fees through her institution from Siemens Healthineers, GE Healthcare, Life Molecular Imaging, Cerveau Technologies, Roche, and Merck. Julien Delrieu has received payment/honoraria from Biogen (presentation for Biogen in 2021); and has participated on a Data Safety Monitoring Board or Advisory Board for French board for Roche in 2020–2021. José Luis Molinuevo is currently a full-time employee of Lundbeck and has served previously as a consultant or on advisory boards for the following for-profit companies, or has given lectures in symposia sponsored by the following for-profit companies: Roche Diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Janssen, Green Valley, MSD, Eisai, Alector, BioCross, GE Healthcare, and ProMIS Neurosciences. Juan Domingo Gispert received research support from GE Healthcare, Hoffmann La Roche, and Roche Diagnostics; and speaker's fees from Philips and Biogen. Alexander Drzezga received research support from Siemens Healthineers, Life Molecular Imaging, GE Healthcare, AVID Radiopharmaceuticals, and SOFIE. Speaker Honorary/Advisory Boards: by Siemens Healthineers, Sanofi, GE Healthcare, Biogen, Novo Nordisk, and Invicro. Stock from: Siemens Healthineers, Lantheus Holding, and Biogen. Patents: Patent pending for 18F-PSMA7 (PSMA PET imaging tracer). He provided expert testimony in a local court. He has participated on a Data Safety Monitoring Board or Advisory Board for GE Healthcare, Siemens Healthineers, Novo Nordisk, Invicro, and Biogen. Frank Jessen received payment/honoraria from Roche and Lilly. He has participated on a Data Safety Monitoring Board or Advisory Board for AC Immune, Biogen, Roche, Eisai, and Grifols. Agneta Nordberg received consulting fees from Hoffman La Roche. Patent: US patent alpha 7 nicotinic PET tracer. She is deputy chairman of Wennergren Foundations. Zuzana Walker received consulting fees from GE Healthcare. Jean-François Demonet: patent (European Patent Office 19705763.1-1132). He has participated on an Advisory Board for Biogen Switzerland. Frederik Barkhof received consulting fees from Combinostics, IXICO, Roche, and Biogen. He has participated on a Data Safety Monitoring Board or Advisory Board for EISAI, Biogen, and Merck. Giovanni B. Frisoni reports grants from Avid Radiopharmaceuticals, Biogen, GE International, Guerbert, IXICO, Merz Pharma, Nestlé, Novartis, Eisai, Piramal, Roche, Siemens, Teva Pharmaceutical Industries, and Vifor Pharma; he has received personal fees from AstraZeneca, Avid Radiopharmaceuticals, Biogen, Roche, Diadem, Neurodiem, Elan Pharmaceuticals, GE International, Lundbeck, Pfizer, and TauRx Therapeutics. The other authors have nothing to disclose.

ORCID

Daniele Altomare https://orcid.org/0000-0003-1905-8993

REFERENCES

1. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2011;1(1):a006189-a006189. https://doi.org/10.1101/cshperspect.a006189
2. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol*. 2004;55(3):306-319. https://doi.org/10.1002/ana.20009
3. Grundman M, Pontecorvo MJ, Salloway SP, et al. Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline. *Alzheimer Dis Assoc Disord*. 2013;27(1):4-15. https://doi.org/10.1097/WAD.0b013e318279d02a
4. Boccardi M, Altomare D, Ferrari C, et al. Assessment of the incremental diagnostic value of florbetapir F 18 imaging in patients with cognitive impairment: the incremental diagnostic value of amyloid PET with [18F]-Florbetapir (INDIA-FBP) Study. *JAMA Neurol*. 2016;73(12):1417-1424. https://doi.org/10.1001/jamaneurol.2016.3751
5. Zwan MD, Bouwman FH, Konijnenberg E, et al. Diagnostic impact of [18F]flutemetamol PET in early-onset dementia. *Alzheimer's Res Ther*. 2017;9(1):2. https://doi.org/10.1186/s13195-016-0228-4
6. Ceccaldi M, Jonveaux T, Verger A, et al. Added value of 18F-florbetaben amyloid PET in the diagnostic workup of most complex patients with dementia in France: a Naturalistic Study. *Alzheimer's Dement*. 2018;14(3):293-305. https://doi.org/10.1016/j.jalz.2017.09.009
7. Brendel M, Schnabel J, Schönecker S, et al. Additive value of amyloid-PET in routine cases of clinical dementia work-up after FDG-PET. *Eur J Nucl Med Mol Imaging*. 2017;44(13):2239-2248. https://doi.org/10.1007/s00259-017-3832-z
8. Carswell CJ, Win Z, Muckle K, et al. Clinical utility of amyloid PET imaging with (18)F-florbetapir: a retrospective study of 100 patients. *J Neurol Neurosurg Psychiatry*. 2017;89(3):294-299. jnnp-2017-316194. https://doi.org/10.1136/jnnp-2017-316194
9. De Wilde A, Van Der Flier WM, Pelkmans W, et al. Association of amyloid positron emission tomography with changes in diagnosis and patient treatment in an unselected memory clinic cohort: the ABIDE project. *JAMA Neurol*. 2018;75(9):1062-1070. https://doi.org/10.1001/jamaneurol.2018.1346
10. Leuzy A, Savitcheva I, Chiotis K, et al. Clinical impact of [18F]flutemetamol PET among memory clinic patients with an unclear diagnosis. *Eur J Nucl Med Mol Imaging*. 2019;46(6):1276-1286. https://doi.org/10.1007/S00259-019-04297-5
11. Chiotis K, Saint-Aubert L, Boccardi M, et al. Clinical validity of increased cortical uptake of amyloid ligands on PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiol Aging*. 2017;52:214-227. https://doi.org/10.1016/j.neurobiolaging.2016.07.012
12. Frisoni GB, Barkhof F, Altomare D, et al. AMYPAD diagnostic and patient management study: rationale and design. *Alzheimer's Dement*. 2019;15(3):388-399. https://doi.org/10.1016/j.jalz.2018.09.003
13. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's Dement*. 2014;10(6):844-852. https://doi.org/10.1016/j.jalz.2014.01.001
14. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7(3):270-279. https://doi.org/10.1016/j.jalz.2011.03.008
15. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7(3):263-269. https://doi.org/10.1016/j.jalz.2011.03.005
16. *EQ-5D-5L*. EQ-5D. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/. Accessed November 25, 2020.
17. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life*

Res. 2011;20(10):1727-1736. https://doi.org/10.1007/s11136-011-9903-x
18. *ICECAP-O*. University of Birmingham. https://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/HE/ICECAP/ICECAP-O/index.aspx. Accessed November 25, 2020.
19. Perry-Duxbury M, van Exel J, Brouwer W, et al. A validation study of the ICECAP-O in informal carers of people with dementia from eight European countries. *Qual Life Res*. 2020;29(1):237-251. https://doi.org/10.1007/s11136-019-02317-3
20. *Brief-COPE*. NovoPsych Psychometrics. https://novopsych.com.au/assessments/brief-cope/. Accessed November 25, 2020.
21. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. *Int J Behav Med*. 1997;4(1):92-100. https://doi.org/10.1207/s15327558ijbm0401_6
22. Eisenberg SA, Shen BJ, Schwarz ER, Mallon S. Avoidant coping moderates the association between anxiety and patient-rated physical functioning in heart failure patients. *J Behav Med*. 2012;35(3):253-261. https://doi.org/10.1007/s10865-011-9358-0
23. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. *JAMA - J Am Med Assoc*. 2019;321(13):1286-1294. https://doi.org/10.1001/jama.2019.2000
24. Saghaei M, Saghaei S. Implementation of an open-source customizable minimization program for allocation of patients to parallel groups in clinical trials. *J Biomed Sci Eng*. 2011;4(11):734-739. https://doi.org/10.4236/jbise.2011.411090
25. Van Der Flier WM, Scheltens P. Amsterdam dementia cohort: performing research to optimize care. *J Alzheimer's Dis*. 2018;62(3):1091-1111. https://doi.org/10.3233/JAD-170850
26. Verhage F. *Intelligence and Age: Study With Dutch People Aged 12-77*. Assen van Gorcum; 1964.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Altomare D, Collij L, Caprioglio C, et al., Description of a European memory clinic cohort undergoing amyloid-PET: The AMYPAD Diagnostic and Patient Management Study. *Alzheimer's Dement*. 2023;19:844–856. https://doi.org/10.1002/alz.12696