Common variants in Alzheimer’s disease and risk stratification by polygenic risk scores

Genetic discoveries of Alzheimer’s disease are the drivers of our understanding, and together with polygenetic risk stratification can contribute towards planning of feasible and efficient preventive and curative clinical trials. We first perform a large genetic association study by merging all available case-control datasets and by-proxy study results (discovery \( n = 409,435 \) and validation size \( n = 58,190 \)). Here, we add six variants associated with Alzheimer’s disease risk (near \( APP, CHRNE, PRKD3/NDUFAF7, PLCG2 \) and two exonic variants in the \( SHARPIN \) gene). Assessment of the polygenic risk score and stratifying by \( APOE \) reveal a 4 to 5.5 years difference in median age at onset of Alzheimer’s disease patients in \( APOE \varepsilon 4 \) carriers. Because of this study, the underlying mechanisms of \( APP \) can be studied to refine the amyloid cascade and the polygenic risk score provides a tool to select individuals at high risk of Alzheimer’s disease.
Thus far, multiple loci associated with Alzheimer’s disease (AD) have been described next to causal mutations in two sub-units of γ-secretases, membrane-embedded aspartyl complexes (PSEN1, PSEN2 genes), and the gene encoding one target protein of these proteases, the amyloid precursor protein gene (APP). The most prominent locus, APOE, was detected almost 30 years ago using linkage techniques. In addition, genome-wide association studies (GWAS) of AD case-control datasets and by-proxy AD case-control studies have identified 30 genomic loci that modify the risk of AD. These signals account for ~31% of the genetic variance of AD, leaving most of the genetic risk as yet uncharacterized. Further disentangling the genetic constellation of common genetic variations underlying AD can drive our biological insights of AD and can point toward novel drug targets.

There are over 50 million people living with dementia and the global cost of dementia is well above 1 trillion US$$. This means there is a medical and economical urgency to efficiently test interventions that are under development. Therefore, to increase power and reduce duration of trials, pre-symptomatic patients that are at high genetic risk of disease are increasingly developed. However, only carriers of causal mutations (APP, PSEN1, and PSEN2) and the APOE ε4 allele are considered high risk, while other common and rare genetic variants are ignored. Despite that, the combined effects of all currently known variants in a polygenic risk score (PRS) is associated with the conversion of mild cognitive impairment to AD, and the neuropathological hallmarks of AD, age at onset (AAO) of disease and lifetime risk of AD.

In this work we aim to comprehend and expand the knowledge of the genetic landscape underlying AD and provide additional evidence that a PRS of variants can be a robust tool to select high risk individuals with an earlier AAO. We first performed a meta-GWAS integrating all currently published GWAS case-control data, by-proxy case-control data, and the data from the Genome Research at Fundació ACE (GR@ACE) study. We confirm the observed associations in a large independent replication study. Then, we construct an update of the PRS and test whether the effects of the PRS are influenced by diagnostic certainty, sex and AAO groups. Lastly, we test whether the PRS could be used to identify individuals at the highest odds of having AD and we compared AAO of the AD cases. This study describes the identification of six variants associated with AD risk and provides an extended PRS tool to select individuals at high risk of AD.

### Results

**Meta-GWAS of AD.** We combined data from three AD GWASs: the summary statistics calculated from the GR@ACE case-control study (6331 AD cases and 6055 controls), the IGAP case-control study (up to 30,344 AD cases and 52,427 controls) and the UKB AD-by-proxy case-control study (27,696 cases of maternal AD with 260,980 controls, and 14,338 cases of paternal AD with 245,941 controls, Fig. 1, Supplementary Data 1). Although we observed inflation in the resulting summary statistics ($λ$ median = 1.08; see Supplementary Fig. 1d), it was not driven by an un-modeled population structure (LD score regression intercept = 1.036). The full details of the studies are described in methods. After study-specific variant filtering and quality-control procedures, we performed a fixed effects inverse-variance-weighted meta-analysis on the summary statistics of the three studies. Using this strategy, we identified a genome-wide significant (GWS) association ($p < 5 \times 10^{-8}$) for 36 independent genetic variants in 35 genomic regions (the APOE region contains signals for ε4 and ε2). As a sensitivity analysis, we removed the AD-by-proxy study and compared the resulted effect estimates with and without this dataset. We found a high correlation between the effect estimates from the case-control and by-proxy studies.

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**Fig. 1 Flow chart of analysis steps.** Discovery meta-analysis in GR@ACE, IGAP stage 1+2 and UKBiobank followed by a replication in 16 independent cohorts. The genome-wide significant signals found in meta-GWAS were used to perform a Polygenic Risk Score in a clinical and pathological AD dataset. See Supplementary Methods for more information about the cohorts included and methods to the PRS generation. Pathologically confirmed AD cases, AD cases diagnosed based on clinical criteria, Controls participants aged 55 years and younger. N = Total of individuals within specified data.
approaches for the significant loci ($R^2 = 0.994$, $p = 8.1 \times 10^{-37}$; Supplementary Fig. 1e). Four genomic regions were not previously associated with AD (see Manhattan Plot, Fig. 2a).

Next, we aimed at replicating the associated loci in 16 cohorts (19,087 AD cases and 39,101 controls in total), many of them collected and analyzed by the European Alzheimer’s Disease Biobank (IPND-EADB) project. We tested all variants with suggestive association ($p < 10^{-5}$) located within a 200 kb region from the sentinel SNP. Overall, 384 variants were tested in the replication datasets (Supplementary Data 2). Discovery and replication were combined, and we identified associations in six variants comprising five genomic loci annotated using FUMA\textsuperscript{23} (Table 1, Fig. 2b–f, Supplementary Fig. 2 and Supplementary Results). In APP, we identified a common (MAF = 0.46) intronic variant associated with a reduced risk of AD (rs2154481, OR = 0.95 [0.94–0.96], $p = 1.39 \times 10^{-11}$, Fig. 2f). In SHARPIN (SHANK Associated RH Domain Interactor) gene, we found two missense mutations (rs34173062/p.Ser17Phe and rs34674752/p.Pro294Ser) that are in linkage equilibrium ($R^2 = 1.3 \times 10^{-6}$, $D' = 0.014$, $p = 0.96$). Both missense variants increased AD risk (p.Ser17Phe, MAF = 0.085, OR = 1.11 [1.09–1.13], $p = 9.6 \times 10^{-13}$ and p.Pro294Ser, MAF = 0.052, OR = 1.13 [1.09–1.18], $p = 1.0 \times 10^{-9}$, Fig. 2b). A variant close to the genes PRKD3 and NDUFAF7 (rs876461, MAF = 0.143) emerged as the most significant variant in the region after the combined analysis (OR = 1.07 [1.05–1.09], $p = 1.3 \times 10^{-9}$, Fig. 2c). In the 3'UTR region of CHRNA (Cholinergic Receptor Nicotinic Epsilon Subunit), rs72835061 (MAF = 0.085) was associated with a 1.09-fold increased risk of AD (95% CI [1.06–1.11], $p = 1.5 \times 10^{-10}$, Fig. 2e). Our analysis also strengthened the evidence of association with AD for three additional genomic loci including an association with a variant in PLCG2 (rs3935877, MAF = 0.13, OR = 0.92 [0.90–0.95], $p = 6.9 \times 10^{-9}$, Fig. 2d), and confirmed another common variant in PLCG2, a stop gain mutation in IL-34 and a variant near HS3ST1 (Table 1, Supplementary Fig. 3 and Supplementary Data 2, 3). We were not able to replicate two loci (ELK2AP and SPPL2A regions) that showed suggestive association with AD ($p < 1 \times 10^{-7}$ in discovery).

**Polygenic risk scores.** In order to assess the robustness and combined effect of the genetic landscape of AD (Fig. 3, Supplementary Data 4), we constructed a weighted PRS based on the 39 genetic variants (excluding APOE genotypes) that showed GWS evidence of association with AD (see Methods, Fig. 4 and Supplementary Data 5). We tested if the association of the PRS with AD is independent of clinically important factors that are considered in the selection of individuals for clinical trials. First, we showed that the association of the PRS with clinically diagnosed AD cases is similar to the association with pathologically confirmed AD (OR = 1.30 vs. 1.38, per 1-SD increase in the PRS). In this setting, adding variants below the GWS threshold did not lead to a more significant association of the PRS with AD (Fig. 4a). Next, we tested whether the PRS was associated with AD in the presence of concomitant brain pathologies (Besides AD). Among our autopsy-confirmed AD patients ($n = 332$), 84% had at least one concomitant pathology, and the PRS was associated with AD in the presence of all tested concomitant pathologies (Fig. 4b). Moreover, the patients often had more than one concomitant pathology (48.8%), but no difference was observed in the effect estimate of the PRS when more than one pathology was present (Fig. 4b). Last, we investigated the effect of sex and AAO (Fig. 4c). Our analysis revealed that the effect of the PRS was the same in both sexes (Fig. 4c) and was consistent with both early-onset (onset before 65 years; OR = 1.58, 95% CI [1.22–2.05], $p = 5.8 \times 10^{-4}$) as well as with late-onset AD (onset later than 85 years; OR = 1.29, 95% CI [1.10–1.51], $p = 1.5 \times 10^{-3}$).

PRSs has the potential to early identify subjects at risk of complex diseases\textsuperscript{24}. To identify people at the highest genetic risk of AD based on the PRS, we used the validated 39-variants

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**Fig. 2 GWAS meta-analysis for AD risk ($N = 467,623$).** a Manhattan plot of overall meta-analysis for genome-wide association in Alzheimer’s disease highlighting in pink the loci associated with AD in this study (PRKD3/NDUFAF7, SHARPIN, CHRNE, PLCG2, and APP). b-f Locus plots for the signals associated with AD in overall meta-analysis results.

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**Table 1** Association for the AD loci selected for follow-up.

| Chr | Closest gene | SNP | A1 | A2 | A1 Freq | A2 Freq | BP | OR (95% CI) | P |
|-----|--------------|-----|----|----|---------|---------|----|-------------|----|
| 4   | PRKD3/NDUFAF7| rs34173062 | A  | G  | 0.085   | 0.915   | 1.16| 1.17 (1.10–1.21) | 7.35 × 10⁻⁵ |
| 5   | SHARPIN      | rs34674752 | 1 | G  | 0.052   | 0.948   | 1.11| 1.16 (1.10–1.21) | 4.02 × 10⁻⁵ |
| 7   | ELK2AP      | rs7153315  | C  | G  | 0.750   | 0.250   | 0.95| 1.01 (0.92–1.10) | 6.81 × 10⁻³  |
| 7   | HS3ST1      | rs4351014  | 1 | T  | 0.684   | 0.316   | 0.98| 1.07 (0.95–1.11) | 9.80 × 10⁻⁴  |
| 8   | APP         | rs2154481  | C  | T  | 0.838   | 0.162   | 0.93| 0.99 (0.92–1.06) | 6.92 × 10⁻³  |
| 8   | APP         | rs3935877  | C  | T  | 0.802   | 0.198   | 1.08| 1.10 (1.04–1.16) | 1.51 × 10⁻²  |
| 10  | APP         | rs4985556  | A  | C  | 0.470   | 0.530   | 0.97| 1.07 (1.02–1.13) | 3.92 × 10⁻⁴  |
| 10  | APP         | rs12444183 | A  | G  | 0.407   | 0.593   | 0.95| 0.95 (0.91–0.99) | 3.31 × 10⁻²  |
| 10  | APP         | rs76523702 | C  | T  | 0.802   | 0.198   | 1.08| 1.10 (1.04–1.16) | 1.51 × 10⁻²  |
| 12  | HS3ST1      | rs12444183 | A  | G  | 0.407   | 0.593   | 0.95| 0.95 (0.91–0.99) | 3.31 × 10⁻²  |
| 12  | HS3ST1      | rs4351014  | 1 | T  | 0.838   | 0.162   | 0.93| 0.99 (0.92–1.06) | 6.92 × 10⁻³  |

**Discussion**

This work adds on the ongoing global effort to identify genetic variants associated with AD (Fig. 3). In the present work, we reported on the largest GWAS for AD risk to date, comprising genetic information of 467,623 individuals of European ancestry. We identified six variants that were not previously associated with the risk of AD and constructed a robust PRS for AD demonstrating its potential value for selecting subjects at risk of AD, especially within APOE ε4 carriers. This PRS was based on European ancestries and may or may not generalize to other ancestries. Validation in other populations will be required. We also acknowledge that controls included in GR@ACE are younger than cases and some of the controls might still develop AD later in life. This fact does not invalidate the analysis although reported estimates must be considered conservative. The differences in risk and AAO determined by the PRS of AD are relevant for design clinical trials that over-represent APOE ε4 carriers, as APOE ε4 heterozygous with highest-PRS values have a similar risk and AAO to APOE ε4 homozygotes (Fig. 5b). These represents ~1% of our control population, which is the same percentage as all APOE ε4 homozygotes. A trial that aims to include APOE ε4 homozygotes, could consider widening the selection criteria and in this way hasten the enrollment process. Also, our PRS could aid at the interpretation of the results of clinical trials, as it determines a relevant proportion of the AAO, which could either mimic or obscure a treatment effect.

The most interesting finding from our GWAS is the discovery of a common protective (MAF (C-allele) = 0.483) intronic variant in the **APP** gene. Our results directly support **APP** production or processing as a causal pathway not only in familial AD but in common sporadic AD. The SNP is in a DNase hypersensitive area of 295 bp (chr21:27473781-27474075) possibly involved in the transcriptional regulation of the **APP** gene. rs2154481 is an eQTL for the **APP** mRNA and an antisense transcript of the **APP** gene named **AP001439.2** in public eQTL databases25 (Supplementary Fig. 4). Functional evidence supports a modified **APP** transcription26 as an LD block of 13 SNPs within the **APP** locus.
(including rs2154481) increased the TFCP2 transcription factor avidity to its binding site and increased the enhancer activity of this specific intronic region. Based on this evidence, we can postulate that a life-long slightly higher APP gene expression protects the brain from AD insults. Still, this seems counter-intuitive as duplications of the gene lead to early-onset AD. A U-shaped effect, or hormesis effect of APP might help explain our observations and it might also fit the accelerated cognitive deterioration observed in AD patients treated with beta-secretase inhibitors as these reduce beta-amyloid in their brain. An alternative hypothesis is that mechanisms underlying the variant are related to the overexpression of protective fragments of the APP protein. Disentangling the molecular mechanism of our finding will help refine and steer the amyloid hypothesis.

Additionally, other three variants identified are altering protein sequence or affecting regulatory motifs. Two independent missense mutations in SHARPIN increased the AD risk. SHARPIN was previously proposed as an AD candidate gene, and functional analysis of a rare missense variant (NM_039974.3.p.Gly186Arg) resulted in the aberrant cellular localization of the variant protein and attenuated the activation of NF-kB, a central mediator of inflammatory and immune responses. Functional analysis of the two identified missense variants will show if the effect on immune reaction in AD is similar. The variant located in the CHRNE which encodes a subunit of the cholinergic receptor (AChR) is a strong modulator of CHRNE expression. The same allele that increases AD risk increases the expression in the brain and other tissues according to GTEx ($p = 2.1 \times 10^{-13}$) (Supplementary Fig. 5). The detection of a potential hypermorphic allele linked to AD risk and affecting cholinergic function could reintroduce this neurotransmitter pathway into the search for preventative strategies. Further functional studies are needed to consolidate this hypothesis.

Altogether, we described six additional loci associated with sporadic AD. These signals reinforce that AD is a complex disease in which amyloid processing and immune response play key roles. We add to the growing body of evidence that the polygenic scores of all genetic loci to date, in combination with APOE genotypes, are robust tools that are associated with AD and its AAO. These properties make PRS promising in selecting individuals at risk to apply preventative therapeutic strategies.

Methods

Data. Participants in this study were obtained from multiple sources, including raw data from case-control samples collected by GR@ACE/DEGESCO, summary statistics data from the case-control samples in the IGAP and the summary statistics of AD-by-proxy phenotype from the UK Biobank. An additional case-control samples from 16 independent cohorts (19,087 AD cases and 39,101 controls) was used for replication, largely collected and analyzed by the European Alzheimer’s Disease Biobank (IPND-EADB) project. Full descriptions of the samples and their respective phenotyping and genotyping procedures are provided in the Supplementary Methods.

GR@ACE. The GR@ACE study recruited AD patients from Fundació ACE, Institut Català de Neurociències Aplicades (Catalonia, Spain), and control individuals from three centers: Fundació ACE (Barcelona, Spain), Valme University Hospital (Seville, Spain), and the Spanish National DNA Bank–Carlos III (University of Salamanca, Spain) (http://www.bancoadm.org). Additional cases and controls were obtained from dementia cohorts included in the Dementia Genetics Spanish Consortium (DEGESCO). At all sites, AD diagnosis was established by a multidisciplinary working group—including neurologists, neuropsychologists, and social workers—according to the DSM-IV criteria for dementia and the National Institute on Aging and Alzheimer’s Association’s (NIA–AA) 2011 guidelines for diagnosing AD. In our study, we considered as AD cases any individuals with dementia diagnosed with probable or possible AD at any point in their clinical course. For further details on the contribution of the sites, see Supplementary Data 10. Written informed consent was obtained from all the participants. The ethics and scientific committees have approved this research protocol (Acta 25/2016, Ethics Committee H., Clinic I Provincial, Barcelona, Spain).

Genotyping. Quality control, and imputation. DNA was extracted from peripheral blood according to standard procedures using the Chemagic system (Perkin Elmer). Samples reaching DNA concentrations of >10 ng/μl and presenting high integrity were included for genotyping. Cases and controls were randomized across sample plates to avoid batch effects.

Genotyping was conducted using the Axiom 815K Spanish biobank array (Thermo Fisher) at the Spanish National Center for Genotyping (CeGEN, Santiago de Compostela, Spain). The genotyping array not only is an adaptation of the Axiom biobank genotyping array but also contains rare population-specific
variations observed in the Spanish population. The DNA samples were genotyped according to the manufacturer’s instructions (Axiom™ 2.0 Assay Manual). The Axiom 2.0 assay interrogates biallelic SNPs and simple indels in a single-assay workflow. Starting with 200 ng of genomic DNA, the samples were processed through a manual target preparation protocol, followed by automated processing of the array plates in the GeneTitan Multi-Channel (MC) instrument. Target preparation involved DNA amplification, fragmentation, purification, and resuspension of the target in a hybridization cocktail. The hyb-ready targets were then transferred to the GeneTitan MC instrument for automated, hands-free processing, including hybridization, staining, washing, and imaging. The CEL files were generated using the GeneTitan MC instrument. Quality control (QC) was performed for samples and plates using the Affymetrix power tool (APT). The generated PRS was validated using logistic regression adjusted by four principal components.

was determined based on the resolution of AT and GC channels in a group of non-polymorphic SNPs (resolution >0.82). Samples with a call rate greater than 97% and plates with an average call rate above 98.5% were included for final SNP calling. The samples were jointly called. Markers passing all the QC tests were used in downstream analysis (SNPs = 729,868; 95.4%) using the SNPolisher R package (Thermo Fisher). To assess the sample genotyping concordance, we intentionally resampled 200 samples and determined a concordance rate of 99.5%.

We also conducted previously described standard QC prior to imputation. In brief, individual QC includes genotype call rates >97%, sex checks, and no excess heterozygosity; we removed population outliers as well (European cluster of 1000 Genomes). We included variants with a call rate of >95%, with a minor allele frequency (MAF) of >0.01, in Hardy–Weinberg equilibrium ($p < 1 \times 10^{-4}$ in controls) and without differential missingness between cases and controls.

Fig. 4 Polygenic risk scores for AD. a The 39-SNP PRS association with clinical (OR = 1.30, 95% CI [1.18–1.44], $p = 1.1 \times 10^{-7}$) and pathologically confirmed AD cases (OR = 1.38, per 1-SD increase in the PRS, 95% CI [1.21–1.58], $p = 1.5 \times 10^{-6}$) from EADB–FACE/BBB dataset. b PRS association with AD in the presence of concomitant brain pathologies (besides AD). c PRS association with AD stratified by sex and AAO. A similar association of the PRS with AD was found in both sexes (ORmales = 1.33, [1.13–1.56], $p = 5.8 \times 10^{-4}$ vs. ORfemales = 1.32, [1.19–1.47], $p = 2.5 \times 10^{-7}$). In (a–c) data are presented as Odds Ratio per 1-SD increase in PRS (95% CI).
covariates. The curve shows the probability a case in one of the eight groups has developed AD by a certain age (Fig. 5). 

Meta-GWAS of AD. After study-specific variant filtering and quality-control procedures, we performed a fixed effects inverse-variance-weighted meta-analysis[26] on the discovery and follow-up stages (Supplementary Data 1 and Supplementary Data 12). To determine the lead SNPs (those with the strongest association per genomic region), we performed clumping on SNPs with a GWS p value ($p < 5 \times 10^{-8}$) (Plink v1.90, maximal linkage disequilibrium (LD) with $R^2 < 0.001$ and physical distance 250 Kb). In the APOE region, we only considered the APOE e4 (rs429358) and APOE e2 (rs7412) SNPs. LD information was calculated using the GR@ACE imputed genotypes as a reference. Polygenicity and confounding biases, such as cryptic relatedness and population stratification, can yield an inflated distribution of test statistics in GWAS. To distinguish between inflation from a true polygenic signal and bias we quantified the utility of self-report of parental history of AD for case ascertainment in GWAS (proxy–AD approach)[21,37,38]. For this study, we used the published summary statistics of Marioni et al.[21]. They included, after stringent QC, 314,278 unrelated individuals for whom AD information was available on at least one parent in the UK Biobank (https://datashare.is.ed.ac.uk/handle/10283/13364). In brief, the 27,696 participants whose mothers had dementia (maternal cases) were compared with the 260,980 participants whose mothers did not have dementia. Likewise, the 14,338 participants whose fathers had dementia (paternal cases) were compared with the 245,941 participants whose fathers did not have dementia[21]. The phenotype of the parents is independent, and therefore, the estimates could be meta-analyzed. After analysis, the effect estimates were made comparable to a case-control setting. Further information on the transformation of the effect sizes can be found elsewhere[21,39]. The data available comprises summary statistics of 7,794,553 SNPs imputed to the HRC reference panel (full panel).

**Fig. 5 Polygenic Risk Scores APOE stratification for AD in n = 12,386 biologically independent samples from GR@ACE/DEGESCO.** a The AD risk of PRS groups compared to those with the 2% lowest risk. The 2% highest risk had a 3.0-fold (95% CI [2.12–4.18], $p = 3.2 \times 10^{-10}$) increased risk compared with those with the 2% lowest risk. No interaction was found between the PRS and APOE genotypes ($p = 0.76$). b The AD risk stratified by PRS and APOE risk groups compared to the lowest risk group (OR 95% CI). Association was found between highest and lowest-PRS percentiles within the APOE genotype groups: $ɛ2/ɛ2$ carriers (OR = 2.48 [1.51–4.08], $p = 3.4 \times 10^{-4}$), $ɛ3/ɛ3$ carriers (OR = 2.67 [1.93–3.69], $p = 3.5 \times 10^{-5}$), $ɛ2/ɛ4$ carriers (OR = 2.51 [1.33–4.73], $p = 1.8 \times 10^{-3}$), $ɛ3/ɛ4$ carriers (OR = 2.02 [1.05–3.85], $p = 3.4 \times 10^{-2}$). Comparisons of the highest and lowest-PRS percentiles with respect to the APOE genotype groups: a difference was found between highest $ɛ2/ɛ2$ carriers vs. lowest $ɛ2/ɛ3$ carriers (OR = 0.51 [0.34–0.75], $p = 7.8 \times 10^{-4}$), but not between highest $ɛ3/ɛ3$ carriers vs. lowest $ɛ2/ɛ4$/$ɛ3/ɛ4$ carriers (OR = 1.17 [0.82–1.66], $p = 0.40$) and highest $ɛ2/ɛ4$/$ɛ3/ɛ4$ carriers vs. lowest $ɛ4/ɛ4$ carriers (OR = 0.89 [0.52–1.53], $p = 0.68$). c The AAO of AD stratified by PRS and APOE risk groups. No difference in odds for AD was found between the PRS percentiles with AAO in APOE $ɛ2/ɛ2$/$ɛ2/ɛ3$ (lowest = 82 years, highest = 83 years, $p_{\text{Wilcoxon}} = 0.39$) and APOE $ɛ3/ɛ3$ (lowest = 82 years, highest = 81 years, $p = 0.16$). However, a 4-year difference was found between APOE $ɛ4$ heterozygotes ($p_{\text{Wilcoxon}} = 4.6 \times 10^{-5}$, 78.5 years compared with 73 years) in APOE $ɛ4$ homozygotes. Data are represented as boxplots as described in the manual of ggplot2 package in R. a-c Logistic regression models adjusted for four population ancestry components were used as statistical covariates. The curve shows the probability a case in one of the eight groups has developed AD by a certain age (x-axis).
Polygenic risk score. We calculated a weighted individual PRS based on the 39 genetic variants that showed GWS evidence of association with AD in the present study, excluding APOE to check the impact of PRS modulating APOE risk (Table 1 and Supplementary Data 3). The selected variants were directly genotyped or imputed with high quality (median imputation score R² = 0.93). The PRSs were generated by multiplying the genotype dosage of each risk allele for each variant by its corresponding effect size from previous IGAP studies [Kunkle et al.42 (36 variants), Sims et al.7 (23 PRS groups)]. We studied the effect of PRS across groups of individuals stratified by APOE ε4 status. We validated using logistic regression models adjusted for four population ancestry elements. As a reference genome, we used GRCh37. Quantile quantile plots, Manhattan plots, and the exploration of genomic inflation factors were performed using the R package qqman.

Risk stratification of the validated PRSs. We searched for the groups at the highest risk of AD in the GR@ACE dataset (6331 AD cases and 6055 controls). We stratified the population into PRS percentiles, taking into account survival bias anticipated at old age18. To eliminate selection bias, we calculated the boundaries of the percentiles in the control participants aged 55 years and younger (n = 3546). Based on the boundaries from this population, the rest of the controls and all AD cases were then assigned into their appropriate percentiles. We first explored risk stratification using only the PRSs. For this, we split the PRSs into 50 groups (2% percentiles) and compared all groups with that which had the lowest PRS. Second, we explored risk stratification considering both the APOE genotypes and the PRSs. The APOE genotypes were pooled in the analyses as APOE ε2/ε2 (n = 998, split into 7 PRS groups), APOE ε2/ε3 (n = 7611, split into 25 PRS groups), APOE ε2/ε4 (n = 3399, split into 15 PRS groups), and APOE ε3/ε4 (n = 382, split into 3 PRS groups). We studied the effect of PRS across groups of individuals stratified by the APOE genotypes with the lowest-PRS group (APOE as the reference group using logistic regression models adjusted for four population ancestry components). Finally, we compared the median AAO using a Wilcoxon test. We implemented a Cox regression model on AAO in the GR@ACE/DEGESCO dataset case-only adjusted for covariates as APOE group, the interaction between the PRS and APOE and four population ancestry components. All analyses were done in R (v3.4.2).

Functional annotation. We used Functional Mapping and Annotation of Genome-Wide Association Studies23 (FUMA, v1.3.4c) to interpret SNP-trait associations (see Supplementary Methods and Supplementary Data 15–18). FUMA is an online platform that annotates GWAS findings and prioritizes the most likely causal SNPs and genes using information from 18 biological data repositories and tools. As input, we used the summary statistics of our meta-GWAS. Gene prioritization is based on a combination of positional mapping, expression quantitative trait loci (eQTL) mapping, and chromatin interaction mapping. Functional annotation was performed by applying a methodology by genome-wide polygenic scores (GWAS) recently described by Jansen et al.29. We referred to the original publication for details on the methods and repositories of FUMA23.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability
The discovery summary statistics of this study are publicly available in Fundación ACE server [https://fundacao-mye.sharepoint.com/u?g=personal/idejases_fundacaoace.org/4IlTwIpgkRdRfi51Ko5h3930LUBaaxjiJHl1C018C96cbbwre=/2&deUty].

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Author contributions
A.Ru and S.rvd.L designed and conceptualized the study, interpreted the data and drafted the manuscript. L.d.r contribute to data acquisition, the analysis, interpreted the data, and co-wrote the paper. S.M.G and N.T. contributed to the analysis and interpreted the data. S.j.v.d.L and I.d.r performed polynomic score analyses. L.C.C. and J.C. conducted the functional analysis of APP, Hhpo, W.d.f, S.j.v.d.L, and A.Ru supervised the study. All authors critically reviewed the manuscript and approved the final version.

Data availability
All data generated and/or analyzed during the study are available in the National Institute on Aging Alzheimer’s Disease Data Coordinating Center (NIA-AA Data Coordinated Center, http://www.nia-aaa.org) and the Alzheimer’s Disease Neuroimaging Initiative (ADNI, http://adni.loni.usc.edu). The accession number is ADNI-D000137.v1.0. All data are freely available for download. The data used in this study are also available through the Alzheimer’s Disease Neuroimaging Initiative (ADNI; http://adni.loni.usc.edu). In addition, the data used in this study are also available through the European Alzheimer’s Disease Network (EADN; http://www.eadn.eu). The study data are available on request. Please contact the corresponding author for the release of the study data.

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Competition interests
The authors declare no competing interests.
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