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### Authors

Chapleau, Marianne

La Joie, Renaud

Yong, Keir

et al.

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## Demographic, clinical, biomarker and neuropathologic correlates in posterior cortical atrophy: an individual participant data meta-analysis

Marianne Chapleau, Ph.D.<sup>1,\*</sup>, Renaud La Joie, Ph.D.<sup>1,\*</sup>, Keir Yong, Ph.D.<sup>3</sup>, Federica Agosta, M.D.<sup>14,25</sup>, Isabel Elaine Allen, Ph.D.<sup>23</sup>, Liana Apostolova, M.D.<sup>17</sup>, John Best, M.D.<sup>1</sup>, Baayla D.C. Boon, M.D.<sup>9</sup>, Sebastian Crutch, Ph.D.<sup>3</sup>, Massimo Filippi, M.D.<sup>14,25</sup>, Giorgio Giulio Fumagalli, M.D.<sup>16</sup>, Daniela Galimberti, Ph.D.<sup>15,27</sup>, Jonathan Graff-Radford, M.D.<sup>4</sup>, Lea T. Grinberg, M.D.<sup>1,21,22</sup>, David J. Irwin, M.D.<sup>11</sup>, Keith A. Josephs, M.D.<sup>4</sup>, Mario F. Mendez, M.D.<sup>10</sup>, Patricio Chrem Mendez, M.D.<sup>18</sup>, Raffaella Migliaccio, M.D.<sup>13</sup>, Zachary A. Miller, M.D.<sup>1</sup>, Maxime Montembeault, Ph.D.<sup>12</sup>, Melissa E. Murray, Ph.D.<sup>9</sup>, Sára Nemes, M.Sc.<sup>17</sup>, Victoria Pelak, M.D.<sup>8</sup>, Daniela Perani, M.D.<sup>14,26</sup>, Jeffrey Phillips, Ph.D.<sup>11</sup>, Yolande Pijnenburg, M.D.<sup>5,6</sup>, Emily Rogalski, Ph.D.<sup>20</sup>, Jonathan M. Schott, M.D.<sup>3,5</sup>, William Seeley, M.D.<sup>1,21</sup>, A. Campbell Sullivan, Psy.D.<sup>19</sup>, Salvatore Spina, M.D.<sup>1</sup>, Jeremy Tanner, M.D.<sup>1,19</sup>, Jamie Walker, M.D.<sup>19</sup>, Jennifer L. Whitwell, Ph.D.<sup>4</sup>, David A. Wolk, M.D.<sup>24</sup>, Rik

**Corresponding Authors:** Marianne Chapleau, Postdoctoral Fellow, Memory and Aging Center, Department of Neurology, University of California, San Francisco, 675 Nelson Rising Lane, San Francisco CA 94158, marianne.chapleau@ucsf.edu, Gil Rabinovici, Edward Fein & Pearl Landrith Distinguished Professor, Memory and Aging Center, University of California, San Francisco, 675 Nelson Rising Lane, San Francisco CA 94158, gil.rabinovici@ucsf.edu.

\*Both authors contributed equally to this work.

### Contributors statement

M.C.: literature search, figures, study design, data collection, data curation, data analysis, data interpretation, project administration, writing – original draft; G.D.R.: data interpretation, supervision, writing– review & editing; R.L.J.: data curation, data analysis, data interpretation, supervision, writing– review & editing; K.Y., F.A., I.E.A., L.A., J.B., B.D.C.B., S.C., M.F., G.G.F., D.G., J.G.R., L.T.G., D.J.I., K.A.J., M.F.M., P.C.M., R.M., Z.A.M., M.M., M.E.M., S.N., V.P., D.P., J.P., Y.P., E.R., J.M.S., W.S., A.C.S., S.S., J.T., J.W., J.L.W., D.A.W., R.O.: data collection, writing– review & editing. M.C. and R.L.J. have accessed and verified the data, and both M.C. and G.D.R. were responsible for the decision to submit the manuscript. All authors have seen and approved of the final text.

### Declaration of interests

L.A. has received personal compensation for serving as a consultant for Biogen, Two Labs, FL Dept Health, Genentech, NIH Biobank, Eli Lilly, GE Healthcare, Eisai, Roche Diagnostics, and for serving on a Data Safety and Monitoring Board for IQVIA. L.A. receives research support from the National Institute on Aging, the Alzheimer’s Association, Roche Diagnostics, AVID radiopharmaceuticals, Life Molecular Imaging, and Eli Lilly. M.F.M. is the section editor for Behavioral Neurology for UpToDate. J.G.R. serves on the Drug Safety Monitoring Board (DSMB) for the National Institute of Neurological Disorders and Stroke (NINDS) StrokeNET. K.A.J. is an Associate Editor for Annals of Clinical and Translational Neurology and is on the editorial boards of Journal of Neurology, Acta Neuropathologica and Neuropathology and Applied Neurobiology. J.L.W. is an Associate Editor for Brain Connectivity and Journal of Alzheimer’s Disease. R.O. has received research support from Avid Radiopharmaceuticals, has given lectures in symposia sponsored by GE Healthcare and is an editorial board member of Alzheimer’s Research & Therapy and the European Journal of Nuclear Medicine and Molecular Imaging. F. Agosta is Associate Editor of NeuroImage: Clinical, has received speaker honoraria from Biogen Idec, Italfarmaco, Roche and Zambon, and receives or has received research supports from the Italian Ministry of Health, the Italian Ministry of University and Research, AriSLA (Fondazione Italiana di Ricerca per la SLA), the European Research Council and Foundation Research on Alzheimer Disease. Prof. Filippi is Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sanofi; speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, Takeda; scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme; he receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Italian Ministry of Health, and Fondazione Italiana Sclerosi Multipla. G.D.R. has served on Scientific Advisory Boards for Alector, Eli Lilly, Genentech, Merck, Roche. He serves on a Data Safety and Monitoring Board for Johnson & Johnson. He is an Associate Editor for JAMA Neurology. No other potential conflicts of interest relevant to this article exist.

**Ossenkoppele, Ph.D.<sup>5,6,7</sup>, Gil D. Rabinovici, M.D.<sup>1,2</sup> on behalf of the PCA International Work Group**

<sup>1</sup>Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA

<sup>2</sup>Department of Radiology & Biomedical Imaging, University of California, San Francisco, CA, USA

<sup>3</sup>Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK

<sup>4</sup>Mayo Clinic, Rochester, MN, USA

<sup>5</sup>Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, The Netherlands

<sup>6</sup>Amsterdam Neuroscience, Neurodegeneration, Amsterdam, The Netherlands

<sup>7</sup>Clinical Memory Research Unit, Lund University, Lund, Sweden

<sup>8</sup>Departments of Neurology and Ophthalmology, Divisions of Neuro-Ophthalmology and Behavioral Neurology, University of Colorado School of Medicine, Aurora, CO, USA

<sup>9</sup>Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

<sup>10</sup>David Geffen School of Medicine, University of California, Los Angeles, CA, USA

<sup>11</sup>Penn Frontotemporal Degeneration Center, University of Pennsylvania, Philadelphia, PA, USA

<sup>12</sup>Douglas Research Centre, Department of Psychiatry, McGill University, Montreal, Canada

<sup>13</sup>Paris Brain Institute (ICM), FrontLab, Institut de la mémoire et de la maladie d'Alzheimer (IM2A), Department of Neurology, Pitié-Salpêtrière hospital, Paris, France

<sup>14</sup>Vita-Salute San Raffaele University, Milan, Italy

<sup>15</sup>Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

<sup>16</sup>Center for Mind/Brain Sciences (CIMEC), University of Trento, Rovereto, Italy

<sup>17</sup>Indiana University School of Medicine, Indianapolis, IN, USA

<sup>18</sup>Memory Center, Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Argentina

<sup>19</sup>Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, TX, USA

<sup>20</sup>Mesulam Center for Cognitive Neurology & Alzheimer's Disease, Northwestern University, Evanston, IL, USA

<sup>21</sup>Department of Pathology, University of California, San Francisco, CA, USA

<sup>22</sup>Department of Pathology, University of Sao Paulo Medical School, Sao Paulo, Brazil

<sup>23</sup>Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

<sup>24</sup>Alzheimer's Disease Research Center, University of Pennsylvania, Philadelphia, PA

<sup>25</sup>Neuroimaging Research Unit, Division of Neuroscience, and Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

<sup>26</sup>Division of Neuroscience IRCCS San Raffaele, San Raffaele University, Milan Italy

<sup>27</sup>Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

## Abstract

**Background:** Posterior cortical atrophy (PCA) is a rare syndrome characterized by early, prominent, and progressive impairment in visuospatial and visuospatial processing. PCA has been associated with underlying Alzheimer's disease (AD) neuropathology, but large-scale biomarker and neuropathologic studies are lacking. We aimed to describe demographic, clinical, biomarker and neuropathologic correlates of PCA in a large international cohort.

**Methods:** We contacted 55 research centers conducting PCA research identified in a literature review (n=1,353 papers) and an additional 7 sites recruited by advertising via the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment Atypical AD Professional Interest Area requesting de-identified, single-subject data from patients diagnosed with PCA. Inclusion criteria were: clinical diagnosis of PCA, *and* availability of AD biomarkers (PET or CSF) and/or autopsy diagnosis. Demographic, clinical, biofluid, neuroimaging, and neuropathologic data were collected.

**Findings:** This exploratory meta-analysis included data from 1,092 patients evaluated at 36 sites in 16 countries. Mean age at symptom onset was 59.4 years [95%CI 58.9–59.8], 60% [95%CI 56–64] were women, and 80% [95%CI 72–89] presented with a "PCA pure" syndrome by Crutch 2017 consensus criteria. CSF amyloid- $\beta$  (536 patients, 28 sites) was positive in 81% [95%CI 75–87] of patients, while CSF phosphorylated tau (503 patients, 29 sites) was positive in 65% [95%CI 56–75]. Amyloid-PET (299 patients, 24 sites) was positive in 94% [95%CI 90–97] while tau-PET (170 patients, 13 sites) was positive in 97% [95%CI 93–100]. At autopsy (145 patients, 13 sites), the most frequent neuropathologic diagnosis was AD (94% [95%CI 90–97]), with common co-pathologies: cerebral amyloid angiopathy (71%, [95%CI 54–88]), Lewy body disease (44% [95%CI 25–62]), and cerebrovascular injury (42% [95%CI 24,60]).

**Interpretation:** PCA typically presents as a "pure," young-onset dementia syndrome that is highly specific for underlying AD pathology.

**Funding:** This primary meta-analysis was unfunded. Funding for all sites is available in Supplementary materials.

## Introduction

Posterior cortical atrophy (PCA) is a clinically defined syndrome characterized by early, prominent, and progressive impairment of visuospatial/visuospatial processing due to progressive atrophy of parietal, posterior temporal, and occipital regions. The most recent consensus criteria<sup>1</sup> define the syndrome's core clinical, cognitive and neuroimaging features. Although heterogeneity is found in both clinical and radiological presentations, most patients present with visual difficulties, such as space perception deficits,

simultanagnosia, object perception deficit, constructional dyspraxia, and environmental agnosia. The disease is often associated with an early age of onset (< 65 years). Current diagnostic criteria define a “PCA pure” syndrome, which captures the syndrome’s core clinical and neuroimaging features. They also define a “PCA plus” syndrome, which additionally includes features suggestive of other neurodegenerative diseases, such as corticobasal degeneration (CBD) or Lewy body disease (LBD). At autopsy, the vast majority of PCA cases in the literature are attributed to Alzheimer’s disease (AD), though individual cases due to primary diffuse LBD, CBD and prion disease have been reported<sup>2–4</sup>. PCA is often sporadic and is rarely present in autosomal dominant cases of AD. The apolipoprotein E  $\epsilon$ 4 allele (*APOE4*) is associated with increased risk of PCA, though the strength of the association is less than that observed in amnesic AD<sup>5</sup>. In vivo biomarkers (PET, CSF and plasma) of amyloid-beta ( $A\beta$ ) or tau can provide evidence for or against the presence of AD neuropathology in patients presenting with clinical PCA<sup>6</sup>, while brain imaging with MRI or <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) PET can support the diagnosis by demonstrating a characteristic pattern of atrophy or hypometabolism in parieto-occipital and parieto-temporal regions<sup>7</sup>.

As a relatively rare syndrome, most reports of PCA have come from single sites, included modest sample sizes, and usually focused on specific clinical, genetic, neuroimaging or fluid biomarker features. A comprehensive clinical overview of the features of PCA in a large and representative sample is lacking. The goal of the present study was to describe demographic, clinical, biomarker and neuropathologic correlates in a large-scale international cohort of PCA patients by pooling together individual participant data.

## Materials and methods

### Search for centers and data collection

We contacted 55 research centers conducting PCA research identified in a literature review following the PRISMA (<http://www.prisma-statement.org/>) guidelines (n=1353 papers), and additional sites were recruited by advertising via the Alzheimer’s Association International Society to Advance Alzheimer’s Research and Treatment (ISTAART) Atypical AD Professional Interest Area (n=7 sites). The search was conducted on PubMed and the terms included: posterior cortical atrophy; PCA; Benson syndrome; visual variant of AD; progressive posterior cortical dysfunction; combined with: biomarkers; neuropathology; autopsy; cerebrospinal fluid; CSF; positron emission tomography; PET. Papers written in English were considered, and there was no restriction on the time period for the search. We requested de-identified, single-subject data from PCA patients (published and unpublished) at the first diagnostic visit. Inclusion criteria were: clinical diagnosis of PCA, *and* availability of AD biomarkers (PET or CSF) *and/or* autopsy diagnosis. Not all PCA patients fulfilled recent consensus criteria, being diagnosed using center-specific procedures *and/or* before development of consensus criteria. After contacting all potential sites, we surveyed potential collaborators to gather data and used the results to create the main database. All variables included in the database are presented in Supplementary Table 1. Demographic variables were: age at diagnostic visit, age at death, age at symptom onset, sex, education, handedness, and *APOE4* carrier status. Clinical variables included: MMSE

total score, CDR global score, any other severity/staging information, diagnosis (PCA pure or PCA plus by Crutch criteria), diagnosis details (other features if PCA plus), Mendez<sup>8</sup> and/or Tang-Wai criteria<sup>2</sup> (fulfilled or not), and other clinical and cognitive information based on the most recent consensus criteria<sup>1</sup>. Sites were also asked which of the 4 non-visuospatial cognitive or neuropsychiatric domains were relatively spared at the time of diagnosis: anterograde memory, speech and nonvisual language, executive functions, and behavior. For the sake of the analyses, these variables were flipped to estimate the frequency of the domains being relatively impaired in patients with PCA.

Biomarker variables included CSF amyloid and p-tau, amyloid and tau PET, MRI scan showing predominant posterior atrophy, 18F-FDG-PET showing predominant posterior hypometabolism, and DaT-SPECT showing dopamine transporter nigrostriatal loss. All centers used their own thresholds and criteria for defining a biomarker as positive or negative.

Neuropathologic variables were collected according to the most recent diagnostic criteria for each neuropathology (see Supplementary Table 1) and included: main neuropathologic and contributing diagnoses, neurofibrillary tangle Braak stage, A $\beta$  plaque Thal phase), neuritic plaque CERAD score, LBD Braak staging, amygdala-predominant LBD, limbic-predominant age-related TDP-43 encephalopathy neuropathological change staging, argyrophilic grain disease staging, hippocampal sclerosis, vascular injury, cerebral amyloid angiopathy, aging-related tau astroglialopathy, chronic traumatic encephalopathy, CBD and prion disease. All neuropathological variables were considered as binary variables (present/absent) due to the small sample sizes and differences in procedures across sites.

### **Institutional Review Board (IRB) review and data agreements**

The University of California in San Francisco (UCSF) was the leading institution of this project. A waiver or alteration of informed consent that applies to all subjects involved in the current study was acquired through the IRB of the Research Protection Program, which reviews and monitors research involving human subjects at UCSF and affiliated institutions to ensure the ethical treatment of the research subjects.

### **Statistical analysis**

The primary goal of the study was to describe key demographic, clinical, biomarker, and neuropathological data from all patients by aggregating data across sites; we did so by using a meta-analysis framework. Mean values for continuous variables (e.g., age, MMSE) were combined using the inverse variance meta-analysis method; only sites with more than one participant on a variable were included. Pooled proportions were calculated for binary variables (e.g., sex, APOE4 status) using a restricted maximum likelihood model. In all meta-analyses, heterogeneity was quantified using the  $I^2$  statistics. In secondary analyses, we compared two groups of patients (e.g., amyloid positive versus negative, men versus women, PCA pure versus PCA plus) using linear mixed effect models for continuous or mixed-effect logistic regression for categorical outcomes. In both cases, a random intercept was included for each site, and 95% confidence intervals (CI) were estimated using likelihood profile method. As this is an exploratory descriptive study, correction for

multiple comparisons was not applied. All statistics were conducted using Jamovi 1.2.27.0 (<https://www.jamovi.org/>) and Stata.

## Results

We collected individual patient data from 1,092 patients evaluated at 36 sites in 16 countries (see Supplementary Table 2 for list of sites and corresponding number of patients). Note that 45% of all patients (and 72% of patients with autopsy) were evaluated in the United States (Supplementary Table 3).

Group-level pooled estimates for main demographic and clinical variables are presented in Table 1; gran-ular (i.e., site-level) data are presented in Supplementary Figures 1–10. The sample consisted of 60% [95%CI 56–64] women, mean age at symptom onset was 59.4 [95%CI 58.9–59.8], mean age at first diagnostic visit was 63.3 [95%CI 62.8–63.6]. 80% [95%CI 72–89] presented with a “PCA pure” and 20% [95%CI 11–28] with a “PCA plus” clinical syndrome, as defined by Crutch 2017 diagnostic criteria <sup>1</sup>. At their diagnostic visit, patients had a mean MMSE score of 20.7 [95%CI 20.4–21.1], and 61% [95%CI 53–71] had a global CDR score <sup>1</sup>. Most patients were right-handed (92% [95%CI 90–95]) and 43% [95%CI 35–50] carried at least one copy of the *APOE-ε4* allele. In the subsample of 228 patients (21 sites) who were reported to be deceased, mean age at death was 70.5 [95%CI 69.5–71.4].

The frequencies of core features and involvement of additional cognitive or neuropsychiatric domains at the first diagnostic visit are shown in Figure 1A and 1B, respectively. Constructional dyspraxia was the most frequently reported (61% [95%CI 51–73]) core PCA clinical feature, followed by space perception deficit (49% [95%CI 38–61]), simultanagnosia (48% [95%CI 36–61]), and acalculia (47% [95%CI 38–57]). The less frequently reported core clinical features were finger agnosia (20% [95%CI 13–28]), oculomotor apraxia (18% [95%CI 11–26]), and apperceptive prosopagnosia (17% [95%CI 10–24]). The as-sociations between core features are presented in Supplementary Figure 11. Besides visuo-perceptual functions, at the time of diagnosis, 47% [95%CI 36–58] of patients had relatively impaired anterograde memory, 40% [95%CI 29–52] had relatively impaired executive functions, 33% [95%CI 21–44] had rel-atively impaired non-visual language and speech, and 32% [95%CI 22–42] had relatively impaired be-havior. It should be noted that data on the frequency of clinical features was highly heterogeneous across studies, as indicated by  $I^2 > 89\%$ .

Biomarker findings are reported in Figure 2 (see also Supplementary Figures 12–19 for site-level data and forest plots). When reported, CSF A $\beta$  was positive (i.e., in the AD range) in 81% [95%CI 75–87] and CSF p-tau was positive in 65% [95%CI 56–75], with marked heterogeneity across sites ( $I^2 > 75\%$ ). PET biomarkers for amyloid and tau were highly positive (amyloid: 94% [95%CI 91–97], tau: 97% [95%CI 93–100]) and the heterogeneity statistics were low ( $I^2 < 15\%$ ). Predominant posterior cortical atrophy was found in 85% [95%CI 79–91] patients while predominant posterior 18F-FDG-PET hypome-tabolism was reported in 97% [95%CI 95–98] of cases. DaT-SPECT scan results were reported in a small



subsample (72 patients from 15 sites) and showed evidence of nigrostriatal loss in 51% [95% CI 33–69] of patients.

To assess the associations between AD biomarker results and clinical variables, we classified the 689 patients (30 sites) with available (PET or CSF) amyloid biomarker as ‘amyloid-positive’ when at least one of the A $\beta$  biomarkers was positive and ‘amyloid-negative’ when both markers, or the only available marker was negative. Group comparisons are shown in Table 2. Compared to amyloid-negative patients, amyloid-positive patients were more likely to have a PCA-pure (86% vs 62%,  $p < 0.0001$ ) than a PCA-plus syndrome; were slightly younger at symptom onset and diagnosis; and tended to have a higher proportion of women (63%, vs, 53%,  $p = 0.085$ ). Other features were similar in A $\beta$ -positive and negative groups.

Thirteen sites shared autopsy results from a total of 145 participants. This subsample included 50% women [95% CI 38–61], with a mean age at symptom onset of 58.6 [95% CI 57.4–59.8], and a mean age at death of 69.4 [95% CI 68.2–70.6]. Across sites, the primary neuropathological diagnosis was AD with a pooled estimate of 94% [95% CI 90–97] and minimal heterogeneity ( $I^2 = 0$ ); see Figure 3a. Most patients with primary AD were found to have one or more co-pathologies, the most common being cerebral amyloid angiopathy (71%), Lewy body disease (44%), and cerebrovascular injury (42%); see Figure 3B and Supplementary Figure 20.

Overall, only 10 cases (from 6 sites) had a non-AD primary neuropathological diagnosis; see Table 3 for details. Briefly, 4 patients had a primary neuropathological diagnosis of Lewy body disease, all of whom also had significant levels of AD neuropathological changes. Other primary etiologies included fronto-temporal lobar degeneration with non-AD tauopathy ( $n = 2$  with corticobasal degeneration,  $n = 1$  with Pick’s disease) or with TDP-43 pathology type A ( $n = 1$ , who was due to a pathogenic granulin (*GRN*) mutation). Lastly, two patients had a primary diagnosis of brain infarct with minimal comorbid AD neuropathology; note that both cases were older (onset at 88 and 90 years old) and were enrolled at the same site.

We investigated the associations between sex and key clinical, biomarker, and neuropathological variables. On average, women had lower MMSE scores at their first diagnostic visit (difference = 1.08 [95% CI 0.3–1.8],  $p = 0.0046$ ), and were more likely to have a PCA pure syndrome compared to men (95% [95% CI 97–98] versus 91% [95% CI 78–97],  $p = 0.0048$ ). As mentioned above, women tended to be more amyloid-positive compared to men: 91% [95% CI 96–94] versus 87% [95% CI 80–92],  $p = 0.089$ . No other sex differences were observed (see Supplementary Table 4).

Lastly, we assessed the relationships between the diagnosis of PCA pure versus PCA plus on key clinical, biomarker, and neuropathological variables. Overall, patients with PCA pure had a younger age of symptom onset (difference = 2.4 years [95% CI 0.9–3.9],  $p = 0.0018$ ) and age at diagnostic visit (difference = 3.6 years [95% CI 2.1–5.0],  $p < 0.0001$ ) compared to patients with PCA plus. The PCA plus group had a lower frequency of women (non-significant trend) and a significantly lower rate of positive amyloid biomarkers compared to the PCA pure group (see Supplementary Table 5 for details).



## Discussion

In this multi-site, international study involving 1,092 participants diagnosed with PCA who had available AD biomarkers and/or autopsy data, we found that the syndrome generally has an early age-of-onset, disproportionately affects women, and often presents in its pure form (i.e., without clinical features of other neurodegenerative diseases) per Crutch 2017 diagnostic criteria.<sup>1</sup> By the time of diagnosis, patients are usually at the dementia stage, and additional cognitive domains are often impaired. While *APOE4* genotype prevalence is enriched compared to a normal population, it is lower than in amnesic AD,<sup>9</sup> suggesting a weaker link between APOE genotype and PCA. Importantly, amyloid biomarkers are positive in over 89% of individuals, and AD was the primary diagnosis in 94% of patients with autopsy data, underscoring that the PCA clinical syndrome is caused by underlying AD neuropathology in most cases.

Our cohort consisted of 60% women versus 40% men. This ratio is consistent with previous findings from smaller studies, which showed that PCA affects women to a larger extent than men<sup>5</sup>. Reports on sex predilection have varied across AD variants, with a higher proportion of women to men in amnesic (just over 50% women in most studies<sup>10</sup> and dysexecutive AD (62% women)<sup>11</sup> and a higher proportion of men in logopenic-variant primary progressive aphasia (lvPPA; 52% men)<sup>12</sup> and behavioral-variant AD (62% men).<sup>13</sup> A previous study reported that the prevalence of mathematical and visuospatial learning disabilities is higher in PCA patients than in other clinical presentations of AD<sup>14</sup>. Given that the prevalence of mathematical learning disabilities is higher in girls versus boys during schooling<sup>15</sup>, women could have a greater cognitive vulnerability to the PCA syndrome. We found that the frequency of acalculia was significantly higher in women versus men, which is consistent with this hypothesis.

PCA is often associated with an early age of onset<sup>16,17</sup>. In our study, average age of onset was 59.4 years old and 75% of patients had an age of onset less than 65 (the 3<sup>rd</sup> quartile of the distribution, see Supplementary Figure 5), the common threshold for early-onset dementia. At the time of diagnosis, mean MMSE was 21 and mean global CDR was 1 (mild dementia), suggesting that symptoms are relatively advanced at the time of first diagnosis.<sup>18</sup> Consistent with this, some clinicians reported involvement of additional cognitive or behavioral domains at first diagnostic visit, likely reflecting progression from an initial pure visuo-perceptual/visuospatial syndrome to a multi-domain dementia. Patients with PCA often face a delay in diagnosis due to their young age and visual-predominant symptoms<sup>19</sup>. Better awareness of the syndrome of PCA amongst primary care providers, optometrists/ophthalmologists and neurologists is needed for earlier detection and treatment.

Previous clinicopathologic studies have shown that AD is the most common neuropathologic cause of PCA, though some cases are due to LBD, CBD and prion disease<sup>2-4</sup>. Although these studies emerged from various sites, the samples were generally small due to the rareness of the syndrome and the challenges associated with postmortem data collection. In this larger multi-site sample, we found a very strong correlation between PCA syndrome and AD neuropathology, which is stronger than the reported relationships between other clinical variants and underlying AD.<sup>12,20</sup> Indeed, previous studies reported that AD pathology

is found in about 70% of patients with an amnesic presentation, and 76% of patients presenting with lvPPA. Here, we found that AD pathology is found in 94% of patients with PCA. Only ten patients received a primary neuropathologic diagnosis that was not AD, and half of them were also found to have intermediate-high ADNC. Therefore, PCA might be the most predictive clinical syndrome for underlying AD. As has been shown in smaller series, other neuropathologies that can be considered in the differential diagnosis of PCA include LBD, CBD, FTLT-DTP Type A and Pick's disease. No cases of prion disease were reported in our sample, but these have been reported previously. Two cases of PCA due to brain infarcts were reported in this series, both occurring in patients in their 90s. It is unclear if these cases would have met current clinical criteria for PCA, which exclude acute or non-progressive presentations. These cases do raise the possibility of alternative etiologies for PCA in the very old.

Biomarkers are useful for supporting or excluding AD as the cause of the dementia syndrome during life, particularly in patients presenting with non-amnesic syndromes or early age-of-onset<sup>28</sup>. Like other clinical variants of AD, CSF A $\beta$ <sub>1-42</sub> concentrations or the ratio of A $\beta$ <sub>1-42</sub> / A $\beta$ <sub>1-40</sub> are lowered, and total and phosphorylated tau 181 levels concentrations are elevated in the early stages of PCA<sup>21-23</sup>. Similarly, previous studies have reported high proportions of amyloid and tau PET positivity in PCA cohorts. In our study, CSF A $\beta$ , amyloid and tau PET all were very frequently in the AD range in patients with PCA, including those with autopsy-confirmed AD. In contrast, CSF p-tau showed limited sensitivity in our cohort. Previous studies have indicated limited sensitivity of CSF p-tau as a "stand-alone" biomarker for ADNC, and diagnostic accuracy is improved by calculating the ratio of CSF p-tau/A $\beta$ <sub>1-42</sub><sup>23</sup>. We found atrophy and hypometabolism in posterior cortical regions in 89% and 97% of participants, making both MRI and 18F-FDG-PET techniques robust techniques to help with PCA diagnosis in vivo by establishing a neurodegenerative basis and posterior cortical localization. Importantly, the prevalence of "PCA-plus" features was significantly higher in amyloid biomarker-negative compared to amyloid-positive individuals, which suggests that non-AD pathologies could be mostly responsible for the "plus" clinical findings (ex: limb rigidity, parkinsonism, etc.).

Our results corroborate syndrome and disease level descriptions outlined in PCA consensus classification in an international multi-center study. The frequency of each of the core clinical features was very similar to what was found in the recent consensus classification paper, and predominantly included mixed ventral and dorsal visual stream features<sup>1</sup>. Constructional dyspraxia, space perception deficit, simultanagnosia, and acalculia were commonly reported (>50%). In the consensus classification paper, the most frequent clinical features were also constructional dyspraxia, space perception deficit and simultanagnosia, although acalculia was slightly less common. Less frequent features in both cohorts, include finger agnosia, oculomotor apraxia and apperceptive prosopagnosia.

One of the major strengths of this study is the size and the geographical diversity of our sample; we collected data from 1,092 patients in 16 different countries and 36 individual sites, which represents by far the largest and most representative study conducted on PCA to date. Another strength of this study is the number of cases with autopsy data. We obtained

the main neuropathologic diagnosis for 145 participants and quantified the prevalence of other common neuropathologies in subsamples ranging from 50 to 145 participants.

Our study also has limitations. This is a retrospective study that aggregated data from multiple centers without a standard clinical protocol. All data, including most notably the diagnosis of PCA, were based on the standards applied at the local site. This enhances generalizability, but also can lead to high heterogeneity (as evidenced by high I2 values for some variables) as well as non-randomness of missing data. It is likely that some biases impacted whether certain clinical features were assessed or whether bi-omarkers were ordered (e.g., DaT-SPECT imaging was only available in 74 patients and may have been ordered only in patients with suspected LBD). We took a conservative approach by assuming clinical features were absent if missing, which may lead to under-estimation of their true prevalence. Data were aggregated at sites over years, during which clinical definitions of PCA evolved. The site data survey was designed to minimize site burden, resulting in less available detail. Future prospective studies of PCA should promote cross-center comparability through standardized protocols and include age- and severity-matched disease control groups (especially with other variants of AD) for comparison<sup>27</sup>. Future work should also include data on race/ethnicity in PCA and provide more detailed information on bi-omarkers (ex: specific CSF assays used). Lastly, as this is an exploratory descriptive study, correction for multiple comparisons in the statistical models was not applied, and no adjustment for confounders was included in the analyses.

In conclusion, this multi-site study refines our understanding of the relationship between pathology, biomarkers, and clinical features in PCA, and provides up-to-date descriptive statistics related to this syndrome. Our results highlight the strong link between PCA and underlying AD and emphasize the importance of AD biomarker testing as part of the diagnostic evaluation of patients with PCA.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data sharing

Applications for data sharing by qualified investigators can be made to the UCSF Alzheimer's Disease Research Center (<https://memory.ucsf.edu/research-trials/professional/open-science>). Data sharing requests will be subject to the limitations specified in data transfer agreements between UCSF and the individual sites providing data for this single-subject meta-analysis.

## References

1. Crutch SJ, Schott JM, Rabinovici GD, et al. Consensus classification of posterior cortical atrophy. *Alzheimers Dement* 2017; 13(8): 870–84. [PubMed: 28259709]
2. Tang-Wai DF, Graff-Radford NR, Boeve BF, et al. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology* 2004; 63(7): 1168–74. [PubMed: 15477533]

3. Alladi S, Xuereb J, Bak T, et al. Focal cortical presentations of Alzheimer's disease. *Brain* 2007; 130(Pt 10): 2636–45. [PubMed: 17898010]
4. Renner JA, Burns JM, Hou CE, McKeel DW, Jr., Storandt M, Morris JC. Progressive posterior cortical dysfunction: a clinicopathologic series. *Neurology* 2004; 63(7): 1175–80. [PubMed: 15477534]
5. Schott JM, Crutch SJ, Carrasquillo MM, et al. Genetic risk factors for the posterior cortical atrophy variant of Alzheimer's disease. *Alzheimers Dement* 2016; 12(8): 862–71. [PubMed: 26993346]
6. Zou K, Abdullah M, Michikawa M. Current Biomarkers for Alzheimer's Disease: From CSF to Blood. *J Pers Med* 2020; 10(3).
7. Whitwell JL, Jack CR Jr., Kantarci K, et al. Imaging correlates of posterior cortical atrophy. *Neurobiol Aging* 2007; 28(7): 1051–61. [PubMed: 16797786]
8. Mendez MF, Ghajarian M, Perryman KM. Posterior cortical atrophy: clinical characteristics and differences compared to Alzheimer's disease. *Dement Geriatr Cogn Disord* 2002; 14(1): 33–40. [PubMed: 12053130]
9. Crean S, Ward A, Mercaldi CJ, et al. Apolipoprotein E epsilon4 prevalence in Alzheimer's disease patients varies across global populations: a systematic literature review and meta-analysis. *Dement Geriatr Cogn Disord* 2011; 31(1): 20–30. [PubMed: 21124030]
10. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology* 2010; 74(3): 201–9. [PubMed: 20042704]
11. Townley RA, Graff-Radford J, Mantyh WG, et al. Progressive dysexecutive syndrome due to Alzheimer's disease: a description of 55 cases and comparison to other phenotypes. *Brain Commun* 2020; 2(1): fcaa068. [PubMed: 32671341]
12. Bergeron D, Gorno-Tempini ML, Rabinovici GD, et al. Prevalence of amyloid-beta pathology in distinct variants of primary progressive aphasia. *Ann Neurol* 2018; 84(5): 729–40. [PubMed: 30255971]
13. Ossenkoppele R, Singleton EH, Groot C, et al. Research Criteria for the Behavioral Variant of Alzheimer Disease: A Systematic Review and Meta-analysis. *JAMA Neurol* 2022; 79(1): 48–60. [PubMed: 34870696]
14. Miller ZA, Rosenberg L, Santos-Santos MA, et al. Prevalence of Mathematical and Visuospatial Learning Disabilities in Patients With Posterior Cortical Atrophy. *JAMA Neurol* 2018; 75(6): 728–37. [PubMed: 29630699]
15. Dirks E, Spyer G, van Lieshout EC, de Sonneville L. Prevalence of combined reading and arithmetic disabilities. *J Learn Disabil* 2008; 41(5): 460–73. [PubMed: 18768777]
16. Suarez-Gonzalez A, Lehmann M, Shakespeare TJ, et al. Effect of age at onset on cortical thickness and cognition in posterior cortical atrophy. *Neurobiol Aging* 2016; 44: 108–13. [PubMed: 27318138]
17. Schott JM, Crutch SJ. Posterior Cortical Atrophy. *Continuum (Minneapolis)* 2019; 25(1): 52–75. [PubMed: 30707187]
18. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. *Lancet Neurol* 2012; 11(2): 170–8. [PubMed: 22265212]
19. Graff-Radford J, Yong KXX, Apostolova LG, et al. New insights into atypical Alzheimer's disease in the era of biomarkers. *Lancet Neurol* 2021; 20(3): 222–34. [PubMed: 33609479]
20. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. *J Neuropathol Exp Neurol* 2012; 71(4): 266–73. [PubMed: 22437338]
21. Grothe MJ, Moscoso A, Ashton NJ, et al. Associations of Fully Automated CSF and Novel Plasma Biomarkers With Alzheimer Disease Neuropathology at Autopsy. *Neurology* 2021.
22. Seeburger JL, Holder DJ, Combrinck M, et al. Cerebrospinal fluid biomarkers distinguish postmortem-confirmed Alzheimer's disease from other dementias and healthy controls in the OPTIMA cohort. *J Alzheimers Dis* 2015; 44(2): 525–39. [PubMed: 25391385]
23. Mattsson-Carlgen N, Grinberg LT, Boxer A, et al. Cerebrospinal Fluid Biomarkers in Autopsy-Confirmed Alzheimer Disease and Frontotemporal Lobar Degeneration. *Neurology* 2022; 98(11): e1137–e50. [PubMed: 35173015]

24. Karanth S, Nelson PT, Katsumata Y, et al. Prevalence and Clinical Phenotype of Quadruple Misfolded Proteins in Older Adults. *JAMA Neurol* 2020; 77(10): 1299–307. [PubMed: 32568358]
25. Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain* 2018; 141(7): 2181–93. [PubMed: 29878075]
26. Spina S, La Joie R, Petersen C, et al. Comorbid neuropathological diagnoses in early versus late-onset Alzheimer’s disease. *Brain* 2021; 144(7): 2186–98. [PubMed: 33693619]
27. Apostolova LG, Aisen P, Eloyan A, et al. The Longitudinal Early-onset Alzheimer’s Disease Study (LEADS): Framework and methodology. *Alzheimers Dement* 2021; 17(12): 2043–55. [PubMed: 34018654]
28. Palmqvist S, Zetterberg H, Mattsson N, et al. Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. *Neurology* 2015; 85(14): 1240–9. [PubMed: 26354982]



## Research in context panel

### Evidence before this study:

We searched PubMed for articles on posterior cortical atrophy (PCA) with no language restrictions from database inception up to August 1<sup>st</sup>, 2022, using the following terms: “posterior cortical atrophy”, “posterior cortical atrophy pathology”, “posterior cortical atrophy Alzheimer’s disease”, “visual variant of Alzheimer’s disease”, “atypical Alzheimer’s disease”, “non-amnesic Alzheimer’s disease”, focusing on studies that reported neuropathologic findings in PCA. A few studies investigated the neuropathologic profiles of patients with PCA and have shown a high prevalence of cases due to Alzheimer’s disease (AD) pathology, although some case series have reported cases due to Lewy body pathology, corticobasal degeneration and prion disease. However, these studies had small sample sizes (ranging from 20 to 40 patients) and none of them systematically reported and analyzed clinical, biomarker and neuropathologic data in a large, multi-site sample of PCA patients.

### Added value of this study:

We collected demographic, clinical, biomarker and neuropathologic data in 1,092 patients with PCA in 16 countries and 36 different sites. Variables included age at symptom onset, at diagnostic visit and at death, apolipoprotein E4 (*APOE4*) status, Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) global scores, diagnostic details per the most recent research criteria (i.e., PCA pure versus PCA plus), individual symptoms, other cognitive domains relatively spared, imaging and fluid markers ((Magnetic Resonance Imaging (MRI), Dopamine Transporter (DaT)-Single-photon emission computed tomography (SPECT), <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) Positron Emission Tomography (PET), amyloid-PET, tau-PET, cerebrospinal fluid (CSF) amyloid and tau)) and neuropathologic findings (main neuropathologic diagnosis, presence/absence of common neuropathologies, staging of specific pathologies). This multi-site study refined our understanding of the relationship between pathology, biomarkers and clinical features in PCA. Our findings highlight the early age-of-onset and female predominance of this syndrome. We showed that AD is by far the most common underlying neuropathology and that PCA may be the most predictive syndrome for AD neuropathology. We also showed that co-pathologies are frequent.

### Implications of all the available evidence:

Our study provides up-to-date demographic, clinical, biomarker and neuropathologic data in PCA. Our findings show a clear added value of *in vivo* biomarkers for AD, and other imaging tools to capture atrophy and hypometabolism patterns, which closely mirror the symptomatology in PCA. Our results are also consistent with the most recent consensus criteria, which stated the importance of distinguishing “PCA pure” (core PCA syndrome only) versus “PCA plus” (core PCA syndrome *and* core features of another neurodegenerative syndrome) presentations, as these two groups may reflect distinctive pathophysiological processes. Further work is needed to understand what drives cognitive vulnerability and progression rates by investigating the contribution of sex, genetics, premorbid cognitive strengths/weaknesses, and brain network integrity. The present study



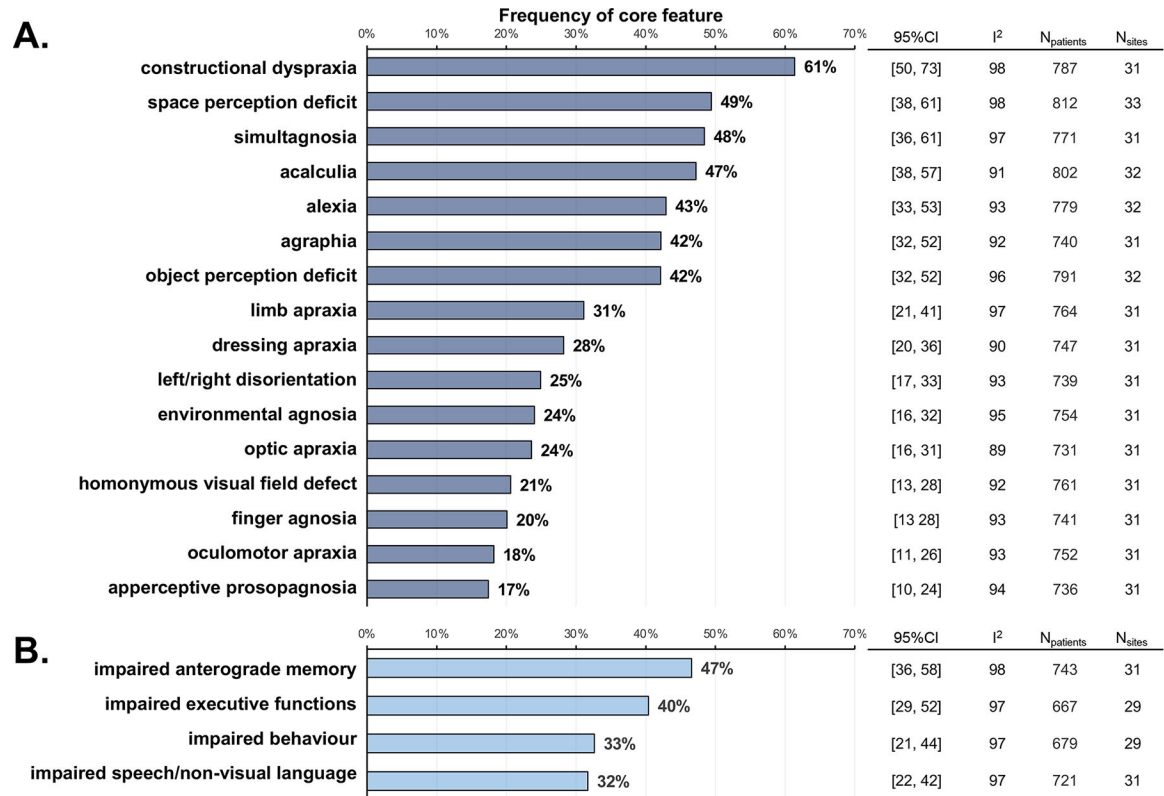
will provide clinicians, patients, and caregivers with a better understanding of the specific clinical features of PCA and their associations with the underlying disease(s).

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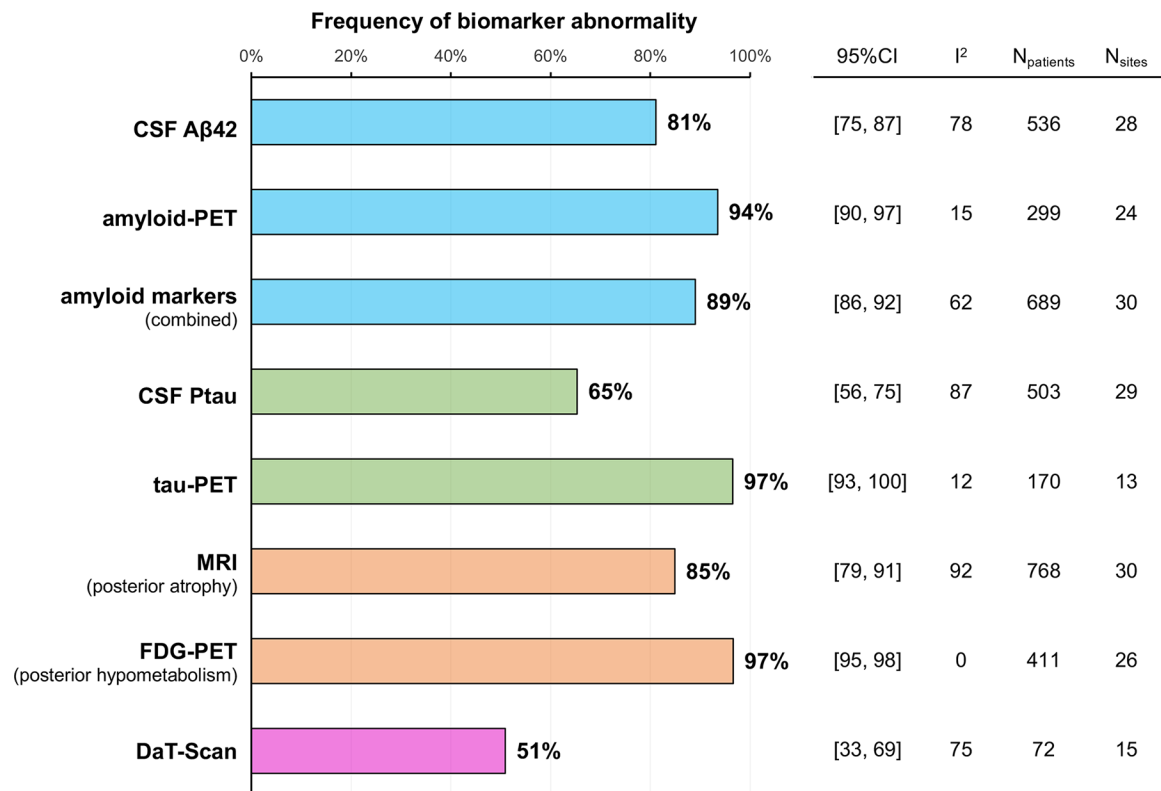
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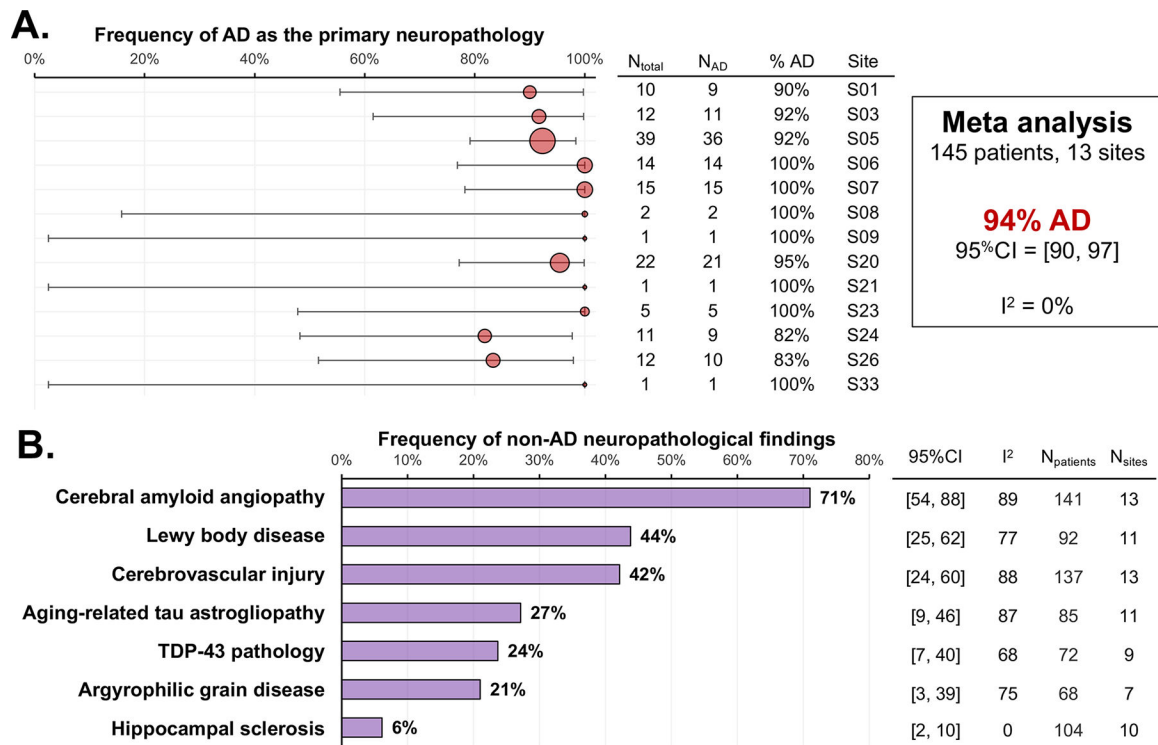
**Figure 1.**

Frequencies of core features and involvement of additional cognitive or neuropsychiatric domains at the first diagnostic visit. Biomarker findings are reported in figure 2 (site-level data are in the appendix pp 20–27). When reported, CSF amyloid  $\beta$  was positive (ie, in the range consistent with underlying brain amyloid or tau deposition) in 81% (95% CI 75–87) of participants and CSF p-tau was positive in 65% (56–75), but findings were heterogeneous across research centres ( $I^2 > 75\%$ ). Amyloid-PET and tau-PET were positive for most participants (amyloid-PET, 94% [95% CI 90–97]; tau-PET 97% [93–100]), and heterogeneity statistics were low ( $I^2 = 15\%$ ). Predominant posterior cortical atrophy on MRI was found in 85% (79–91) of participants, and predominant posterior [18F]FDG-PET hypometabolism was reported for 97% (95–98). DaT-SPECT scan results were reported in a small subsample (72 participants from 15 research centres) and showed evidence of nigrostriatal loss in 51% (95% CI 33–69) of participants.



**Figure 2.**

Frequency of biomarker abnormality. To assess associations between Alzheimer's disease biomarker results and clinical variables, 689 participants from 30 research centres who had either amyloid-PET or CSF amyloid biomarker data (or both) were classified as amyloid-positive when at least one of the biomarkers was positive, and as amyloid-negative when both markers (or the only available marker) were negative. Group comparisons are shown in table 2. Patients who were amyloid-positive were more likely to have posterior cortical atrophy pure than were amyloid-negative patients (95% vs 81%,  $p < 0.0001$ ). Age at symptom onset and age at diagnosis, sex, and other clinical features did not differ by amyloid status.



**Figure 3.**

Frequency of neuropathological findings in the sample. Only ten participants from six research centres had a primary neuropathological diagnosis that was not Alzheimer's disease (table 3). Four had a primary neuropathological diagnosis of Lewy body disease, all of whom also had significant levels of Alzheimer's disease neuropathological changes. Other primary diagnoses were frontotemporal lobar degeneration with non-Alzheimer's disease tauopathy (n=3, two with corticobasal degeneration and one with Pick's disease) or TDP-43 type A (n=1, due to a pathogenic granulin [GRN] mutation), and brain infarct with minimal comorbid Alzheimer's disease neuropathology (n=2; both cases had late age at onset [ages 88 years and 90 years] and were from the same research centre).

**Table 1.**

Demographical and clinical description of the full sample

	Pooled estimate (mean/frequency)	95%CI	N <sub>patients</sub>	N <sub>sites</sub>	I <sup>2</sup>
<b>Demographics</b>					
Sex (% women)	60%	[56, 64]	1092	36	35.0
Handedness (% right)	93%	[90, 95]	872	32	42.8
Years of education	14.1	[13.9, 14.2]	949	35	93.1
APOE (% e4 carriers)	43%	[35, 50]	451	22	55.5
<b>Clinical</b>					
Age at symptom onset, years	59.4	[58.9, 59.8]	1031	34	77.4
Age at diagnosis, years	63.2	[62.8, 63.6]	1067	36	76.8
Age at death, years	70.5	[69.5, 71.4]	227	20	72.7
Diagnosis (% PCA pure)	80%	[72, 89]	968	34	97.9
MMSE at diagnosis, points (range : 0–30)	20.7	[20.4, 21.1]	904	31	69.9
CDR at diagnosis (% CDR 1)	62%	[53, 71]	558	27	81.1
Mendez criteria (% fulfilled)	75%	[60, 90]	535	21	99.4
Tang-Wai criteria (% fulfilled)	80%	[68, 92]	535	21	98.6
Early disturbance of posterior function (% yes)	91%	[85, 97]	992	36	98.1
Insidious onset and gradual progression (% yes)	99%	[98, 99]	809	34	0

Mean values or frequency, and their corresponding 95% confidence intervals are derived from the meta-analysis of all available data. Sites with only one available datapoint (two sites for “MMSE”, one site for “age at death”) were not included in the meta-analysis. Raw data, including breakdown of each site, is presented in Supplementary Figures 1–10. Abbreviations: MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating scale.

**Table 2.**

Comparison of the demographic and clinical characteristics of amyloid-positive and amyloid-negative patients

	N <sub>patients</sub>	N <sub>sites</sub>	Estimate [95%CI]	p	Marginal means [95%CI]	
					A $\beta$ -negative	A $\beta$ -positive
Age at symptom onset	644	28	-1.322 [-3.130, 0.477]	0.15	60.4 [58.4, 62.4]	59.1 [57.8, 60.4]
Age at diagnosis	671	30	-1.415 [-3.18, 0.348]	0.12	63.9 [62.0, 65.8]	62.5 [61.4, 63.6]
MMSE at diagnosis	596	28	-0.059 [-1.350, 1.290]	0.93	20.8 [19.5, 22.2]	20.7 [19.9, 21.6]
CDR at diagnosis (%CDR-1)	413	21	0.118 [-0.573, 0.818]	0.74	61% [42, 77]	58% [46, 70]
Sex (% Women)	689	30	0.406 [-0.058, 0.867]	0.085	53% [42, 63]	63% [59, 67]
APOE (% e4 carriers)	342	22	0.089 [-0.639, 0.818]	0.81	45% [29, 62]	47.5% [40, 55]
PCA diagnosis (% PCA pure)	625	29	1.506 [0.769, 2.26]	<0.0001	81% [56, 94]	95% [86, 98]
MRI (% posterior atrophy)	543	27	0.226 [-0.605, 1.060]	0.59	92% [78, 97]	94% [85, 97]
FDG-PET (% post. hypometabolism)	324	22	0.578 [-0.896, 2.05]	0.44	97% [84, 99]	98% [94, 99]

For each variable, a separate linear mixed model (continuous outcomes) or generalized mixed effect model (binary outcomes) was run, using amyloid status as a fixed effect and site as a random effect. Estimate 95%CI were obtained using the likelihood profile method. Number of participants and sites with available data varies from one variable to the other. A $\beta$ -positive patients included those who received a positive result on CSFA $\beta$ 42 and/or amyloid-PET, and A $\beta$ -negative patients received negative results from CSF or PET. This sample included 390 with CSF only, 153 with PET only, and 146 with both; in this subgroup 27 patients had discrepant results (3 CSF+/PET-, 24 CSF-/PET+) and were included in the amyloid-positive group.

**Table 3.** Clinical characteristics of the 10 patients with non-AD primary neuropathological diagnosis

Primary neuropathological diagnosis	Age at symptom onset	Age at death	Diagnosis	sex	APOE4 status	Thal phase	NFT Braak stage	CERAD score	ADNC level	Site
LBD	67	71	PCA plus	M	e4 carrier	5	IV	moderate	intermediate	S01
LBD	61	70	PCA pure	F	-	-	IV	frequent	intermediate	S03
LBD	58	68	-	M	e4 carrier	5	VI	frequent	high	S05
LBD	79	87	-	M	non-carrier	4	V	frequent	high	S05
FTLD-tau (CBD)	58	64	PCA plus	M	e4 carrier	2	II	sparse	low	S20
FTLD-tau (CBD)	51	57	PCA pure	M	non-carrier	0	0	none	none	S24
Brain infarct	90	91	-	F	-	1	0	sparse	low	S26
Brain infarct	88	94	-	F	-	0	0	none	none	S26
FTLD-TDP43 Type A	59	68	PCA pure	M	-	0	0	none	none	S24
FTLD-tau (Pick's)	58	68	PCA pure	F	e4 carrier	2	I	moderate	low	S05

Abbreviations: LBD: Lewy body disease, FTLD: frontotemporal lobar degeneration, CBD: corticobasal degeneration, TDP-43: TAR DNA-binding protein 43, APOE4: allele  $\epsilon 4$  of the apolipoprotein E gene, NFT: Neurofibrillary Tangles, CERAD: Consortium to Establish a Registry for Alzheimer's Disease, ADNC: Alzheimer's Disease Neuropathological changes, MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating scale. Corresponding site descriptions can be found in Supplementary Table 2.