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Association of *APOE*-Independent Alzheimer Disease Polygenic Risk Score With Brain Amyloid Deposition in Asymptomatic Older Adults

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Abstract

Background and Objectives

Brain amyloid deposition, a major risk factor for Alzheimer disease (AD), is currently estimated by measuring CSF or plasma amyloid peptide levels or by PET imaging. Assessing genetic risks relating to amyloid deposition before any accumulation has occurred would allow for earlier intervention in persons at increased risk for developing AD. Previous work linking amyloid burden and genetic risk relied almost exclusively on *APOE*, a major AD genetic risk factor. Here, we ask whether a polygenic risk score (PRS) that incorporates an optimized list of common variants linked to AD and excludes *APOE* is associated with brain amyloid load in cognitively unimpaired older adults.

Methods

We included 291 asymptomatic older participants from the INveStIGation of AlzHeimer's PredicTors (INSIGHT pre-AD) cohort who underwent amyloid imaging, including 83 amyloid-positive (+) participants. We used an Alzheimer's (A) PRS composed of 33 AD risk variants excluding *APOE* and selected the 17 variants that showed the strongest association with amyloid positivity to define an optimized (oA) PRS. Participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study (228 participants, 90 amyloid [+]) were tested as a validation cohort. Finally, 2,300 patients with AD and 6,994 controls from the European Alzheimer's Disease Initiative (EADI) were evaluated.

Results

A-PRS was not significantly associated with amyloid burden in the INSIGHT or ADNI cohorts with or without correction for the *APOE* genotype. However, oA-PRS was significantly associated with amyloid status independently of *APOE* adjustment (INSIGHT odds ratio [OR]: 5.26 [1.71–16.88]; ADNI OR: 3.38 [1.02–11.63]). Of interest, oA-PRS accurately discriminated amyloid (+) and (−) *APOE* ε4 carriers (INSIGHT OR: 181.6 [7.53–10,674.6]; ADNI OR: 44.94 [3.03–1,277]). A-PRS and oA-PRS showed a significant association with disease status in the EADI cohort (OR: 1.68 [1.53–1.85] and 2.06 [1.73–2.45], respectively). Genes assigned to oA-PRS variants were enriched in ontologies related to β-amyloid metabolism and deposition.

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INSIGHT pre-AD study group coinvestigators are listed in Appendix 2 at the end of the article.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **A-PRS** = Alzheimer's polygenic risk score; **CL** = Centiloid; **EADI** = European Alzheimer's Disease Initiative; **gnomAD** = Genome Aggregation Database; **GO** = Gene Ontology; **GWAS** = genome-wide association study; **HRC** = Haplotype Reference Consortium; **HWE** = Hardy-Weinberg equilibrium; **INSIGHT** = INveStIGation of AlzHeimer's PredicTors; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **oA-PRS** = optimized Alzheimer's polygenic risk score; **OR** = odds ratio; **PRS** = polygenic risk score; **sAD** = sporadic AD; **SNV** = single-nucleotide variation; **SUVR** = standard uptake value ratio; **TOPMed** = Trans-Omics for Precision Medicine.

Discussion

PRSs relying on AD genetic risk factors excluding *APOE* may improve risk prediction for brain amyloid, allowing stratification of cognitively unimpaired individuals at risk of AD independent of their *APOE* status.

Alzheimer disease (AD) is the most common cause of dementia and a major public health concern, with >130 million cases worldwide anticipated by 2050. AD is a complex disease with autosomal dominant transmission in rare early-onset familial AD[1] and a nonmendelian inheritance pattern in late-onset sporadic AD (sAD) that may explain 60%–80% of the attributable risk.[2] The first identified genetic variant associated with AD was the *APOE* ε4 allele.[3] Heterozygous carriers have a 3-fold higher AD risk, whereas homozygous individuals have a 15-fold higher AD risk.[4] The AD risk for homozygous individuals is estimated to be 30% at age 75 years and over 50% by age 85 years.[5] Since 2009, genome-wide association studies (GWAS) have identified more than 40 loci associated with sAD.[4,6]

Notably, the risk of developing AD associated with these GWAS variants is low, and therefore, it is of interest to calculate a weighted sum of identified risk variants to establish the cumulative risk of disease or phenotypic trait for a given individual, known as a polygenic risk score (PRS). Such approaches have been used to differentiate AD-related dementia stages[7-11] and to predict the age at disease onset[12-14] and/or clinical progression.[7-11] In some cases, the association was dependent on the *APOE* genotype.[7,12]

Few studies focused on the association of a PRS with relevant AD-linked phenotypes in cognitively unimpaired older adults. In participants without dementia, the PRS was associated with cerebral accumulation of β-amyloid (Aβ) measured by PETs. 5 Similarly, a study of middle-aged individuals with a familial history of sAD revealed that specific PRSs that included *APOE* were associated with PET and CSF amyloid load.[16] A recent study based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort separated participants with AD-associated dementia, AD-associated mild cognitive impairment (MCI), and controls into amyloid (+) and amyloid (−) groups based on amyloid PET. Among the groups, a high-content PRS generated from 162,957 single-nucleotide variations (SNVs, formerly SNPs) did not predict amyloid status better than the *APOE* genotype alone.[10] Nevertheless, when using pathway-specific PRSs, lists related to lipid-protein interactions and cholesterol transport were significantly associated with brain amyloid load, even when excluding *APOE*.[10] Finally, a recent study using 39 AD genetic variants found that a high PRS and *APOE* ε4 separately predicted AD dementia in a retrospective cohort.[17]

Here, our objective was to test whether we could generate a PRS linked to amyloid status in cognitively unimpaired participants using a list of SNVs previously associated with AD but excluding *APOE*. A PRS optimized for amyloid status could identify at-risk individuals, encouraging them to seek future targeted prevention efforts.

Methods

Discovery Cohort: INSIGHT Cohort

We used data from the INveStIGation of AlzHeimer's PredicTors in a subjective memory complainer pre-Alzheimer disease (INSIGHT pre-AD) cohort comprising cognitively unimpaired volunteers, aged 70 years and older, who consulted at the Pitié-Salpêtrière University Hospital for memory complaints. All participants included had a Mini-Mental State Examination (MMSE) score of ≥27,[18] a Dementia Rating Score of 0, and normal episodic memory performance (assessed with the Free and Cued Selective Reminding Test). Additional available data for this population include age, sex, weight, body mass index, *APOE* genotype, medical treatments, education, residence location, and extensive neuropsychological and neuroimaging (MRI and FDG-PET) data. Participants underwent an initial ^{18}F-florbetapir PET scan to assess their brain amyloid load and were classified as amyloid (+) or amyloid (−). The global amyloid PET standard uptake value ratio (SUVR) was calculated as described previously.[18-20] To compare amyloid burden in several large cohorts using different radiotracers and analysis methods, a standardized

scale of amyloid burden quantification was proposed by Klunk.[21] This scale goes from 0 to 100, using a new unit called a Centiloid (CL). SUVR values were transformed to CL values using the center for acquisition and image processing (CATI) platform[22] by applying a 3-level method accounting for the radiotracer and the pipeline used to process the PET amyloid data.[21,23] INSIGHT participants were then divided into amyloid (−) and amyloid (+) groups using a 20-CL threshold, corresponding to an SUVR value of 0.79 and the following conversion equation: CL = (151 × SUVR) − 98.9. A cutoff of 20 CL was previously validated in populations with postmortem findings.[24,25] The ethics committee of the Pitié-Salpêtrière University Hospital approved the study protocol. All participants provided written informed consent through a form given and explained to them 2 weeks before enrollment. Neither the participants nor the investigators were aware of any participant's amyloid status.

Validation Cohort: ADNI Cohort

Additional data were obtained from the ADNI database.[26] The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of the ADNI is to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

The ADNI cohort is an independent cohort including controls and participants with MCI or AD.[26] We selected control participants from the ADNI cohort who underwent an ^{18}F-florbetapir PET scan, as with the INSIGHT cohort; had an MMSE score of ≥27; and were within the same age range as the INSIGHT cohort. SUVR values from the ADNI were transformed to CL using the following formula: CL = (196.9 × SUVR) − 196.03. We used the same threshold for amyloid positivity as for the INSIGHT cohort (20 CL).

AD Study: European Alzheimer's Disease Initiative

The European Alzheimer's Disease Initiative (EADI) is composed of several case-control studies and 1 population-based cohort, 3C.[27] The case-control studies are composed of AD cases and cognitively normal controls across France. The population-based cohort is from a prospective study on the relationship between vascular factors and dementia conducted in the 3 French cities: Bordeaux, Montpellier, and Dijon. AD status was defined based on 12 years of follow-up for Dijon participants, 14–15 years of follow-up for Montpellier participants, and 17–18 years of follow-up for Bordeaux participants. Participants without dementia from the 3C cohort were included as controls. All AD cases in the case-control studies and in 3C were ascertained by neurologists, and the clinical diagnosis of probable AD was established according to the *DSM-III-R* and NINCDS-ADRDA criteria.[28]

Genotyping

INSIGHT participants were genotyped using the Illumina NeuroX2 chip, a semicustom microarray based on a HumanCore-24+ v1.0 backbone containing 306,670 variants, with an additional 179,467 custom variants relevant for neurologic diseases. The design of this chip was reported previously.[29] Data quality control was performed using GenomeStudio 2.0 software (Illumina) and plink v.1.9 beta.[30] Quality control filtering removed 21,644 SNVs with low GenTrain scores (<0.7) and low genotyping rates (<98%), as well as those deviating from the Hardy-Weinberg equilibrium (HWE test p value $<10^{-6}$). Samples were checked for low call rate (<98%), individual relatedness, and ethnic discrepancies. The inbreeding coefficient was considered excessive when Fhat2 <−0.8. Sex discrepancies were checked and data updated where possible. Following these criteria, 10 participants were removed from further analyses. Imputation was performed using the Sanger Imputation Service on the Haplotype Reference Consortium dataset (release 1.1).[31] Low-imputation-quality variants were filtered using a threshold of $r^2 < 0.3$.

The ADNI cohort was genotyped using different Illumina microarrays; therefore, quality control and imputation were conducted separately using the same procedures. Variants were filtered for GenTrain score <0.7, clusterSeparation score ≤0.3, low call rate (<99%), rare variants (minor allele frequency <5%), and deviation from the HWE with $p < 10^{-6}$. Samples were filtered for missingness (>2%), relatedness, sex discrepancy, and excess heterozygosity. Imputation was performed using the Sanger Imputation Service on the Haplotype Reference Consortium dataset. Low-imputation-quality variants were filtered at a threshold of $r^2 < 0.3$.

The EADI study cohort was genotyped using the Illumina Human 610 Quad BeadChip at the Centre National de Recherche en Génomique Humaine (CNRGH, Evry, France). The genotyping chip was assessed using probe alignment and a remapping and normalization step according to the GRCh37 and GRCh38 assemblies. Sample quality control was performed as previously detailed.[32] Relatedness and variant quality control were recomputed as previously described.[33] Briefly, variants with a minor allele frequency of <0.01, missingness >0.05, a p value from the HWE test performed in controls $<5e^{-8}$, or a p value of the Fisher exact test on cases/controls missing calls $<1e^{-10}$ were excluded. The remaining variants were then assessed by comparing their frequencies against 2 reference panels (i.e., the Haplotype Reference Consortium r1.1 [HRC][31] excluding 1000 Genomes samples and the Genome Aggregation Database v3 [gnomAD] non-Finnish European samples[34]). Allele counts were then compared with the EADI counts by performing a χ^2 test; variants showing a χ^2 of >1,500 in both the HRC and gnomAD, or a χ^2 of >1,500 in one reference panel and not present in the other, were excluded. All samples and variants passing quality control were then imputed with the Trans-Omics for Precision Medicine (TOPMed) Freeze 5 reference panel[35] on the Michigan Imputation Server.[36] Low-imputation-quality variants were filtered at a threshold of $r^2 < 0.3$.

PRS Calculation and Statistical Analysis

To calculate the Alzheimer's PRS (A-PRS), we used a list of previously described SNVs.[6] that were confirmed to be linked to AD. SNVs were included only if their allelic frequency was higher than 1% in the population (including *TREM2* rs75932628, *PLCG2* rs72824905, *HESX1/IL17RD/APPL1* rs184384746, *CNTAP2* rs114360492, and *TM2D3* rs139709573). All included SNVs are considered to be sentinel SNVs and were used in the calculation of the A-PRS. Exceptions were rs9271058 and rs12881735, which did not pass quality control in our cohort and were substituted by the closest available SNVs after confirming the linkage disequilibrium between them, and rs113260531, for which no odds ratio (OR) has been published[37] (Table 1).

All statistics and PRS calculations were performed on R 4.0.2.[38] Polygenic risk scores were calculated as described previously,[39] using a weighted method with the following formula: $\mathrm{PRS} = \frac{\sum_{n=1}^{nSNP} \mathrm{Dose} \times \ln(\mathrm{OR})}{\sum_{n=1}^{nSNP} \ln(\mathrm{OR})}$. Dose varied between 0 and 2, with 0 corresponding to no risk allele, 1 to 1 risk allele, and 2 to 2 risk alleles. For imputed alleles, the dose was a continuous value between 0 and 2.

χ^2 and Kruskal-Wallis analyses were performed to determine differences in population demographics. All correlations were obtained using the Spearman correlation method. *APOE* status was defined according to the ε4 carrier status of the participant, and only participants with ε3/ε4 and ε4/ε4 genotypes were included in the E4 carriers, whereas all remaining participants were included among the E4 noncarriers. To calculate the association of the PRS and/or *APOE* group with amyloid status, models were fitted for a binomial response adjusted for age, sex, and the first 3 principal components of each population to account for the internal structure of the INSIGHT cohort and 10 principal components to account for the internal structure of the ADNI. Only the first 3 principal components were included for INSIGHT because it is a homogeneous population, whereas the ADNI cohort is multiethnic. Principal components were calculated using the pca function of PLINK (v1.90b3w) and plotted against the 1000G dataset. Non-European outliers were identified and removed from the INSIGHT cohort. These models were subsequently used to obtain the beta value of the PRS using the R reghelper package. We present uncorrected *p* values.

PRS Optimization

The optimized Alzheimer's PRS (oA-PRS) was obtained using the INSIGHT discovery cohort and validated in the ADNI validation cohort. We generated n − 1 lists of SNVs excluding the *APOE* SNVs, taking out a single SNV every time. The PRS for each of these lists was calculated, and models were fitted as described above. Results from each list were compared, and the list with higher beta and lower *p* values compared with the original list was kept. This process was repeated k times (here 16 times), with the best list replacing the original list until neither the beta nor the *p* values could be improved by deleting a single SNV.

Gene Ontology Category Enrichment

SNVs from the A-PRS and oA-PRS lists were analyzed for Gene Ontology (GO) biological process enrichment. If a SNV was located between 2 genes (i.e., *ZCPW1/NYAP1*), both genes were included in the analysis. GO enrichment analysis was performed using the Enrichr site.[40,41] Only processes that reached an adjusted *p* value of 0.05 were considered significant.

Results

Demographic Description of the INSIGHT Discovery Cohort

Genomic data were obtained from 298 of the original 318 participants included in the INSIGHT pre-AD study. We removed participants with the *APOE* ε2/ε4 genotype based on the observation that those 2 alleles show differential effects on amyloid deposition.[42] Genomic data were available from 291 participants. Most participants (208, 71.5%) had amyloid CL values lower than 20 and were therefore classified as amyloid (−). Our population was 61.2% female, and this proportion was similar in amyloid (−) and (+) groups. As expected, participants in the amyloid (+) group were more likely to be *APOE* ε4 carriers ($p = 0.001$) and less likely to be *APOE* ε2 carriers ($p = 0.002$) (Table 2). In addition, as previously described,[25] the distribution of CL values did not follow a normal distribution, and there was a weak correlation of these values with age ($p = 0.036$). However, despite this weak correlation, all subsequent models included age as a confounding factor.

Discovery Cohort: PRS Association With Amyloid Status

We used a list of 33 SNVs associated with AD risk[6] (excluding *APOE*) to generate a first PRS, named A-PRS (Table 1), adjusted for age, sex, and population structure (PC1, PC2, and PC3). We did not observe any association between the A-PRS and amyloid status (Figure 1A and Table 3). This lack of association was also observed in an *APOE*-stratified analysis (Figure 1B and Table 3; no interaction between *APOE* status and A-PRS was detected). Therefore, in the discovery cohort, the A-PRS was not associated with amyloid deposition in cognitively unimpaired participants. As expected, because of *APOE* genotype distribution, a model including only *APOE* status showed an association with amyloid status (Table 3) (OR = 4.08 [2.17–7.78]).

We then hypothesized that this lack of association may occur because loci associated with AD risk are not linked to amyloid deposition processes. We used an iteration process to select a combination of SNVs leading to a PRS associated with amyloid status. At the end of this process, we obtained an optimized A-PRS (oA-PRS) based on 17 of the original 33 SNVs excluding *APOE* that showed the strongest association with brain amyloid load in the INSIGHT cohort (denoted by — in Table 1). This association was

Table 1 List of Loci and SNVs for the A-PRS and oA-PRS

Locus	SNV	Chr	Position	EA	OA	OR	Optimized AD list
ADAMTS4	rs4575098	1	161155392	A	G	1.04	
CR1	rs4844610	1	207802552	A	C	1.17	—
BIN1	rs6733839	2	127892810	T	C	1.2	
INPP5D	rs10933431	2	233981912	G	C	0.91	—
CLNK	rs6448453	4	11026028	A	G	1.07	—
HLA	rs9271192 (1)	6	32578530	C	A	1.1	
OARD1	rs114812713	6	41034000	C	G	1.32	—
CD2AP	rs9473117	6	47431284	C	A	1.09	—
ZCWPW1/NYAP1	rs12539172	7	100091795	T	C	0.92	—
EPHA1	rs10808026	7	143099133	A	C	0.9	—
PTK2B	rs73223431	8	27219987	T	C	1.1	
CLU	rs9331896	8	27467686	C	T	0.88	—
ECHDC3	rs7920721	10	11720308	G	A	1.08	
CELF1/SPI1	rs3740688	11	47380340	G	T	0.92	
MS4A	rs7933202	11	59936926	C	A	0.89	
PICALM	rs3851179	11	85868640	T	C	0.88	
SORL1	rs11218343	11	121435587	C	T	0.8	—
FERMT2	rs17125924	14	53391680	G	A	1.14	—
SLC2A4/RIN3	rs10498633 (2)	14	92926952	T	G	0.93	
ADAM10	rs593742	15	59045774	G	A	0.93	—
APH1B	rs117618017	15	63569902	T	C	1.1	—
IQCK	rs7185636	16	19808163	C	T	0.92	
KAT8	rs59735493	16	31133100	A	G	0.96	—
WWOX/MAF	rs62039712	16	79355857	A	G	1.16	
SCIMP/RABEP1	rs113260531	17	5138980	A	G	[a]	
MAPT	rs2732703	17	44353222	G	T	0.73	
ABI3	rs616338	17	47297297	T	C	1.43	—
TSPOAP1	rs2632516	17	56409089	C	G	0.94	
ACE	rs138190086	17	61538148	A	G	1.3	—
ABCA7	rs3752246	19	1056492	G	C	1.15	—
AC074212.3	rs76320948	19	46241841	T	C	1.18	—
CD33	rs3865444	19	51727962	A	C	0.94	
CASS4	rs6024870	20	54997568	A	G	0.88	
ADAMTS1	rs2830500	21	28156856	A	C	0.93	

Abbreviations: AD = Alzheimer disease; A-PRS = Alzheimer's PRS; Chr = chromosome; EA = effect allele; OA = other allele; oA-PRS = optimized Alzheimer's PRS; OR = odds ratio; PRS = polygenic risk score; SNV = single-nucleotide variation.
SNVs were selected from the study by Bellenguez et al.[6] SNVs selected for the optimized A-PRS are denoted by (—). For each SNV locus, Chr, position within the chromosome (hg19), EA, OA, and published OR are indicated; (1) substituted by rs9271058 at position 32575406 and (2) substituted by rs12881735 at position 92932828.
[a] No OR has been published for this SNV, and it was excluded in the PRS analysis (30).

Table 2 Demographic Description of the INSIGHT, ADNI, and EADI Cohorts

	INSIGHT			ADNI			EADI	
	Amyloid (−) (n = 208, 71.5%)	Amyloid (+) (n = 83, 28.5%)	Total (n = 291)	Amyloid (−) (n = 138, 60.5%)	Amyloid (+) (n = 90, 39.5%)	Total (n = 228)	Controls (n = 6,215, 73%)	AD (n = 2,300, 27%)
Age	76.31 ± 3.5 (69.9–86)	77.25 ± 3.3 (70–86)	76.4 ± 3.5 (69.9–86)	76.35 ± 4.41 (69.1–85.7)	77.05 ± 4.74 (69.2–85.9)	76.62 ± 4.55 (69.1–85.9)	80.0 ± 7.6 (40.0–102.3)	74.3 ± 10.2 (37.0–99.3)
Sex, n (%)								
Female	130 (62.5)	48 (57.8)	178 (61.2)	60 (43.5)	55 (61.1)	115 (50.4)	3,749 (60.3)	1,515 (65.9)
Male	78 (37.5)	35 (42.1)	113 (38.8)	78 (56.5)	35 (38.9)	113 (49.6)	2,466 (39.7)	785 (34.1)
Centiloid	4.56 ± 7.84 (−17.68 to 19.64)	52.21 ± 29.25 (20.04 to 139.26)	18.05 ± 27.44 (−17.68 to 139.26)	1.65 ± 10.83 (−28.49 to 19.91)	65.5 ± 33.42 (20.06 to 202.8)	26.86 ± 38.56 (−28.49 to 202.8)		
***APOE*, n (%)**								
ε2/ε2	1 (0.48)	0 (0)	1 (0.34)	1 (0.72)	0 (0)	1 (0.43)	38 (0.6)	7 (0.3)
ε2/ε3	30 (14.4)	6 (7.2)	36 (12.4)	16 (11.6)	9 (10)	25 (10.96)	772 (12.4)	127 (5.5)
ε3/ε3	153 (73.6)	48 (57.8)	201 (69.1)	98 (71.0)	49 (54.4)	147 (64.47)	4,241 (68.2)	1,063 (46.2)
ε3/ε4	21 (10.1)	26 (31)	47 (16.1)	22 (15.9)	30 (33.3)	52 (22.81)	1,105 (17.8)	879 (38.2)
ε4/ε4	3 (1.4)	3 (3.6)	6 (2.1)	1 (0.72)	2 (2.2)	3 (1.32)	59 (0.9)	224 (9.7)

Abbreviations: AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; EADI = European Alzheimer's Disease Initiative; INSIGHT = INveStIGation of AlzHeimer's PredicTors.
For each cohort, detailed descriptions of the amyloid (−) and amyloid (+) participants or controls and patients with AD and total cohorts are reported. For numerical variables, values represent mean ± SD and value (range). For categorical variables, values include the total number of participants and the percentage in the cohort.

improved when the model was adjusted for *APOE* status (Figure 1C and Table 3) (OR without *APOE* = 5.26 [1.71–16.88], OR with *APOE* = 5.93 [1.85–19.83]). The *APOE*-stratified analysis showed a significant association of the oA-PRS with amyloid status both in ε4 carriers and noncarriers (Figure 1D and Table 3, $p = 0.12$ for interaction between oA-PRS and *APOE* status). A significant correlation between CL values and oA-PRS was observed in the total population (total group: $\rho = 0.13$, $p = 0.03$; amyloid [−]: $\rho = -0.048$, $p = 0.49$; amyloid [+]: $\rho = 0.17$, $p = 0.13$), which could be caused by the lower CL values in the amyloid (−) population. The large variations observed in the OR among *APOE* ε4 carriers could be attributed to the small sample size (29 and 32 amyloid [+] and 24 and 23 amyloid [−] *APOE* ε4 carriers in INSIGHT and ADNI, respectively) compared with the whole population (83 and 90 amyloid [+] and 208 and 138 amyloid [−] from INSIGHT and ADNI, respectively).

To assess differences between A-PRS and oA-PRS, we performed pathway-enrichment analysis (eTable 1, links.lww.com/WNL/C25, for A-PRS, and eTable 2, links.lww.com/WNL/C26, for oA-PRS). Biological processes related to Aβ metabolism and oligomerization represented 6 of the 12 (50%) and 5 of the 7 (71%) significantly enriched pathways when the analysis was performed based on genes assigned to SNVs used in the A-PRS or oA-PRS, respectively (Figure 2).

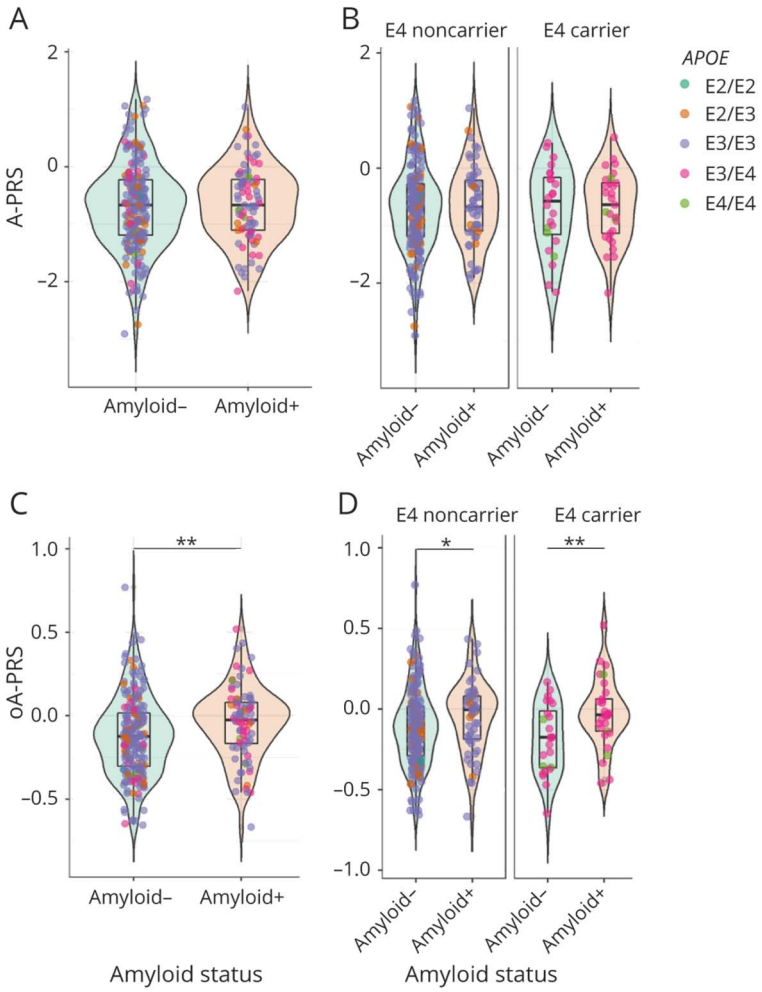
Demographic Description of the ADNI Validation Cohort

We selected 230 control participants from the ADNI cohort[43] to validate the oA-PRS. Two participants with the *APOE* ε2/ε4 genotype were excluded. This ADNI validation cohort had a mean age of 76.6 years and a mean MMSE score of 29.3, similar to the INSIGHT cohort.[18] Sex distribution was significantly different between cohorts ($p = 0.002$). Finally, 90 (39.5%) participants from the ADNI cohort were classified as amyloid (+), which was significantly higher than in the INSIGHT cohort ($p = 0.0002$). In addition, amyloid (−) participants in the validation cohort had lower CL values than amyloid (−) participants in the discovery cohort ($p = 0.03$), whereas the opposite was observed for amyloid (+) participants ($p = 0.0042$). As observed in the discovery cohort, the proportion of ε4 carriers was higher in the amyloid (+) group ($p = 0.004$) (Table 2). Likewise, the CL values followed a non-normal distribution, and no significant correlation was found between age and CL status. However, age was still included in the models to make them comparable with the INSIGHT analyses.

Validation Cohort: PRS Association With Amyloid Status

The 2 PRSs developed in the discovery cohort were tested in the validation cohort. The A-PRS was not significantly associated with amyloid status in the validation cohort even after stratifying by *APOE* genotype (Figure 3A and Table 3). As

Figure 1 PRS in Amyloid (+) and Amyloid (−) Participants From the INSIGHT Cohort: A-PRS (A and B) and oA-PRS (C and D)



Green-colored violin plots correspond to amyloid (−) participants, and orange-colored plots correspond to amyloid (+) participants. Each participant is represented by a colored dot corresponding to their *APOE* status: dark green for ε2/ε2, orange for ε2/ε3, violet for ε3/ε3, pink for ε3/ε4, and light green for ε4/ε4. For the stratified graphs, participants who did not carry any ε4 allele were classified as an "E4 noncarrier," and those who did were classified as an "E4 carrier." The A-PRS is not associated with amyloid status in the whole INSIGHT cohort (A) and in the ε4 carriers (B). The oA-PRS is significantly associated with amyloid status (C) (p = 0.005), and this association persists in the ε4 carriers (p = 0.0034) (D); asterisks indicate statistically significant differences (*p < 0.05, **p < 0.001). The A-PRS and oA-PRS were not significantly different between *APOE* statuses among amyloid (+) and (−) participants. A-PRS = Alzheimer's PRS; oA-PRS = optimized Alzheimer's PRS; PRS = polygenic risk score.

expected, *APOE* was also strongly associated with amyloid status (OR = 3.36 [1.73–6.7]).

However, the oA-PRS was significantly associated with amyloid status in the validation cohort (Table 3 and Figure 3C), independent of the addition of *APOE* status in the model. This association remained significant in the *APOE* ε4 carriers, as observed in the INSIGHT discovery cohort (Table 3 and Figure 3D). In this case, however, there was no significant correlation between oA-PRS and CL values (total group: ρ = 0.046, p = 0.49; amyloid [−]: ρ = −0.075, p = 0.36; amyloid [+]: ρ = −0.0017, p = 0.99).

Demographic Description of the EADI Cohorts

Finally, we tested the power of the oA-PRS to discriminate between controls and patients with AD in the EADI study. After excluding participants for whom data for age or *APOE* genotype were not available and participants who were *APOE* ε2/ε4, we had a total of 8,515 participants (Table 2). As expected, the AD group had a higher percentage of *APOE* ε4 carriers than the control group (47.9% vs 18.7%, respectively).

EADI Cohorts: PRS Association With Disease Status

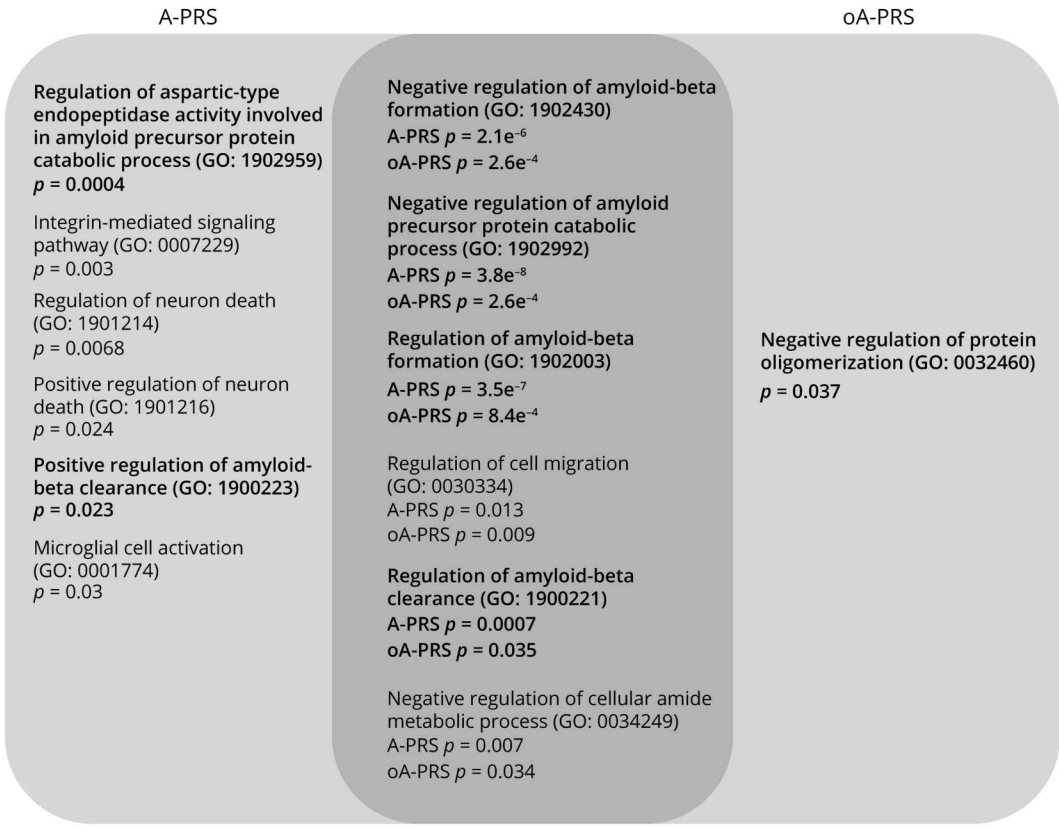
Two variants from the A-PRS were not present in the TOPMed imputations (*IQCK* rs7185636 and *MAPT* rs2732703) and were thus replaced by proxy variants based on the linkage disequilibrium in the Haplotype Reference Consortium (rs11865116 and rs2532332, respectively). For the calculation of the A-PRS and the oA-PRS, the weights used were based on the respective log(OR) from the stage II analyses of the European Alzheimer & Dementia Biobank consortium meta-analysis[33] when available or otherwise from the stage I analyses (i.e., *AC074212.3* rs76320948, *ACE* rs138190086, *IQCK* rs11865116, *CD33* rs3865444, and *WWOX/MAF* rs62039712). PRS association analyses were adjusted for sex, age, and the first 3 principal components. We found that the A-PRS was associated with disease status (controls or AD) in the EADI cohort whether (OR: 1.68 [1.53–1.85]) or not (OR: 1.66 [1.50–1.83]) we accounted for *APOE* status. Stratified analysis according to the *APOE* ε4 genotype showed significant associations independent of the *APOE* group (Table 4). The oA-PRS was also significantly

Table 3 Association Models Fitted for the Discovery Cohort (INSIGHT) and the Validation Cohort (ADNI) in ε4 Carriers and Noncarriers and the Unstratified Cohort

	APOE	A-PRS	A-PRS + *APOE*	oA-PRS	oA-PRS + *APOE*
INSIGHT					
ε4 noncarriers (amyloid [−]: 184; amyloid [+]: 54)					
β		0.111		0.314	
SE		0.159		0.158	
***p* Value**		0.49		0.047	
OR (95% CI)		1.16 (0.76–1.78)		3.77 (1.03–14.37)	
ε4 carriers (amyloid [−]: 24; amyloid [+]: 29)					
β		0.178		1.187	
SE		0.311		0.414	
***p* Value**		0.57		0.004	
OR (95% CI)		1.31 (0.53–3.45)		181.6 (7.53-10,674.6)	
Total cohort					
β	0.544	0.088	0.110	0.389	0.417
SE	0.126	0.134	0.139	0.136	0.141
***p* Value**	0.000015	0.51	0.43	0.004	0.003
OR (95% CI)	4.08 (2.17–7.78)	1.13 (0.79–1.63)	1.16 (0.8–1.71)	5.26 (1.71–16.88)	5.93 (1.85–19.83)
ADNI					
ε4 noncarriers (amyloid [−]: 115; amyloid [+]: 58)					
β		0.103		0.147	
SE		0.179		0.183	
***p* Value**		0.56		0.42	
OR (95% CI)		1.16 (0.69–1.95)		1.8 (0.43–7.79)	
ε4 carriers (amyloid [−]: 23; amyloid [+]: 32)					
β		0.511		0.976	
SE		0.34		0.387	
***p* Value**		0.14		0.012	
OR (95% CI)		1.84 (0.86–4.45)		44.94 (3.03–1,277)	
Total cohort					
β	0.520	0.158	0.186	0.304	0.339
SE	0.147	0.149	0.151	0.154	0.157
***p* Value**	0.0004	0.29	0.22	0.049	0.03
OR (95% CI)	3.36 (1.73–6.7)	1.24 (0.83–1.87)	1.29 (0.86–1.96)	3.38 (1.02–11.63)	3.88 (1.16–13.69)

Abbreviations: AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; A-PRS = Alzheimer's PRS; INSIGHT = INveStIGation of AlzHeimer's PredicTors; oA-PRS = optimized Alzheimer's PRS; OR = odds ratio; PRS = polygenic risk score; SNV = single-nucleotide variation.
Models were fitted to binomial models (amyloid [−] and amyloid [+]) using age and sex as confounders and correcting for the population structure (with the first 3 principal components for INSIGHT and first 10 principal components for ADNI). Values presented include beta, SE, *p* value, OR, and its 95% CI for the PRS and its *p* value for the A-PRS (33 SNVs) and oA-PRS (17 SNVs). The *APOE* model includes INSIGHT participants binarized according to ε4 status (ε4 noncarriers, ε4 carriers).

Figure 2 Overlap Between Enriched GO Biological Processes in the A-PRS and oA-PRS



In bold are GO biological processes involved in amyloid pathology. A-PRS = Alzheimer's PRS; GO = Gene Ontology; oA-PRS = optimized Alzheimer's PRS; PRS = polygenic risk score.

associated with disease status with slightly higher ORs (oA-PRS OR: 2.06 [1.73–2.45], oA-PRS + *APOE* OR: 1.99 [1.66–2.38]).

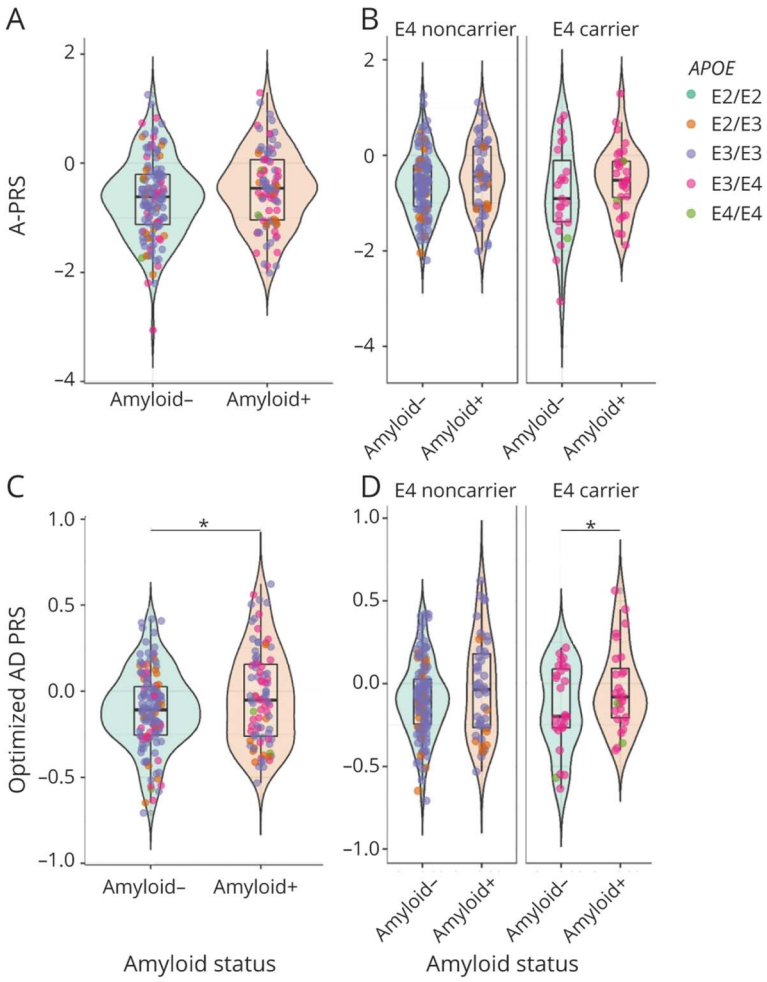
Discussion

This study identified an optimized PRS associated with amyloid status based on a shortlist of validated AD-risk–associated SNVs (excluding *APOE*) in 2 independent cohorts of participants without cognitive impairment. Stratified analyses showed that the association prevailed in *APOE* ε4 carriers. This observation indicates that AD-associated genetic risk factors other than *APOE* ε4 may increase the risk of amyloid deposition in *APOE* ε4 carriers who are already at high risk for AD. Of interest, most of the significant enriched pathways (71.3%) corresponding to the genes assigned to the selected SNVs are linked to APP metabolism and brain amyloid deposition. Finally, we showed that the oA-PRS restricted to 17 SNVs was also associated with disease status, suggesting its improved utility compared with PRS based on a higher number of SNVs.

Few studies have assessed the association of PRSs with amyloid deposition in AD. Among these studies, only 1 described a PRS association independent of *APOE* status.[15] However, this study included individuals with dementia. Two other studies identified *APOE*-dependent associations of PRS,[9,16] but only 1 included cognitively unimpaired participants (with a family history of AD).[16] This heterogeneity in terms of population studied and PRS design makes comparison between studies difficult. A recent retrospective study of a cohort of cognitively unimpaired individuals found that a PRS comprising 39 AD SNVs was associated with an increased likelihood of amyloid positivity in the CSF independent of *APOE* status.[17] In addition, this PRS could predict progression to AD dementia.[17] This PRS shares 22 loci (16 SNVs) with the A-PRS and 12 loci (8 SNVs) with the oA-PRS. Our study and the recent ones demonstrate that genetic factors beyond *APOE* can affect not only amyloid pathology but also the risk of developing AD.

Although *APOE* ε4 carriers have an established higher risk for amyloid deposition and AD, it is of interest to identify risk modifiers, such as the oA-PRS. The oA-PRS is not exclusive for *APOE* ε4 carriers, but we found a higher association with amyloid load in *APOE* ε4 carriers. On the other hand, the oA-PRS did not correlate with the numerical florbetapir CL values in amyloid-positive individuals and *APOE* ε4 carriers in the discovery or validation cohorts, and it was thus unable to

Figure 3 PRS in Amyloid (+) and Amyloid (−) Participants From the ADNI Cohort: A-PRS (A and B) and oA-PRS (C and D)



Green-colored violin plots correspond to amyloid (−) participants, whereas orange-colored plots correspond to amyloid (+) participants. Each participant is represented by a colored dot corresponding to their *APOE* status: dark green for ε2/ε2, orange for ε2/ε3, violet for ε3/ε3, pink for ε3/ε4, and light green for ε4/ε4. For the stratified graphs, participants who did not carry any ε4 allele were classified as "E4 noncarrier," and those who did were classified as "E4 carrier." The A-PRS was not significantly associated with amyloid status in the whole ADNI cohort (A) ($p = 0.05$) or in the *APOE*-stratified groups (B). The oA-PRS is significantly associated with amyloid status in the whole cohort (C) ($p = 0.049$) and in the ε4 carriers (D) ($p = 0.012$); asterisks indicate statistically significant differences (*$p < 0.05$). The A-PRS and oA-PRS were not significantly different between *APOE* statuses among amyloid (+) and (−) participants. A-PRS = Alzheimer's PRS; oA-PRS = optimized Alzheimer's PRS; PRS = polygenic risk score.

predict the level of brain amyloid in this subgroup. Additional studies are needed to test this prediction in larger sample sizes. Of note, the oA-PRS was correlated with CL values in the total population.

Owing to the small number of participants (9) in the INSIGHT cohort who converted to dementia, we could not evaluate the predictive power of the oA-PRS for AD. Therefore, we used the EADI cohort, which includes both AD and control participants, to evaluate the association of the oA-PRS with disease status. Data on brain amyloid deposition were not available. We found that both PRSs (A-PRS and oA-PRS) were associated with disease status in this population. The association of the A-PRS with disease status in the EADI cohort, but not with amyloid deposition in the ADNI and INSIGHT cohorts, suggests that genetic factors in the A-PRS are linked to disease but not to amyloid deposition in asymptomatic older participants. These factors could be potentially linked to the risk of dementia. Nevertheless, the association of the oA-PRS with AD suggests that genetic risk factors for brain amyloid deposition could predict disease outcome.

Both the A-PRS and oA-PRS lists were enriched in processes linked to amyloid deposition. However, the A-PRS included pathways that were not directly involved in amyloid deposition, confirming that there are mechanisms linked to AD that may not be associated with amyloid status. Likely, these pathways contribute to later stages of the disease or to processes that occur independently of amyloid deposition in cognitively unimpaired participants. These could include pathways related to neuroinflammation, tau, insulin resistance, oxidative stress, or others.

Our study is limited by the sample size of the existing cohorts. Although we acknowledge the value of multiple comparison corrections, here we present the results without correction because the results with correction would not be significant. Nevertheless, we were able to validate the oA-PRS in 2 independent cohorts with slightly different genetic backgrounds: the INSIGHT cohort composed of White individuals mostly living in Île-de-France, and the ADNI cohort, which is a multiethnic cohort mostly composed of White non-Hispanic Americans. Risk conferred by the ε4 variant of

Table 4 Association Models Fitted for the AD Cohort (EADI) in ε4 Carriers and Noncarriers and the Unstratified Cohort

	A-PRS	A-PRS + *APOE*	oA-PRS	oA-PRS + *APOE*
ε4 noncarriers (controls: 5,051; AD: 1,197)				
β	0.480		0.677	
SE	0.061		0.114	
***p* Value**	5.960E-15		4.074E-09	
OR (95% CI)	1.62 (1.43–1.82)		1.95 (1.56–2.44)	
ε4 carriers (controls: 1,164; AD: 1,103)				
β	0.537		0.669	
SE	0.086		0.160	
***p* Value**	3.475E-10		2.242E-05	
OR (95% CI)	1.71 (1.45–2.02)		1.97 (1.44–2.69)	
Total cohort (controls: 6,215; AD: 2,300)				
β	0.521	0.506	0.721	0.686
SE	0.048	0.049	0.089	0.092
***p* Value**	1.490E-27	1.631E-24	6.004E-16	8.520E-14
OR (95% CI)	1.68 (1.53–1.85)	1.66 (1.50–1.83)	2.06 (1.73–2.45)	1.99 (1.66–2.38)

Abbreviations: AD = Alzheimer disease; A-PRS = Alzheimer's PRS; EADI = European Alzheimer's Disease Initiative; INSIGHT = INveStIGation of AlzHeimer's PredicTors; oA-PRS = optimized Alzheimer's PRS; OR = odds ratio; PRS = polygenic risk score; SNV = single-nucleotide variation.
Models were fitted to binomial models (controls and AD) using age and sex as confounders and correcting for the population structure (with the first 3 principal components). Values presented include beta, SE, *p* value, OR, and its 95% CI for the A-PRS (33 SNVs) and oA-PRS (17 SNVs). The *APOE* model includes participants binarized according to ε4 status (ε4 noncarriers, ε4 carriers).

APOE has been shown to differ across populations, with lower values in populations of African ancestry than in populations of European or Asian ancestries.[44] Additional studies are necessary to validate the oA-PRS in non-White populations. Another limitation of our study is the age range because we evaluated people older than 70 years who are cognitively unimpaired. In the future, it will be interesting to include younger participants. This exploratory study will need to be validated in larger cohorts of cognitively unimpaired individuals with brain amyloid imaging.

In conclusion, our findings robustly highlight a PRS excluding *APOE* that is significantly associated with amyloid status in 2 independent cohorts of cognitively unimpaired individuals. Currently, amyloid load can be measured through plasma or CSF amyloid biomarkers and PET imaging. Genetic risk assessment of amyloid load early in life before any possible detection in plasma or the brain would allow initial screening to establish patient priority for a more detailed follow-up of those at higher risk. In addition, such assessment would provide stratification for potential preventive or curative treatments based on patient-specific risk factors. A GWAS focusing on cognitively unimpaired participants with significant brain amyloid deposition should unveil new SNVs, some of which could be unrelated to AD, while improving prediction of amyloid load. Beyond genetic data, a combination of omics, genetic, biochemical, and environmental (exposome, diet, and microbiome) features could also allow for a more accurate prediction of amyloid deposition.

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Disclosure

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Continued

Appendix 1 *(continued)*

Name	Location	Contribution
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Bruno Dubois, MD, PhD	ICM Paris Brain Institute, CNRS UMR7225, INSERM U1127, Sorbonne University, Hôpital de la Pitié-Salpêtrière; Centre des Maladies Cognitives et Comportementales, IM2A, AP-HP, Sorbonne Université, Hôpital de la Salpêtrière; Department of Neurology, Hôpital Pitié-Salpêtrière, AP-HP Sorbonne Université, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design
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Appendix 2 Coinvestigators

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Habib Benali, PhD	Centre de Recherche, IUGM, Montreal, Quebec, Canada	Coinvestigator	Major role in the acquisition of MRI data and study protocol design
Hugo Bertin, MD	GE Healthcare, Bruxelles, Belgium	Coinvestigator	Major role in the acquisition of PET data
Joel Bonheur, MD	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of clinical data
Laurie Boukadida, MD	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of clinical data

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Enrica Cavedo, PhD	Sorbonne University, Paris, France	Coinvestigator	Design and conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content
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Marion Dubois	IM2A, Paris, France	Coinvestigator	Analyzed the data and revised the manuscript for intellectual content
Stéphane Epelbaum, MD, PhD	ICM, Paris, France	Coinvestigator	Major role in the acquisition of clinical data
Geoffroy Gagliardi	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of neuropsychological data
Remy Genthon, MD	IM2A, Paris, France	Coinvestigator	Major role in the coordination of the study
Harald Hampel, MD	Sorbonne University, Paris, France	Coinvestigator	INSIGHT pre-AD Scientific Committee
Marion Houot	Sorbonne University, Paris, France	Coinvestigator	Analyzed the data and revised the manuscript for intellectual content
Aurélie Kas, MD	APHP, Paris, France	Coinvestigator	Major role in the acquisition of PET data
Foudil Lamari, PhD	APHP, Paris, France	Coinvestigator	INSIGHT pre-AD Scientific Committee
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Christiane Metzinger	ICM, Paris, France	Coinvestigator	Data management
Fanny Mochel, MD, PhD	ICM, Paris, France	Coinvestigator	INSIGHT pre-AD Scientific Committee
Francis Nyasse	IM2A, Paris, France	Coinvestigator	Major role in the coordination of the study
Catherine Poisson	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of data
Marie Revillon	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of neuropsychological data
Antonio Santos	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of clinical data
Katia Santos Andrade	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of clinical data
Marine Sole	IM2A, Paris, France	Coinvestigator	Major role in the acquisition of EEG data

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Association of *APOE*-Independent Alzheimer Disease Polygenic Risk Score With Brain Amyloid Deposition in Asymptomatic Older Adults

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