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Transferability of European-derived Alzheimer's disease polygenic risk scores across multiancestry populations

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A polygenic score (PGS) for Alzheimer's disease (AD) was derived recently from data on genome-wide significant loci in European ancestry populations. We applied this PGS to populations in 17 European countries and observed a consistent association with the AD risk, age at onset and cerebrospinal fluid levels of AD biomarkers, independently of apolipoprotein E locus (*APOE*). This PGS was also associated with the AD risk in many other populations of diverse ancestries. A cross-ancestry polygenic risk score improved the association with the AD risk in most of the multiancestry populations tested when the *APOE* region was included. Finally, we found that the PGS/polygenic risk score captured AD-specific information because the association weakened as the diagnosis was broadened. In conclusion, a simple PGS captures the AD-specific genetic information that is common to populations of different ancestries, although studies of more diverse populations are still needed to better characterize the genetics of AD.

Over the last 15 years, genome-wide association studies (GWASs) have fostered the development of powerful approaches for characterizing disease processes and the introduction of diagnostic/prognostic tools such as polygenic scores (PGSs)[1,2]. Given the high estimated heritability (60–80%, in twin studies) of Alzheimer's disease (AD)[3], a number of PGSs have been developed; associations with AD risk or related phenotypes have been described for almost all of the scores[4–10]. However, interstudy comparisons are complicated by marked differences in the populations analyzed, the PGS calculation methods, the summary statistics used and the variants included[11]. Furthermore, most PGSs have been developed from studies of European ancestry populations, and only a few studies have investigated PGSs performance in populations of different ancestries[12–15].

Here, we describe the generation of a PGS (PGS^{ALZ}) that includes the genome-wide significant, independent sentinel single nucleotide polymorphisms (SNPs) at the loci reported by Bellenguez et al.[16], excluding the apolipoprotein E (*APOE*) locus ($n = 83$; see Supplementary Table 1 for the list of variants). We studied the associations between PGS^{ALZ} and AD risk or relevant endophenotypes in populations from 17 European countries and then extended the analysis to populations of diverse ancestries (from Asia, Africa, Latin America and North America). Finally, as already performed for other complex human diseases[17–20], and with a view to improving the predictive performance of PGS^{ALZ} (refs. 2,21), we generated a cross-ancestry polygenic risk score (PRS) by integrating GWAS summary statistics from several populations.

We first evaluated the association between PGS^{ALZ} and AD risk in case–control studies of European countries (see Supplementary Table 2 for population description and adjustments used in each population and Supplementary Figs. 1–3 for PGS^{ALZ} distributions). PGS^{ALZ} was associated significantly with AD risk irrespective of *APOE* adjustment (Extended Data Fig. 1a and Supplementary Fig. 4). PGS^{ALZ} was similarly associated with AD risk in men and in women (Extended Data Fig. 1b and Supplementary Fig. 6). Furthermore, the score was associated with a younger age at onset (Extended Data Fig. 2). It is noteworthy that when the PGSs were adjusted for difference in PGS^{ALZ} distribution between the European populations, the association with AD remained similar (Supplementary Fig. 5).

As we did not identify any potential bias/heterogeneity when comparing PGS^{ALZ} in the European populations, we performed a combined analysis (mega-analysis) of our European datasets to assess

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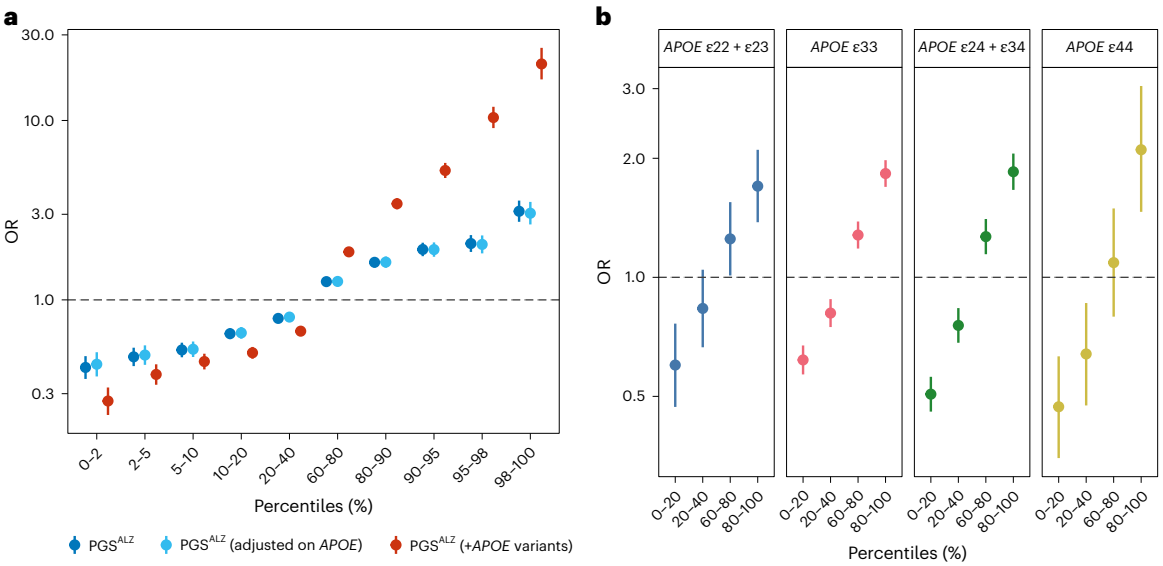

Fig. 1 | Associations between the various PGSs and the risk of developing AD as a function of *APOE* status (25,782 AD cases and 35,280 controls). a, The risk of developing AD, by PGS^{ALZ} stratum (0–2%, 2–5%, 10–20%, 20–40%, 60–80%, 80–90%, 90–95%, 95–98% and 98–100%). The 40–60% PGS^{ALZ} stratum was used as the reference. **b**, Risk of developing AD, by PGS^{ALZ} stratum (0–20%, 20–40%, 60–80% and 80–100%) and by *APOE* genotype (by grouping together the ε2ε2/ε2ε3, ε3ε3, ε2ε4/ε3ε4 and ε4ε4 carriers). The 40–60% PGS^{ALZ} stratum was used as the reference. OR per s.d. was calculated by logistic regression adjusted for age, gender, 14 first PCs and chip center if necessary. The lines indicate the 95% CI of each OR. ε2ε2/ε2ε3 carriers (960 AD cases and 3,604 controls), ε3ε3 (15,623 AD cases and 17,782 controls), ε2ε4/ε3ε4 (8,780 AD cases and 6,242 controls) and ε4ε4 carriers (2,309 AD cases and 479 controls).

the risk of developing AD within various PGS^{ALZ} strata: 0–2%, 2–5%, 10–20%, 20–40%, 60–80%, 80–90%, 90–95%, 95–98% and 98–100%, with the 40–60% PGS^{ALZ} stratum as the reference. We also generated a PGS that included both the sentinel AD GWAS loci and the two SNPs defining the ε2/ε3/ε4 *APOE* alleles. As expected, the risk of developing AD in the most extreme strata was particularly high when *APOE* was included (Fig. 1a). The association with PGS^{ALZ} was also significant in all strata analyzed, irrespective of *APOE* adjustment. In the 0–2% and 98–100% strata, PGS^{ALZ} was associated with a greater than two-fold decrease in AD risk and a greater than threefold increase in AD risk, respectively, compared with the 40–60% stratum (Fig. 1a and Supplementary Table 3).

Since these results suggested that association of PGS^{ALZ} was independent of *APOE*, we leveraged our mega-analysis to determine how PGS^{ALZ} interacted with the *APOE* genotypes. We found a weak interaction between PGS^{ALZ}, the number of *APOE* ε4 alleles and AD risk ($P = 3 \times 10^{-4}$). Next, we stratified the mega-analysis into four *APOE* genotype groups (ε2ε2/ε2ε3, ε3ε3, ε2ε4/ε3ε4 and ε4ε4) and assessed the association between PGS^{ALZ} and AD risk per quintile (0–20%, 20–40%, 60–80% and 80–100%) for each subpopulation (reference, 40–60% stratum). PGS^{ALZ} was associated with AD risk to a similar extent in all strata, although a stronger association might be present among ε4ε4 carriers (Fig. 1b and Supplementary Table 4).

To determine whether PGS^{ALZ} is associated with AD pathophysiological processes, we analyzed GWAS data on CSF levels of Aβ42, tau and p-tau ($n = 13{,}051$ individuals), as described previously[22]. PGS^{ALZ} was associated with a decrement in $A\beta_{42}$ levels and an increment in tau and p-tau levels, whatever the adjustment for *APOE* (Fig. 2a,b and Supplementary Fig. 7). We also checked for a possible association between PGS^{ALZ} and $A\beta_{42}$ levels, tau and p-tau levels in quintiles (0–20%, 20–40%, 60–80% and 80–100%); again, the 40–60% stratum served as the reference. As expected, PGS^{ALZ} was associated with the lowest and highest levels of p-tau and $A\beta_{42}$ in the 0–20% strata and, conversely, the highest and lowest levels of p-tau and $A\beta_{42}$ in the 80–100% stratum (Fig. 2c and Supplementary Table 5).

We then extended the PGS^{ALZ} analyses to other European ancestry populations (United States, Australia), populations from India, East Asia (China, Japan and Korea), North Africa (Tunisia), sub-Saharan Africa (Central African Republic/the Congo Republic), South America (Argentina, Brazil, Chile and Colombia) and African American, Native American and Latin American ancestry populations from US studies (that is, more than 75% African American or Native American ancestry or self-reporting for Latin American populations; see Extended Data Fig. 3a and Supplementary Table 2 for a description of the population). With the exception of the analyses for Korea and Japan (where 72 and 74 SNPs, respectively, were available), most PGSs were built from 78 to 85 SNPs (including *APOE* variants; see Supplementary Table 1 and Supplementary Figs. 8–10 for PGS^{ALZ} distributions). The strength of the *APOE* ε4-AD association differed from one population to another, as observed previously[23,24]. The odds ratios (ORs) ranged from 1.36 in sub-Saharan Africa to 5.46 in North Africa (Extended Data Fig. 3b).

As expected, the association between PGS^{ALZ} and AD risk was strongest in European ancestry populations (United States and Australia). PGS^{ALZ} was also significantly associated with AD risk in North African, East Asian, Latin American and African American populations (Fig. 3a and Supplementary Fig. 11). Finally, PGS^{ALZ} was not associated with AD risk in the sub-Saharan African and Indian populations; this might be related to the small sample size and corresponding lack of statistical power. PGS^{ALZ} was associated with a younger age at onset in most of the populations studied, with the notable exception of the Chinese and Korean populations (Extended Data Fig. 4). Of note, the APOE ε2/ε3/ε4 alleles influenced age at onset in Chinese and Korean populations (Supplementary Fig. 12).

To refine our analysis of these populations of diverse ancestries, we calculated the association between AD and PGS^{ALZ} quintiles (0–20%, 20–40%, 60–80% and 80–100%; reference, 40–60%) and meta-analyzed them by ancestry (Fig. 3b,c and Supplementary Tables 6 and 7). The Indian, North African and sub-Saharan African populations were excluded because of the small sample size. The strength of the association with PGS^{ALZ} decreased from the European American, East Asian and Latin American populations to the African American population, in that order (Fig. 3b and Supplementary Table 6). PGS^{ALZ} generated from a European ancestry population GWAS performed poorly in African ancestry populations.

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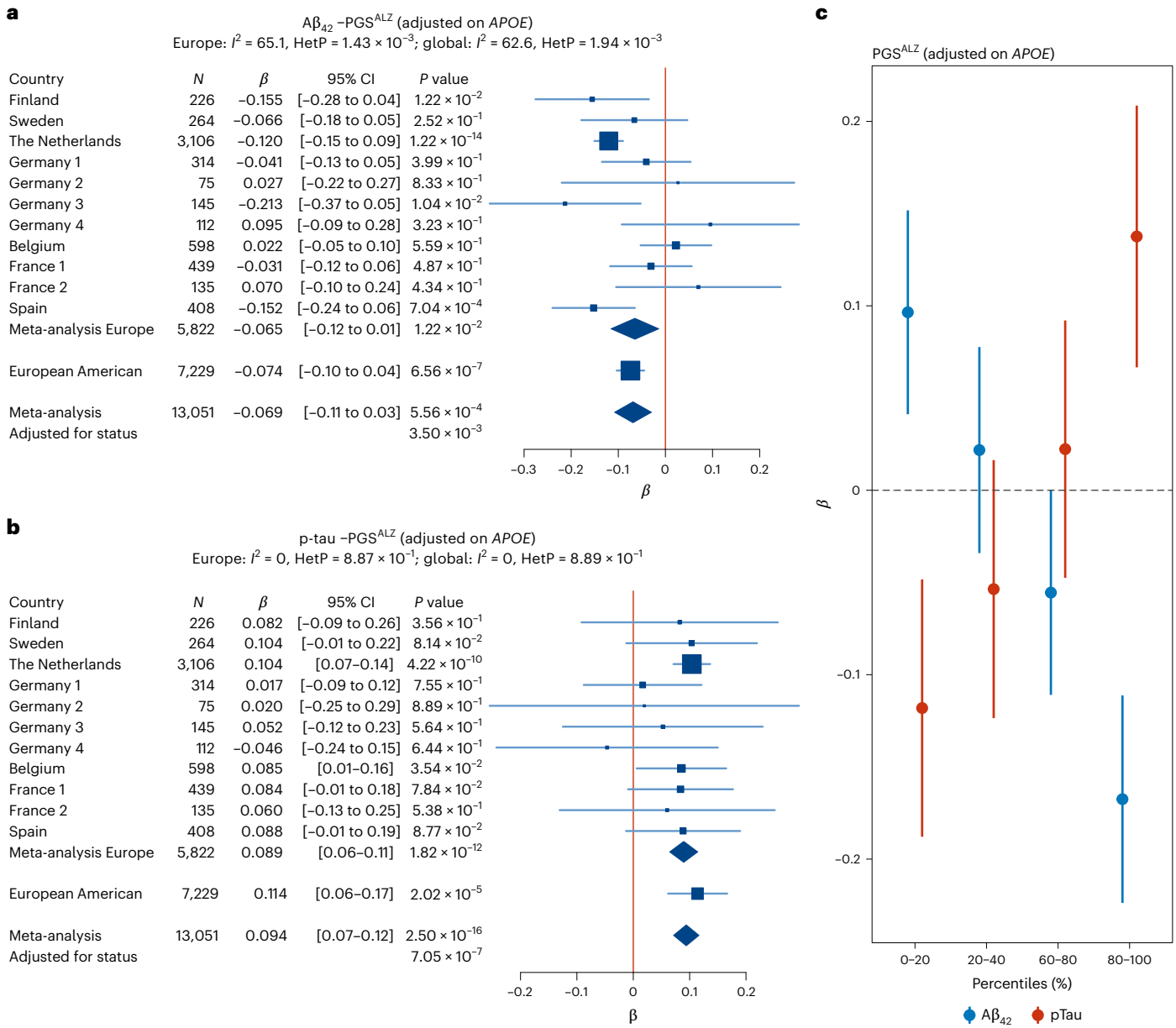

Fig. 2 | Association of PGS^{ALZ} with Aβ$_{42}$ and p-tau in cerebrospinal fluid. **a**–**c**, Association of PGS^{ALZ} with the level of normalized Aβ$_{42}$ (**a**) and p-tau (**b**) in cerebrospinal fluid (n = 13,004) across European ancestry populations and according to PGS^{ALZ} strata (0–20%, 20–40%, 60–80% and 80–100%) (**c**); the 40–60% PGS^{ALZ} stratum was used as the reference. β values were calculated by general linear model and logistic regression adjusted for *APOE*, age, gender, ten first PCs and chip center if necessary. The horizontal lines in the forest plots indicate the 95% CI of each β value. If heterogeneity P (HetP) < 0.05, a random effect is shown for the meta-analysis results. I^2; heterogeneity.

The latter observation was strengthened by analyzing the association between PGS^{ALZ} and AD risk as a function of the African American admixture. The strength of the association decreased as the percentage of African ancestry increased, and ultimately reached a level similar to that observed in our sub-Saharan African population: the association between PGS^{ALZ} and AD risk in populations in whom more than 90% of the members were of African ancestry had an OR of 1.09 (95% confidence interval (CI) 0.98–1.21; $P = 1.4 \times 10^{-1}$, adjusted for *APOE*). Of note, a similar pattern was observed in the Native American population of the Alzheimer Disease Sequencing Project: the strength of the association decreased as the Native American ancestry percentage increased, from OR = 1.21 (95% CI, 1.12–1.32; $P = 5.3 \times 10^{-6}$) and OR = 1.14 (95% CI, 1.05–1.25; $P = 2.6 \times 10^{-3}$) to OR = 1.12 (95% CI, 1.02–1.24; $P = 1.4 \times 10^{-2}$ in the populations with more than 50%, 75% and 90% of individuals of Native American ancestry, respectively, after adjustment for *APOE*. A similar result was found for Chilean and Argentinian populations: the PGS^{ALZ} association weakened as the proportion of individuals with Native American ancestry rose[14].

We next checked that we had fully captured the genetic information in the GWAS-defined loci in the non-European populations. To this end, we developed a PGS (PGS^{ALZ+}) that included other SNPs associated with AD risk in non-European multiancestry populations ($P < 10^{-3}$) at the European GWAS-defined loci (Methods). We used the summary statistics generated by Kunkle et al.[25], Lake et al.[26] and Shigemizu et al.[27], and added 30, 13 and 47 variants to the initial 83 PGS^{ALZ} variants for Latin American, East Asian and African American ancestries, respectively (Supplementary Table 8). We did not detect any increment in (1) the strength of the PGS^{ALZ+} association with the AD risk or (2) PGS^{ALZ+}'s predictive performance, relative to PGS^{ALZ} (Supplementary Table 9).

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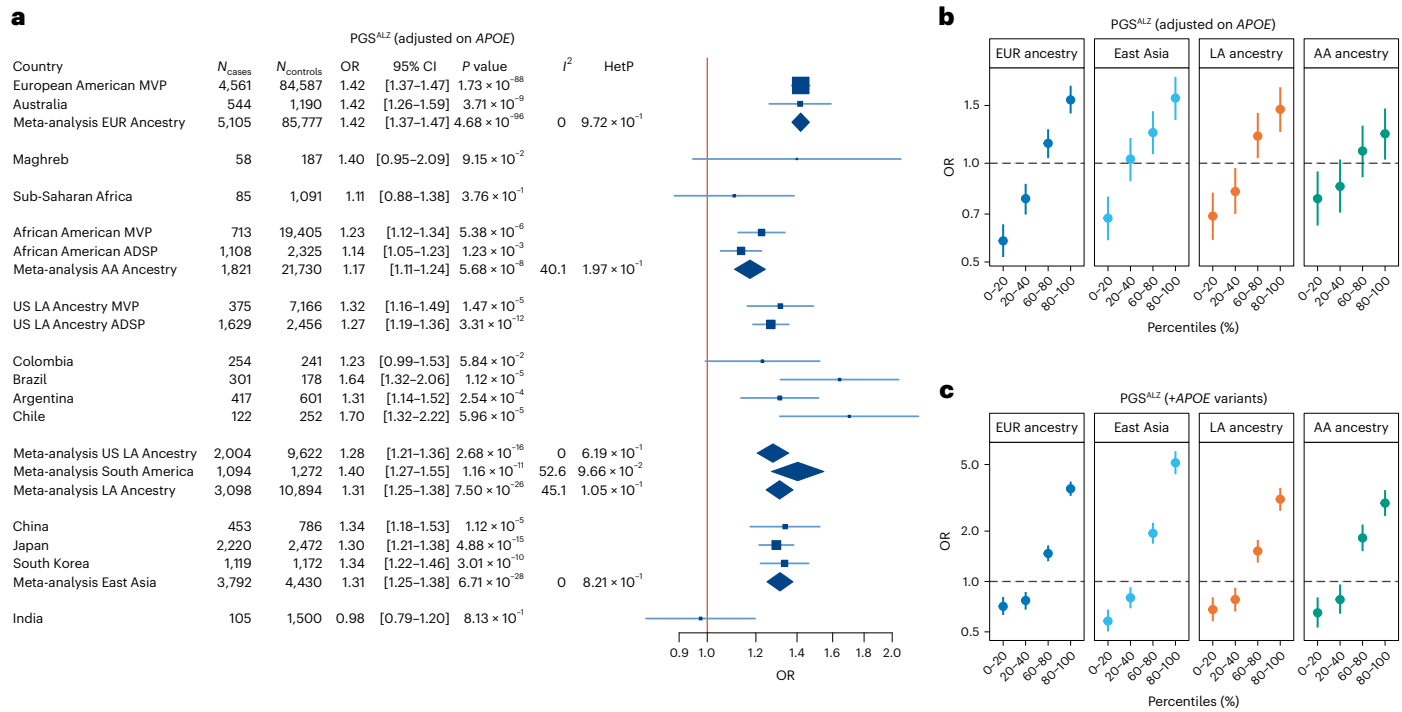

Fig. 3 | Association of PGS^{ALZ} across multiancestry populations. a, Association of PGS^{ALZ} with the risk of developing AD in multiancestry populations. The European ancestry meta-analysis includes MVP and Australia. The African American ancestry (more than 75% AA ancestry) meta-analysis includes MVP and ADSP. The East Asia meta-analysis includes China, Korea and Japan. The Latin American ancestry (self-reported) meta-analysis includes MVP and ADSP. The South America meta-analysis includes Argentina, Brazil, Chile and Colombia. **b**, The risk of developing AD, according to PGS^{ALZ} (logistic regression adjusted or not for *APOE* or included *APOE* variants) strata (0–20%, 20–40%, 60–80% and 80–100%) in multiancestry populations. The 40–60% PGS^{ALZ} stratum was used as the reference in each population, and results were meta-analyzed. The European ancestry meta-analysis includes MVP and Australia. The African American ancestry meta-analysis includes MVP and ADSP. The East Asia meta-analysis includes China, Korea and Japan. The Latin American ancestry meta-analysis includes MVP and ADSP. The South America meta-analysis includes Argentina, Brazil, Chile and Colombia. N_{cases}, number of cases; $N_{controls}$, number of controls. OR per s.d. was calculated by logistic regression adjusted for *APOE*, age, sex and specific PCs according to the study (Supplementary Table 2). The lines in the Forest plots indicate the 95% CI of each OR. If HetP < 0.05, a random effect is shown for the meta-analysis results. AA, African American; EUR, European; LA, Latin American.

By initially restricting our analyses to the genome-wide significant loci from European ancestry AD GWAS, we probably excluded genetic information associated with AD risk in both European populations and (especially) non-European multiancestry populations (for which ancestry-specific loci may exist). Furthermore, the effect sizes used to construct PGS^{ALZ} were extracted from European ancestry populations without taking account of population differences. To deal with these various questions, we used the Bayesian polygenic modeling method PRS-CSx to build a cross-ancestry PRS[20]. The PRS re-estimates variant effect sizes by coupling various summary statistics with external ancestry-matched allele frequencies and local linkage disequilibrium structure, according to the sparseness of the genetic architecture of AD. We used GWAS summary statistics generated from European (36,569 AD cases and 63,137 controls), African American (2,784 AD cases and 5,222 controls), Latin American (1,088 AD cases and 1,152 controls) and East Asian (3,962 AD cases and 4,074 controls) populations[25–27]. PRSs (all adjusted for the population structure) were generated in multiancestry populations from the Million Veteran Program (MVP; European American, Latin American and African American ancestries), EPIDEMCA (sub-Saharan Africa ancestry) and GARD studies (East Asian ancestry; Supplementary Fig. 13).

We assessed potential increments in the association of PRS with the AD risk and in predictive performance when the summary statistics of the European American, African American, Latin American or East Asian multiancestry populations were applied independently (PRS^{EUR}, PRS^{AA}, PRS^{LA} and PRS^{EA}, respectively) or when the statistics were combined (PRS^{COMB}) at various sparseness values (10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-2} and 1). We initially excluded the *APOE* region, to facilitate the comparison with PGS^{ALZ}. We did not observe any increases in the association with AD risk or in predictive performance in the different multiancestry populations (Fig. 4, Supplementary Fig. 14 and Supplementary Table 10), with the exception of the Latin American MVP population. However, we cannot rule out overfitting as the reason for this improvement. Next, we included the *APOE* region when generating the different PRSs. Whereas no impact on European ancestry populations was observed when comparing PRS^{EUR} and PRS^{COMB}, we detected an increment in both the strength of association with the AD risk and in the predictive performance when comparing PRS^{EUR} and PRS^{COMB} for all other populations. This indicated that a cross-ancestry PRS is more effective than a PRS constructed solely from European summary statistics when the *APOE* region is included, whatever the overall shrinkage value used (Fig. 5, Supplementary Fig. 14 and Supplementary Table 10).

Finally, we leveraged the MVP data to determine how the association between PGS^{ALZ} or PRS^{COMB} (without the APOE region) and AD risk changed in multiancestry populations as a function of diagnostic specificity. We looked at how a PGS^{ALZ}/PRS^{COMB} derived from AD case/control studies performed when the diagnosis was broadened to dementia. In all the multiancestry population studied, the association between PGS^{ALZ}/PRS^{COMB} and AD risk weakened as the diagnosis became broader (Fig. 6 and Supplementary Table 11).

Our work produced several important findings. First, the associations between PGS^{ALZ} and AD risk in European populations may be influenced slightly by the *APOE* genotype; this suggests the existence of two independent genetic entities for sporadic AD: one associated

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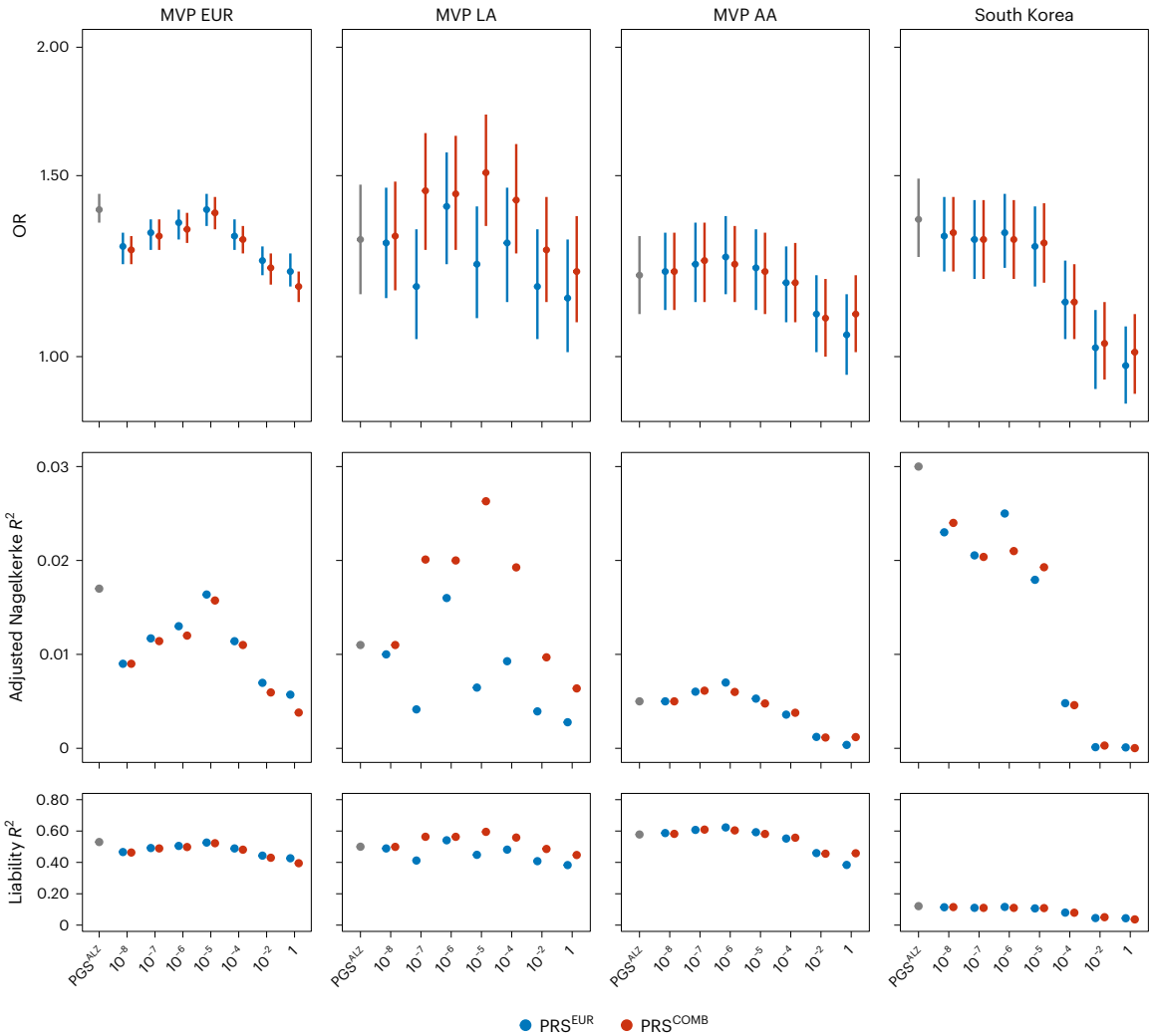

Fig. 4 | Comparison of the association of PGS^{ALZ} or PRS (excluding the *APOE* region) with the AD risk and the corresponding predictive values (adjusted Nagelkerke R^2 and liability R^2). All PGS^{ALZ} and PRS values were adjusted for interpopulation differences in distribution; PRS^{EUR} were generated by using only European ancestry summary statistics; PRS^{COMB} were generated by combining European, African American, Latin American and East Asian ancestry summary statistics. The sparseness parameter was set to 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-2} or 1. OR per s.d. was calculated by logistic regression adjusted for age, sex and specific PCs according to the study (Supplementary Table 2). MVP EUR (4,561 AD cases and 84,587 controls), MVP LA (375 AD cases and 7,166 controls), MVP AA (713 AD cases and 19,405 controls) and South Korea (1,119 AD cases and 1,172 controls).

with *APOE* ε4 and the other not, as suggested previously[28]. Second, the simple PGS^{ALZ} (based on the European GWAS-defined loci) seems to be enough to detect an AD genetic risk in most ancestry populations. Our results thus suggest that most of the various ancestry populations are likely to be affected by shared pathophysiological processes that are driven in part by genetic risk factors. Third, in contrast to what has been observed in the genetics of complex traits[29] and other multifactorial diseases[17,30,31], a cross-ancestry PRS built with a Bayesian polygenic modeling method did not systematically outperform a simple PGS^{ALZ} when the *APOE* locus was excluded. This observation might be due to the small population size of GWAS for the various ancestry populations, which can significantly limit the power of the PRS-CSx approach. However, this might also indicate that a high proportion of AD genetic risk is already accounted for by the European ancestry GWAS-defined loci. Fourth, the *APOE* region appears to contain additional multiancestry genetic variability, as suggested previously[32–35]. Finally, the PGS/PRS associations capture mainly genetic information related to AD because they weakened as the diagnosis was broadened. This observation suggests that the quality of the clinical diagnosis can interfere with the measurement of the association between the PGS/PRS and the AD risk in a given population.

In conclusion, our study of diverse ancestry populations and AD highlights the importance of cross-ancestry analyses for characterizing the genetic complexities of this disease. However, the AD genetics field is still limited by the size of GWASs in these diverse ancestry populations. Furthermore, it is likely that different ancestry populations will differ strongly regarding rare/very rare variants associated with AD risk; this would significantly impact the association of PRSs with AD risk and their predictive abilities[36]. Better characterization of AD genetics thus requires both GWASs and sequencing studies of more diverse populations.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41588-025-02227-w.

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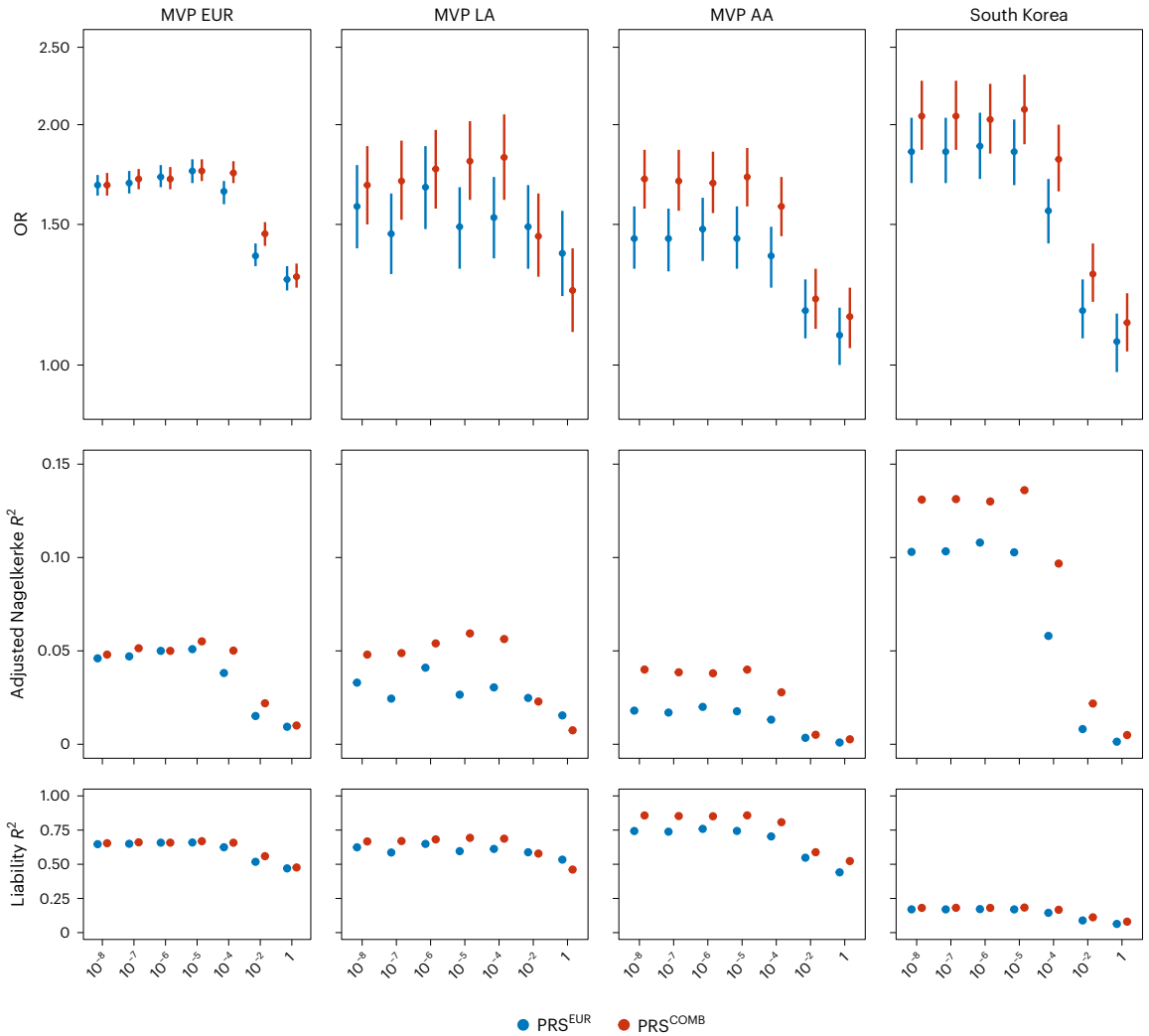

Fig. 5 | Association of PRS (including the *APOE* region) with the AD risk and the corresponding predictive values (adjusted Nagelkerke R^2 and liability R^2). All PRS were adjusted for interpopulation differences in distribution; PRS^{EUR} were generated by using only European ancestry summary statistics; PRS^{COMB} were generated by combining European, African American, Latin American and East Asian ancestry summary statistics. The sparseness parameter was set to 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-2} or 1. OR per s.d. was calculated by logistic regression adjusted for age, sex and specific PCs according to the study (Supplementary Table 2). MVP EUR (4,561 AD cases and 84,587 controls), MVP LA (375 AD cases and 7,166 controls), MVP AA (713 AD cases and 19,405 controls) and South Korea (1,119 AD cases and 1,172 controls).

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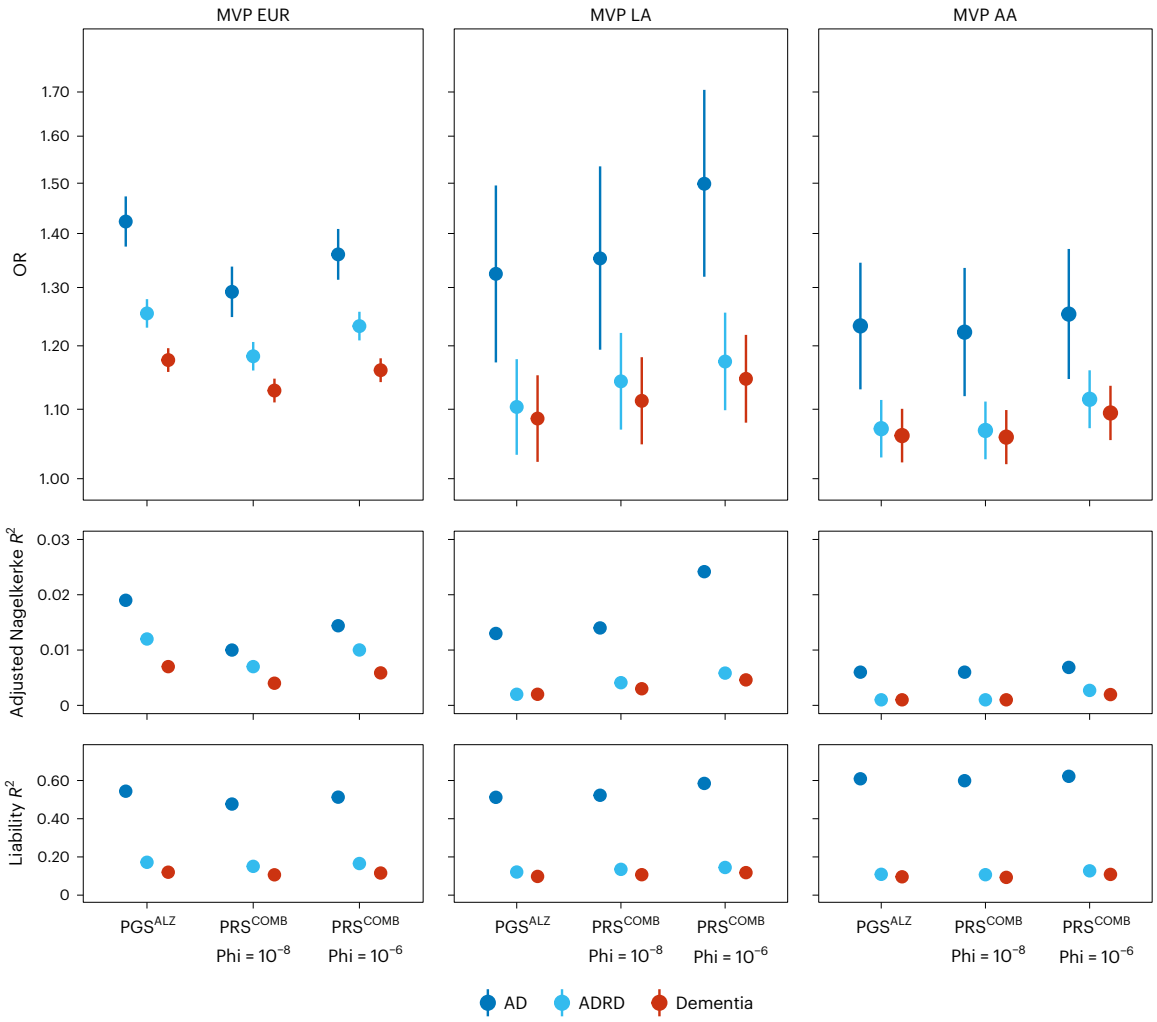

Fig. 6 | Association of PGS^{ALZ} or PRS^{COMB} (excluding the *APOE* region) with AD, AD and related dementia (ADRD) and dementia in MVP, and the corresponding predictive values (adjusted Nagelkerke R^2 and liability R^2). PGS^{ALZ} and PRS^{COMB} were adjusted for interpopulation differences in distribution; PRS^{COMB} were generated by combining European, African American and Latin American and East Asian ancestry summary statistics. The sparseness parameter was set to 10^{-8} and 10^{-6}. OR per s.d. was calculated by logistic regression adjusted for age, sex and specific PCs according to the study (Supplementary Table 2). MVP EUR (4,561 AD, 17,519 ADRD, 26,473 dementia cases and 84,587 controls), MVP LA (375 AD; 1,527 ADRD; 1,981 dementia cases and 7,166 controls), MVP AA (713 AD; 4,016 ADRD; 4,702 dementia cases and 19,405 controls).

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Methods

Sample and variant quality controls

Written informed consent was obtained from study participants or, for those with substantial cognitive impairment, a caregiver, legal guardian or other proxy. Study protocols for all cohorts were reviewed and approved by the appropriate institutional review boards (Supplementary Information).

To ensure that the β values were completely independent of the summary statistics, all samples from ADGC, CHARGE and FinnGen GWASs were filtered out. Sample overlap was assessed systematically, and there was no sample overlap between any of the non-US studies analyzed. Overlap between Alzheimer's Disease Sequencing Project ADSP and MVP is likely to be negligible—no more than a few cases. For the biomarker analysis, there is a 460-sample overlap between the American samples used in the biomarker analyses and the ADGC (which is included in the summary statistics we used to generate the β values for the PGS^{ALZ}). However, this overlap is small (less than 2.5%). Furthermore, we analyzed the association of PGS^{ALZ} only with quantitative traits (p-tau, tau and Aβ42 CSF concentrations) in these samples, which limited the risk of inflation.

After each sample had met the conventional GWAS gold standard for quality control, it was included in the analyses[16]. If a discordance in a variant dose, covariate or *APOE* status (the difference between the imputation and the genotyping results (if available)) was observed, the sample was discarded. After the quality control, each study's demographics were described (Supplementary Table 1)[37]. Genotyped variants had to meet the gold standard for GWAS variant quality control[16]. All studies containing genotyping data were imputed with the TOPmed reference panel[37,38]. If the variants were imputed, those with an R^2 value below 0.3 were excluded. For whole-genome sequencing data, only variants passing the corresponding quality control were selected (see the Supplementary Information for the ADSP and China samples) (Supplementary Table 2). The global ancestry of each person in the ADSP samples was determined with SNPweights v.2.1 (ref. 39) using a set of ancestry-weighted variants computed on reference populations from the 1000 Genomes Project (as in ref. 40). By applying a global ancestry percentage cutoff of >75%, the samples were assigned to the different ancestry populations. The ancestry of MVP participants was determined using the harmonized ancestry and race/ethnicity (HARE) method[41]. HARE is like other genotype-based ancestry calling methods, except that concordance between self-reported ancestry and genetically inferred ancestry is checked. Participants with discrepant ancestry calls are not assigned to a HARE category. Within-group principal components (PCs) for ancestry were computed using FlashPCA2 (ref. 42).

Mega-analysis of European populations

We merged samples from five datasets: EADB-core, GERAD, EADI, Demgene and Bonn. To adjust for population structure, we computed PCs using the following procedure. From the list of 146,705 variants used in the PC analysis of EADB-core[42], we extracted the TOPMed imputed variants with an imputation quality ≥0.9 in each dataset; this resulted in 91,353 variants. Next, we set a genotype to 'missing' if none of the genotype probabilities were greater than 0.8. Finally, all datasets were merged, and variants with a proportion of missing genotypes greater than 0.02 were removed. Ultimately, 90,471 variants were included in the PC analysis (performed with FlashPCA2). The analyses were adjusted for the first 14 PCs, the genotyping chip and the center.

PGS and PRS computations

All codes for PGS and PRS analyses have been made available[43]. The equation used to calculate the PGSs and the PRSs is as follows:

$$\mathrm{PGS}^{\mathrm{ALZ}}_{\mathrm{sample}} \text{ or } \mathrm{PRS}_{\mathrm{sample}} = \sum_{i=1}^{n} (\beta_i \times \mathrm{genotype}_i, \mathrm{sample})$$

where the PGS^{ALZ}_{sample} PRS_{sample} is the sum per sample of the product of the variant i effect size β_i (extracted from GWAS summary statistics) and the number of risk alleles of this variant i (either as a dosage or as a genotype).

PGS^{ALZ} includes the 83 independent signals associated with AD[13] and listed in Supplementary Table 1. We also calculated another PGS^{ALZ} combining the same 83 independent signals and the two SNPs encoding the APOE ε2 (rs7412) and APOE ε4 alleles (rs429358). PGS^{APOE} includes only these two last SNPs. The stage I meta-analysis of EADB studies[13] (without the United Kingdom (UK) Biobank samples) contained 36,659 clinically diagnosed AD cases, and the stage II meta-analysis (including the ADGC, CHARGE and FinnGen data) contained 25,392 (ref. 13). To ensure independence between the samples and the GWAS summary statistics, the European summary statistics used in the PGS analyses were from stage II. In the PGS^{ALZ}/PRS analyses adjusted for the difference in distribution between populations, the European more powerful summary statistics (that is, the stage I meta-analysis of EADB) were preferred.

The PGS^{ALZ+} score was developed to include additional SNPs in the GWAS-defined loci, to capture more genetic information in non-European ancestry populations. First, the 'start and end positions' of each locus (as specified in the GRCh38 assembly) were defined manually by looking at the regional plots and extracting (1) recombination rate peak positions, (2) chromosome start and end positions, (3) specific variant positions or (4) the start/end positions of regions containing no variants. Next, insertions and deletions were excluded. Variants that were not ambiguous (that is, A/T or C/G) and present in the 1000 Genomes Phase 3 data (1000GP3) and had an imputation quality above 0.3 in the EADB-core TOPMed imputations were selected. To extract information on these variants in non-European ancestry populations, we used the summary statistics generated by Lake et al., Shigemizu et al. and Kunkle et al. to represent Latin American, East Asian and African American ancestries, respectively[25–27]. Since these summary statistics were based on the GRCh37 assembly, we lifted their positions and alleles in the GRCh38 assembly by using the Picard LiftoverVcf tool (v.2.27.5) and restricting the process to variants with a minor allele frequency above 0.01. To remove variants in linkage disequilibrium with the sentinel variant of each locus, we computed the linkage disequilibrium for each sentinel variant versus all the other variants in the locus by using the 1000GP3 data restricted to samples representing European ancestries (the EUR superpopulation), Latin American ancestries (the AMR superpopulation plus the IBS population), Japanese ancestries (the JPT population) and African American ancestries (the AFR superpopulation). Since one of the sentinel variants (chr. 9:104903697:C:G) was not present in the 1000GP3 data, we replaced it with a proxy variant (chr. 9:104903754:G:GC, $R^2 = 1$ in the EUR superpopulation). In each set of summary statistics, we removed variants with $R^2 > 0.1$ in either the European summary statistics or the summary statistics for the corresponding ancestry. Finally, we performed a clumping procedure on the remaining variants in each of the three ancestries by using plink v.1.9, a P value threshold of 1×10^{-3}, an R^2 of 0.05 (as estimated in the corresponding 1000GP3 data samples, as described above) and a distance of 1 Mb. For the PGS^{ALZ+}, this led us to select 30, 13 and 47 variants (in addition to the initial 85 PGS variants) for the Latin American, East Asian and African American ancestries, respectively.

At the time of our analysis, PRS-CSx[20,44] was one of the best-performing methods for modeling a cross-ancestry PRS[45,46] without a validation dataset and using GWAS summary statistics. With a Bayesian high-dimensional regression framework model based on continuous shrinkage priors, the variant effect sizes were adaptively re-estimated by coupling cross-ancestry GWAS summary statistics[13,25–27], external ancestry-matched allele frequencies and local linkage disequilibrium structure, according to a global shrinkage parameter. This global shrinkage parameter corresponded to the sparseness of the genetic

architecture of AD by avoiding overshrinkage of true signals and by shrinking noisy signals. The sparseness was modeled for the values of $1, 10^{-2}, 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}$ and 10^{-8}, with the --meta option and the Strawderman–Berger prior default parameters ($a = 1$ and $b = 0.5$). The initial 1,297,432 variants present in the 1000 Genomes reference panel were lifted over in GRCh38. Next, new ancestry-specific or joint-ancestry effect size estimates were obtained with PRS-CSx, leading to a maximum number of 1,292,532 variants in the joint-ancestry summary statistics and potentially included in the PRS computations. The PRSs were computed per chromosome with joint-ancestry, European ancestry and ancestry-specific PRS-CSx-effect size estimates, using PLINK (v.2.0.a) software[47] and its --score option. Finally, the PRSs were summed across all chromosomes.

Adjustment for interpopulation differences in the PGS^{ALZ}/PRS distribution

To account for the population structure, PRS_{raw} and $PGS^{ALZ}{}_{raw}$ were adjusted for interpopulation differences in distribution[48]. The adjustment was performed with a selection of 84,035 independent and well-imputed ($R > 0.8$) variants common to all studies. Starting from this list of variants, FlashPCA2 projected the samples into the 1000GP3 PC-space and calculated the projected PCs. For each study, the raw score was fitted into a linear model in controls, according to the first five projected PCs. This model was used to compute a predicted score in all the samples. The resulting adjusted score was the difference between the raw score and the predicted score.

Statistical analyses

The PGSs and PRSs were standardized to a normal distribution, using the mean and s.d. calculated for the samples as a whole. The associations between AD status and the various scores were tested in logistic regressions named according to the score and the covariates used. Hence, the name 'ALZinclAPOE' was attributed if the score included variants in the APOE region (from 43 Mb to 47 Mb). The other covariates included age and sex, as well as the covariates specific to each study (Supplementary Table 2).

- Model PGS^{ALZ}: AD ~ PGS^{ALZ} + COV
- Model PGS^{ALZ}: AD ~ PGS^{ALZ} + COV + the count of APOE ε2 alleles + the count of APOE ε4 alleles (when adjusted for *APOE*)
- Model PRS: AD ~ PRS + COV
- Model PRS: AD ~ PRS + COV + the count of APOE ε2 alleles + the count of APOE ε4 alleles (when adjusted for *APOE*)
- Model $PRS^{ALZinclAPOE}$: AD ~ $PRS^{ALZinclAPOE}$ + COV

To estimate the proportion of phenotypic variance explained by the variance in the score, we computed Nagelkerke's Pseudo-$R^2{}_{Full}$ using the Nagelkerke function implemented in the rcompanion package in R[49,50]. A Pseudo-$R^2{}_{Null}$ was also computed for the covariates only. The adjusted Pseudo-R^2 is the difference between Pseudo-$R^2{}_{Full}$ and the tied Pseudo-$R^2{}_{Null}$. This adjusted Pseudo-R^2 corresponds to the phenotypic variance explained by the genetic score only. The adjusted Pseudo-R^2 was also transformed into a liability scale for ascertained case–control studies[51], using a prevalence value of 0.15. We consider this value of 0.15 to be consistent for populations with a mean age greater than 75 years. However, this prevalence is different in multiethnic populations of the same mean age. Furthermore, the AD prevalence increases with age, so genetic liability is not homogeneous in all age groups. AD heritability cannot be expressed as a single number because it depends on the ages of the cases and controls[52].

Quantile and percentile analyses

Depending on the value of the corresponding PGS^{ALZ}, the samples were classified into the reference group or into one of the test groups. In the mega-analysis, the reference group corresponded to the 40–60% percentile and was tested across other percentiles (0–2%, 2–5%, 5–10%, 10–20%, 20–40%, 60–80%, 80–90%, 95–98% and 98–100%). In the *APOE*-stratified analysis and in the multiancestry analyses, the reference group was defined as the 40–60% percentile and was tested across the other quintiles (0–20%, 20–40%, 60–80%, 80–100%). The multiancestry analyses were performed on each population and then meta-analyzed per genetic ancestry by using the inverse variance method, as implemented in METAL[53]. It should be noted that the Indian, North African and sub-Saharan African populations were excluded because of their small sample size.

- Model PGS^{ALZ}: AD ~ $Group_{0/1}(PGS^{ALZ})$ + COV
- Model PGS^{ALZ}: AD ~ $Group_{0/1}(PGS^{ALZ})$ + COV + number of APOE ε2 alleles + number of APOE ε4 alleles (when adjusted for *APOE*)
- Model $PGS^{ALZinclAPOE}$: AD ~ $Group_{0/1}(PGS^{ALZinclAPOE})$ + COV

Reporting summary

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

Data availability

The EADB GWAS (without UK biobank) summary statistics used to develop PRS have been deposited with the European Bioinformatics Institute GWAS Catalog under accession no. GCST90565439. Summary statistics from African American multiancestry population used to develop PRS were accessed through NIAGADS under accession number NG00100. Summary statistics from Japan populations were accessed through the National Bioscience Database Center (NBDC) at the Japan Science and Technology Agency (JST) with accession number hum0237.v1.gwas.v1. 1000GP3 data is available at http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/1000_genomes_project/release/20190312_biallelic_SNV_and_INDEL/). GRCh37 assembly data is available at https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/001/405/GCF_000001405.25_GRCh37.p13/GCF_000001405.25_GRCh37.p13_genomic.fna.gz. GRCh38 assembly data is available at https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/001/405/GCF_000001405.39_GRCh38.p13/GCF_000001405.39_GRCh38.p13_genomic.fna.gz. ADSP data is available at https://dss.niagads.org/datasets/ng00067/.

Code availability

All codes developed and shared with collaborators to run PGS and PRS are available via Zenodo at https://doi.org/10.5281/zenodo.15164089 (ref. 43). Based on IRB and protected status of the Latin American population in dbGaP access process for this data, the summary statistics of the Latin American GWAS cannot be shared. The code to generate it as well as the mandated dbGaP link are respectively available here: https://github.com/NIH-CARD/MA_MA_meta and https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000496.v1.p1. SNPweights v.2.1. is available at https://hsph.harvard.edu/research/price-lab/software/. FlashPCA2 is available at https://github.com/gabraham/flashpca. Picard LiftoverVcf tool (v.2.27.5) is available at https://broadinstitute.github.io/picard/. plink v.1.9 is available at https://www.cog-genomics.org/plink2/. PLINK (v.2.0.a) is available at https://www.cog-genomics.org/plink/2.0/. rcompanion package is available at https://cran.r-project.org/web/packages/rcompanion/. METAL v2020–05–05 is available at https://github.com/statgen/METAL.

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Author contributions

A.N. and J.-C.L. coordinated the project. A.N., Y.LG., J.G., M.D.G., S.v.d.L, E.N.D.M., J.-F.D., H.A., V.E.-P., A. Ruiz, K.H.L., T.I., A. Ramirez, M.L. and J.-C.L. coordinated data collection. A.N., R. Sherva, B.G.-B., Y.K., M.K., J.T., I.D.R., C.D., X.Z., Y.L.G., C.E.A.-B., M.A.C.B., M. Guerchet, S.v.d.L., M. Goss, A.C., C.B. and F.K. analyzed the data. I.d.R., A.C., S.v.d.L., C.B., F.K., O.P., A. Schneider, M.D., D.R., N. Scherbaum, J.D., S.R.-H., L.H., L.M.-P., E.D., T.G., J. Wiltfang, S.H.-H., S. Moebus, T.T., N. Scarmeas, O.D.-I., F.M., J.P.-T., M.J.B., P.P., R.S.-V., V.Á., M.B., P.G.-G., R. Puerta, P. Mir, L.M.R., G.P.-R., J.M.G.-A., J.L.R., E.R.-R., H. Soininen, T.K., A.d.M., S. Mehrabian, J. Hort, M.V., K.L.R., J.Q.T., Y.A.L.P., H.H. J.C.v.S., H. Seelaar, J.A.H.R.C., W.J.S., I. Ramakers, F.V., A.v.d.L. P. Scheltens, S.B., V.F., G.S., C.G., G.P., V.G., G.N., C. Dufouil, F.P., O.H., S.D., A.B., J.-F. Deleuze, E.G., J.P., P. Sachdev, K.A.M., D.G., B. Arosio, P. Mecocci, V.S., L.P., A. Squassina, L.T., B. Borroni, B.N., P.C., D.S., I. Rainero, A. Daniele, J. Williams, C. Masullo, P.A., F.J., P.K., C.V.D., R.F.-S., M.T., P.S.-J., K.S., M.I., G.R., M.H., R. Sims, W.v.d.F., O.A.A., A. Ruiz, A. Ramirez and J-C.L. contributed to EADB sample collection, T.P. and S.M.L. provided the Australian sample. R. Sherva, R.L.H., V.M., M.P., R.Z., J.M.G., C.L.L. and M.L. contributed the MVP sample. M. Goss, C.L.B., B.F., Q.Y., A.J.G., T.F., J. Haines, L.F., A. DeStefano, E.W., R.M., M. P.-V., B.K., A. Goate, G.D.S., B.V., L.-S.W., Y.Y.L., C.L.D., A. Saykin, H.L.L., J.S.Y., M.A.N., S.S. and C. Cruchaga provided US populations. M. Guerchet, P.-M.P., P. Mbelesso, B. Bandzouzi, N.B.S., L. Cherni and J.-F. Dartigues contributed the African sample. Y.K., M.K., X.Z., H.C., N.Y.I., A.K.Y.F., F.C.F.I., A.M., N.H., K.O., S.N., J.G., V.E.-P., K.H.L. and T.I. contributed the East Asia sample. M.C.D., C.E.A.-B., M.A.C.B., N.O., T.J.-C., C. Muchnik, C. Cuesta, L. Campanelli, P. Solis, D.G.P., S.K., L.I.B., J.O.-R., A.G.C.M., M.F.M., R. Pardo, G.A., L.A.d.M., M.A.R.S., B.d.M.V., M.T.G.C., T.J.-C., B. Angel, S.G., M.V.C., R.A., P.O., A. Slachevsky, C.G.-B., C.A., P.F., E.N.d.M., L.M., H.A., A. Ruiz and A. Ramirez contributed the South America sample. The core writing group were A.N., B.G.-B. and J.-C.L.

Competing interests

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Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41588-025-02227-w.

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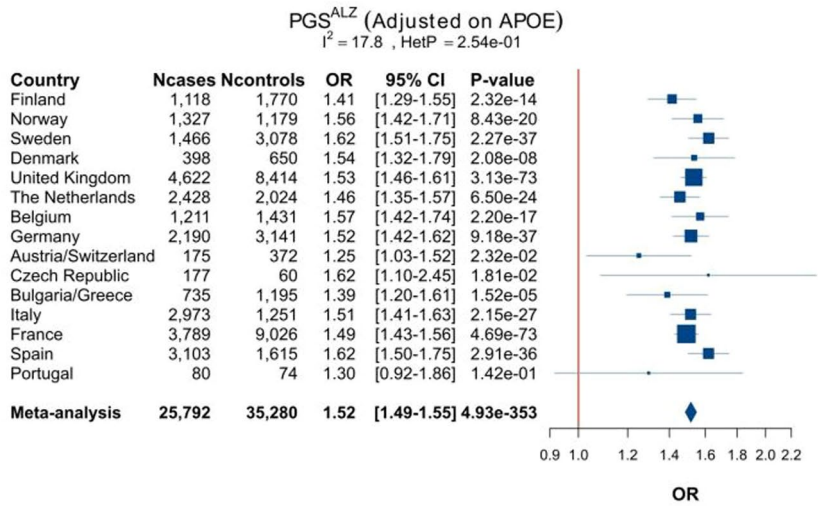
a



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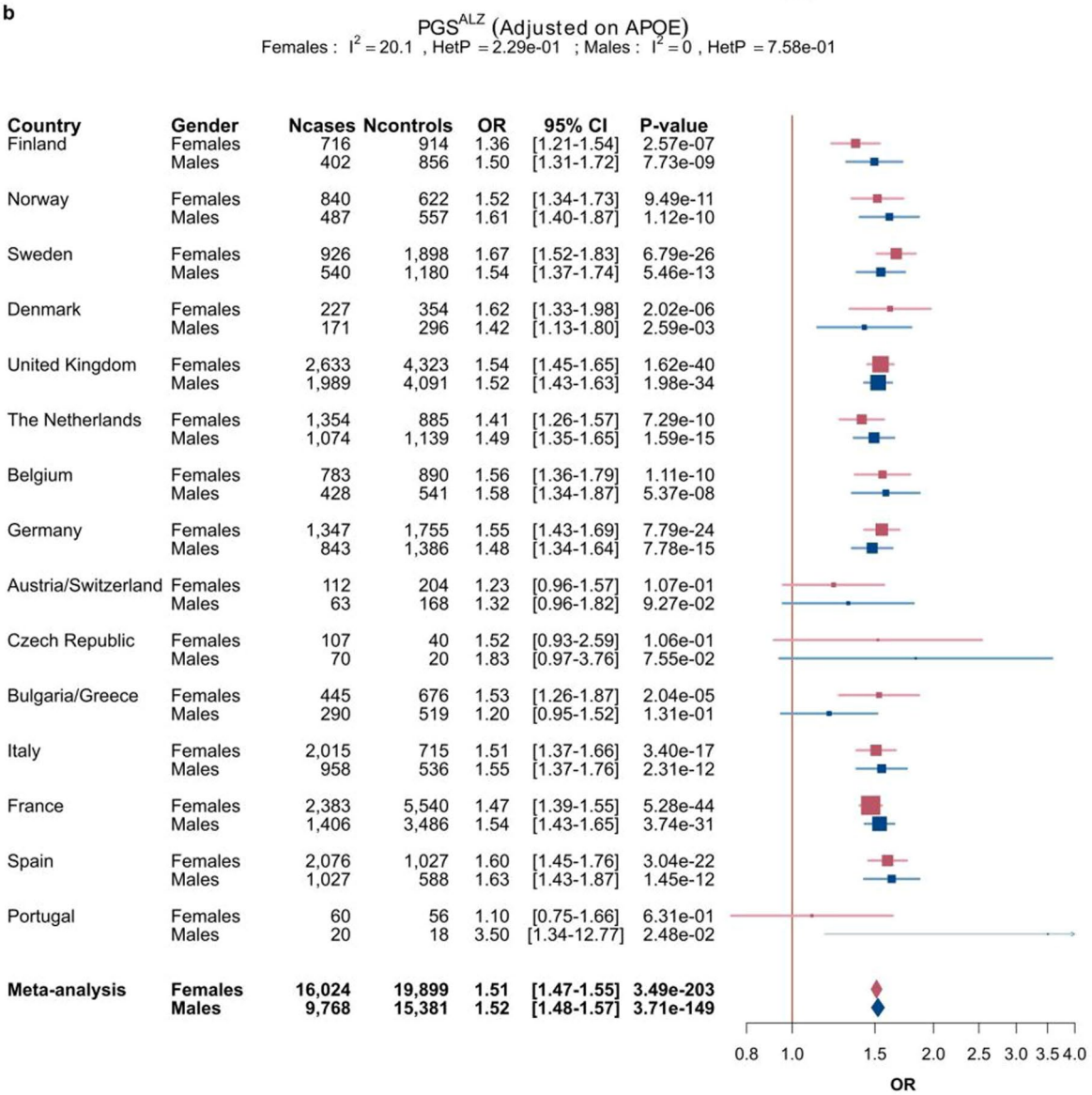

Extended Data Fig. 1 | Association of PGS^{ALZ} with the risk of developing AD (a) in 17 European countries and (b) in Men and Women. Ncases, number of cases; Ncontrols, number of controls; OR, Odds ratio per Standard deviation were calculated using logistic regressions adjusted for age, gender and PCs according to the population studied (Supplementary Table 2). The lines in the Forest plots indicate the 95% confidence interval for the ORs.

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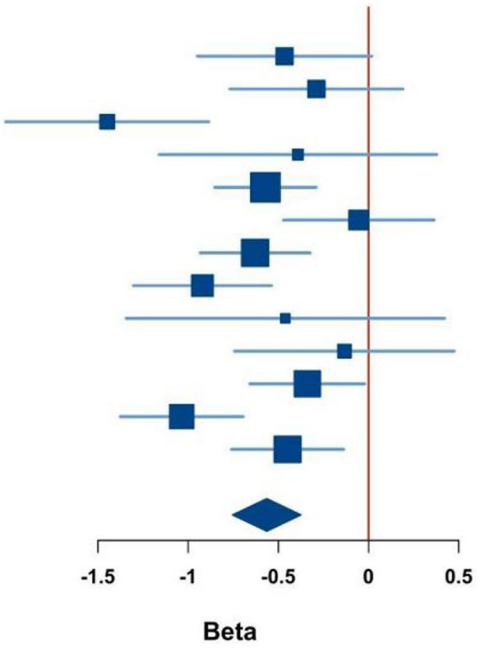
a

PGS^{ALZ}

$I^2 = 62.4$, HetP = 1.42e-03

Country	Ncases	Beta	95% CI	P-value
Finland	1,118	-0.47	[-0.95;0.02]	5.99e-02
Norway	1,327	-0.29	[-0.77;0.19]	2.39e-01
Sweden	1,466	-1.45	[-2.01;-0.88]	5.30e-07
Denmark	398	-0.39	[-1.16;0.38]	3.19e-01
United Kingdom	4,622	-0.57	[-0.85;-0.29]	7.29e-05
The Netherlands	2,428	-0.05	[-0.47;0.36]	8.00e-01
Belgium	1,211	-0.63	[-0.93;-0.32]	5.95e-05
Germany	2,190	-0.92	[-1.30;-0.54]	2.79e-06
Austria/Switzerland	175	-0.46	[-1.35;0.42]	3.04e-01
Bulgaria/Greece	735	-0.13	[-0.74;0.48]	6.67e-01
Italy	2,973	-0.34	[-0.66;-0.02]	3.76e-02
France	3,789	-1.04	[-1.38;-0.69]	3.18e-09
Spain	3,103	-0.45	[-0.76;-0.14]	4.85e-03
Meta-analysis	**25,535**	**-0.56**	**[-0.75;-0.37]**	**6.87e-09**

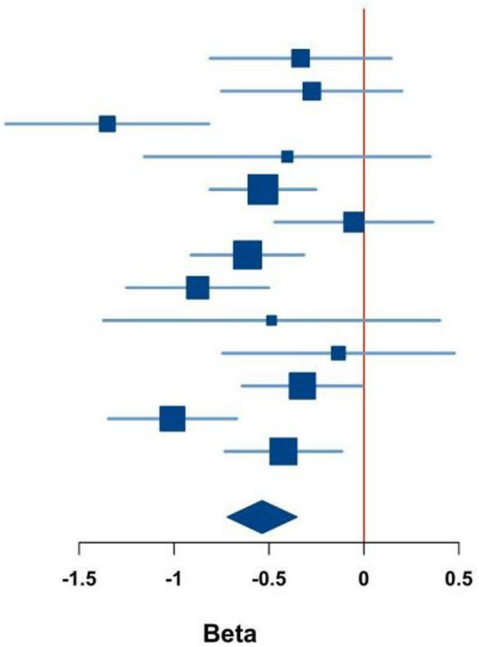


b

PGS^{ALZ} (Adjusted on APOE)

$I^2 = 60.9$, HetP = 2.17e-03

Country	Ncases	Beta	95% CI	P-value
Finland	1,118	-0.33	[-0.81;0.15]	1.72e-01
Norway	1,327	-0.28	[-0.75;0.20]	2.57e-01
Sweden	1,466	-1.35	[-1.89;-0.82]	8.54e-07
Denmark	398	-0.40	[-1.16;0.35]	2.93e-01
United Kingdom	4,622	-0.53	[-0.81;-0.25]	2.01e-04
The Netherlands	2,428	-0.05	[-0.47;0.36]	8.01e-01
Belgium	1,211	-0.61	[-0.91;-0.31]	6.06e-05
Germany	2,190	-0.88	[-1.25;-0.50]	4.93e-06
Austria/Switzerland	175	-0.49	[-1.37;0.40]	2.81e-01
Bulgaria/Greece	735	-0.13	[-0.75;0.48]	6.66e-01
Italy	2,973	-0.32	[-0.64;-0.01]	4.62e-02
France	3,789	-1.01	[-1.35;-0.67]	5.83e-09
Spain	3,103	-0.42	[-0.73;-0.11]	7.28e-03
Meta-analysis	**25,535**	**-0.54**	**[-0.72;-0.35]**	**1.27e-08**



Extended Data Fig. 2 | Associations between (a) PGS^{ALZ} or (b) PGS^{ALZ} adjusted for *APOE* and age at onset of AD in European countries. N_{cases}, the number of cases. Since HetP <0.05, the random effect is shown for the meta-analysis results. βs were calculated using a general linear model adjusted for *APOE*, gender and PCs according to the population studied (Supplementary Table 2).

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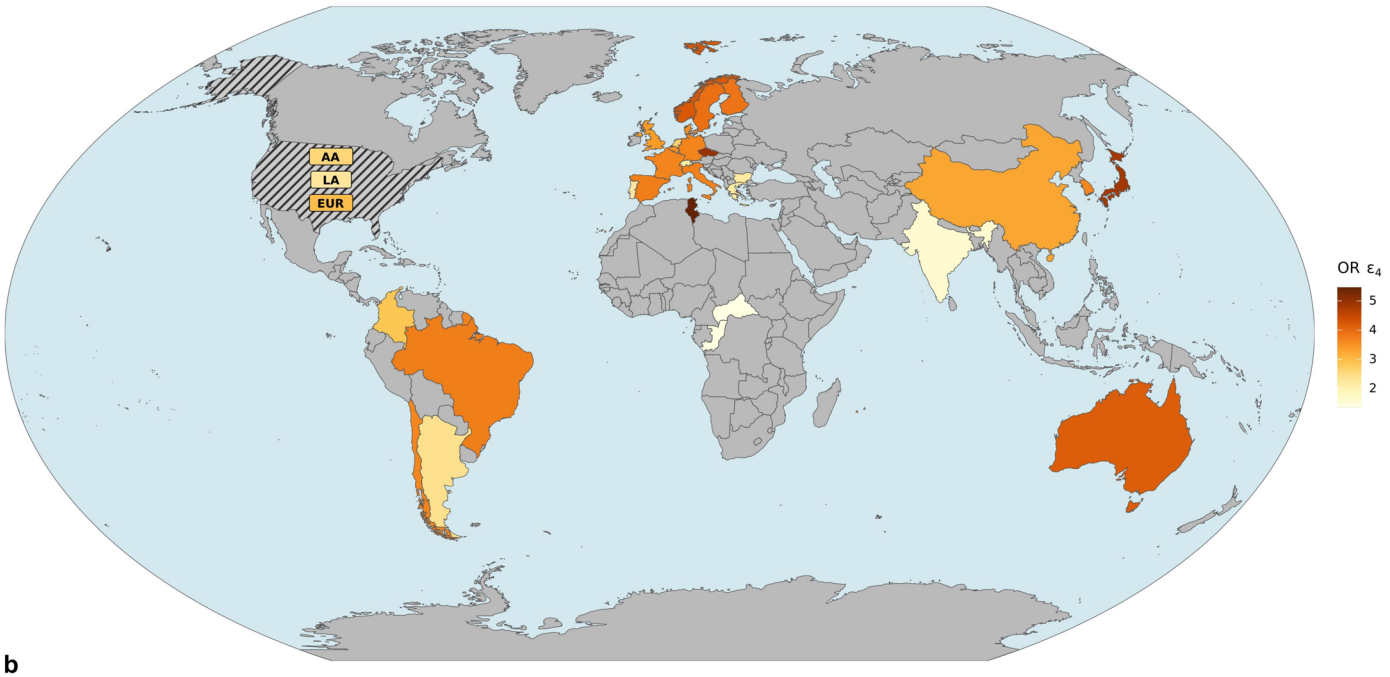
a



b

Country	Cases			Controls			OR ε_4
	ε_4	ε_3	ε_2	ε_4	ε_3	ε_2	
Finland	0.42	0.56	0.02	0.16	0.79	0.05	3.85 [3.33-4.46]
Norway	0.43	0.54	0.03	0.17	0.76	0.08	4.23 [3.62-4.95]
Sweden	0.41	0.57	0.03	0.16	0.77	0.08	3.90 [3.47-4.39]
Denmark	0.34	0.60	0.07	0.15	0.76	0.09	3.51 [2.71-4.53]
United Kingdom	0.33	0.63	0.04	0.13	0.79	0.08	3.39 [3.14-3.67]
The Netherlands	0.42	0.55	0.03	0.19	0.73	0.07	2.67 [2.38-2.98]
Belgium	0.31	0.64	0.05	0.13	0.79	0.08	3.50 [2.92-4.20]
Germany	0.33	0.63	0.05	0.12	0.79	0.09	3.67 [3.28-4.11]
Austria/Switzerland	0.19	0.74	0.07	0.10	0.82	0.08	2.11 [1.43-3.10]
Czech Republic	0.32	0.66	0.02	0.11	0.82	0.07	4.94 [2.22-10.99]
Bulgaria/Greece	0.23	0.74	0.03	0.09	0.85	0.06	2.17 [1.63-2.89]
France	0.30	0.66	0.04	0.10	0.82	0.07	3.65 [3.37-3.94]
Italy	0.25	0.73	0.03	0.09	0.86	0.05	3.69 [3.13-4.36]
Spain	0.27	0.70	0.03	0.10	0.85	0.06	3.73 [3.21-4.33]
Portugal	0.30	0.66	0.04	0.18	0.77	0.05	2.20 [1.19-4.05]

Country	Cases			Controls			OR ε_4
	ε_4	ε_3	ε_2	ε_4	ε_3	ε_2	
European American	0.26	0.68	0.06	0.12	0.80	0.08	2.96 [2.78-3.15]
African American	0.36	0.57	0.07	0.20	0.70	0.11	2.59 [2.35-2.84]
US LA Ancestry	0.23	0.73	0.04	0.10	0.85	0.05	2.25 [2.02-2.52]
Maghreb	0.27	0.72	0.02	0.10	0.87	0.03	5.46 [2.50-11.94]
Sub-Saharan Africa	0.28	0.62	0.11	0.23	0.65	0.12	1.36 [0.91-2.03]
Colombia	0.31	0.66	0.03	0.14	0.81	0.05	2.85 [1.97-4.13]
Brazil	0.28	0.68	0.03	0.12	0.81	0.07	3.73 [2.44-5.69]
Argentina	0.27	0.70	0.03	0.11	0.84	0.05	2.40 [1.73-3.33]
Chile	0.29	0.70	0.01	0.10	0.86	0.04	3.64 [2.26-5.86]
China	0.21	0.72	0.07	0.08	0.83	0.09	3.26 [2.49-4.26]
Japan	0.31	0.67	0.02	0.09	0.87	0.05	4.83 [4.24-5.49]
South Korea	0.26	0.70	0.04	0.08	0.86	0.06	3.64 [3.02-4.38]
India	0.17	0.79	0.04	0.11	0.84	0.05	1.61 [1.08-2.39]
Australia	0.40	0.57	0.03	0.14	0.77	0.09	4.16 [3.43-5.04]

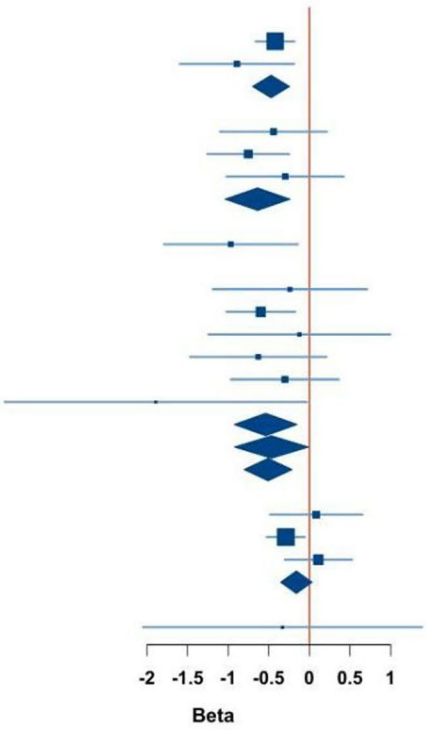
Extended Data Fig. 3 | Distribution and association of *APOE* ε2/ε3/ε4 alleles with AD risk worldwide. (a) World map showing the populations analyzed. A color gradient indicates the strength of the association between *APOE* ε2/ε3/ε4 alleles and the risk of developing AD in different countries **(b)** frequencies of *APOE* ε2/ε3/ε4 alleles in case and controls as well association of *APOE* ε4 alleles with the risk of developing AD in different countries. OR, Odds ratio were calculated using logistic regressions adjusted for age, gender and PCs according to the population studied (Supplementary Table 2). Sample sizes are reported in Supplementary Table 2. The map was generated using ggplot2 and royalty-free data from rnaturalearth (https://www.naturalearthdata.com/about/terms-of-use/).

https://doi.org/10.1038/s41588-025-02227-w

a

PGS^{ALZ}

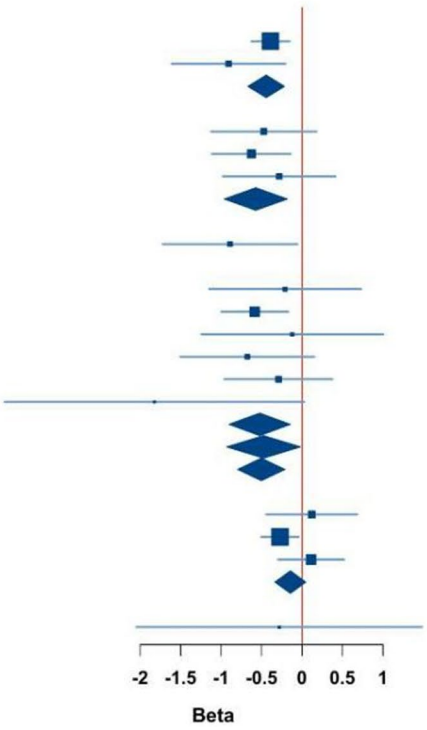
Country	Ncases	Beta	95% CI	P-value	I^2	HetP
European American MVP	4,561	-0.42	[-0.66;-0.18]	5.98e-04		
Australia	544	-0.89	[-1.60;-0.19]	1.32e-02		
Meta-analysis EUR Ancestry	**5,105**	**-0.47**	**[-0.70;-0.24]**	**4.98e-05**	**34.5**	**2.16e-01**
African American MVP	713	-0.44	[-1.10;0.22]	1.88e-01		
African American ADSP	1,108	-0.75	[-1.26;-0.25]	3.56e-03		
*African American ADSP (90%)**	502	-0.30	[-1.02;0.42]	4.17e-01		
Meta-analysis AA Ancestry	**1,821**	**-0.64**	**[-1.04;-0.24]**	**1.81e-03**	**0.0**	**4.64e-01**
Native American (90%)	534	-0.97	[-1.79;-0.14]	2.18e-02		
US LA Ancestry MVP	375	-0.24	[-1.19;0.71]	6.19e-01		
US LA Ancestry ADSP	1,629	-0.60	[-1.02;-0.17]	5.87e-03		
Colombia	254	-0.12	[-1.24;1.00]	8.28e-01		
Brazil	301	-0.63	[-1.47;0.21]	1.43e-01		
Argentina	417	-0.30	[-0.97;0.36]	3.74e-01		
Chile	122	-1.89	[-3.75;-0.03]	4.64e-02		
Meta-analysis US LA Ancestry	**2,004**	**-0.54**	**[-0.93;-0.15]**	**6.51e-03**	**0.0**	**5.00e-01**
Meta-analysis South America	**1,094**	**-0.47**	**[-0.92;-0.01]**	**4.53e-02**	**1.5**	**3.85e-01**
Meta-analysis LA Ancestry	**3,098**	**-0.51**	**[-0.80;-0.21]**	**7.52e-04**	**0.0**	**6.15e-01**
China	453	0.08	[-0.49;0.66]	7.70e-01		
Japan	2,220	-0.29	[-0.53;-0.05]	1.60e-02		
South Korea	1,119	0.11	[-0.31;0.53]	6.02e-01		
Meta-analysis East Asia	**3,792**	**-0.16**	**[-0.35;0.03]**	**1.03e-01**	**43.0**	**1.73e-01**
India	105	-0.33	[-2.05;1.39]	7.03e-01		



b

PGS^{ALZ} (Adjusted on APOE)

Country	Ncases	Beta	95% CI	P-value	I^2	HetP
European American MVP	4,561	-0.39	[-0.63;-0.15]	1.40e-03		
Australia	544	-0.91	[-1.61;-0.20]	1.16e-02		
Meta-analysis EUR Ancestry	**5,105**	**-0.44**	**[-0.67;-0.22]**	**1.22e-04**	**46.8**	**1.70e-01**
African American MVP	713	-0.47	[-1.13;0.18]	1.55e-01		
African American ADSP	1,108	-0.63	[-1.11;-0.14]	1.18e-02		
*African American ADSP (90%)**	502	-0.28	[-0.98;0.42]	4.29e-01		
Meta-analysis AA Ancestry	**1,821**	**-0.57**	**[-0.96;-0.18]**	**4.09e-03**	**0.0**	**7.12e-01**
Native American (90%)	534	-0.89	[-1.72;-0.06]	3.62e-02		
US LA Ancestry MVP	375	-0.21	[-1.15;0.73]	6.62e-01		
US LA Ancestry ADSP	1,629	-0.58	[-1.00;-0.17]	5.83e-03		
Colombia	254	-0.12	[-1.25;1.01]	8.34e-01		
Brazil	301	-0.68	[-1.50;0.15]	1.10e-01		
Argentina	417	-0.29	[-0.96;0.38]	3.93e-01		
Chile	122	-1.82	[-3.68;0.03]	5.35e-02		
Meta-analysis US LA Ancestry	**2,004**	**-0.52**	**[-0.90;-0.14]**	**6.90e-03**	**0.0**	**4.73e-01**
Meta-analysis South America	**1,094**	**-0.48**	**[-0.93;-0.02]**	**4.11e-02**	**0.0**	**3.94e-01**
Meta-analysis LA Ancestry	**3,098**	**-0.50**	**[-0.79;-0.21]**	**7.17e-04**	**0.0**	**6.19e-01**
China	453	0.12	[-0.44;0.68]	6.74e-01		
Japan	2,220	-0.27	[-0.51;-0.04]	2.17e-02		
South Korea	1,119	0.11	[-0.30;0.52]	5.90e-01		
Meta-analysis East Asia	**3,792**	**-0.14**	**[-0.33;0.05]**	**1.38e-01**	**43.6**	**1.70e-01**
India	105	-0.28	[-2.05;1.48]	7.52e-01		



Extended Data Fig. 4 | See next page for caption.

https://doi.org/10.1038/s41588-025-02227-w

Extended Data Fig. 4 | Association between (a) PGS^{ALZ} or (b) PGS^{ALZ} (adjusted for *APOE*) and age at onset of AD in multi-ancestry populations. N_{cases}, number of cases. The African-American-ancestry meta-analysis (more than 75% of the population with African-American ancestry) included the MVP and ADSP datasets. The East Asia meta-analysis included datasets from China, Korea, and Japan. The Latin American (LA) ancestry (self-reporting) meta-analysis included the MMVP and ADSP datasets. The South America meta-analysis included the datasets from Argentina, Brazil, Chile, and Colombia. * not used in the meta-analysis. βs were calculated using a general linear model adjusted for gender and PCs according to the population studied (Supplementary Table 2).

nature portfolio

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	All codes developed and shared with collaborators to run PGS and PRS are available at https://doi.org/10.5281/zenodo.15164089 Based on IRB and protected status of the Latin-American population in dbGaP access process for this data, the summary statistics of the Latin-American GWAS cannot be shared. The code to generate it as well as the mandated dbGaP link are respectively available here: https://github.com/NIH-CARD/MA_MA_meta and https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000496.v1.p1
Data analysis	SNPweights v.2.1., https://hsph.harvard.edu/research/price-lab/software/ FlashPCA2, https://github.com/gabraham/flashpca Picard LiftoverVcf tool (v2.27.5): https://broadinstitute.github.io/picard/ plink v1.9: https://www.cog-genomics.org/plink2/ PLINK (v.2.0.a): https://www.cog-genomics.org/plink/2.0/ rcompanion package: https://cran.r-project.org/web/packages/rcompanion/ METAL v2020-05-05: https://github.com/statgen/METAL

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- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
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The EADB GWAS (without UK biobank) summary statistics used to develop PRS have been deposited to the European Bioinformatics Institute GWAS Catalog (https://www.ebi.ac.uk/gwas/) under accession no. GCST90565439.
Summary statistics from African-American multi-ancestry population used to develop PRS were accessed through NIAGADS (https://www.niagads.org/) under accession number NG00100.
Summary statistics from Japan populations were accessed through the National Bioscience Database Center (NBDC) at the Japan Science and Technology Agency (JST) at https://humandbs.biosciencedbc.jp/en/ through accession number hum0237.v1.gwas.v1.
1000GP3: http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/1000_genomes_project/release/20190312_biallelic_SNV_and_INDEL/)
GRCh37 assembly:
https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/001/405/GCF_000001405.25_GRCh37.p13/GCF_000001405.25_GRCh37.p13_genomic.fna.gz
GRCh38 assembly:
https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/001/405/GCF_000001405.39_GRCh38.p13/GCF_000001405.39_GRCh38.p13_genomic.fna.gz
ADSP: https://dss.niagads.org/datasets/ng00067/

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	All analyses were systematically adjusted for sex
Reporting on race, ethnicity, or other socially relevant groupings	multi-ancestry populations were defined according to genetic structure at the exception of latino-American populations, defined on self-declaration.
Population characteristics	We used multiple independent sets of participants in this study. We adjusted the analysis for principal components. Sample sizes, age and gender characteristics for our sample can be found per cohort and overall in Supplementary Tables 1 and Supplementary Information.
Recruitment	Participants from case-control studies were primarily recruited from clinics, nursing homes, disease registries, and hospitals, with controls being drawn from various ongoing studies and screened to exclude dementia/cognitive decline.
Ethics oversight	Written informed consent was obtained from study participants or, for those with substantial cognitive impairment, from a caregiver, legal guardian, or other proxy, and the study protocols for all populations were reviewed and approved by the appropriate Institutional review boards (IRB's). More details can be found per cohort in Supplementary Information.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

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Sample size	Raw data and summary statistics were collected by the EADB consortia and summary statistics were recruited by external sources used for meta-analysis. Sample size was not pre-determined and was chosen based on all known available cohorts with relevant data collected to date, after quality control steps were performed in each cohort (described in detail in Supplementary Information).
Data exclusions	We exluded samples and variants based on standard quality control procedures for GWAS. Details of our quality control procedures are provided in the methods and supplementary information section of the manuscript.
Replication	PGS/PRS analyses were performed in several independent populations when possible
Randomization	The studies used in this work are observational case-control studies, hence there is no equivalent process of randomization.

Blinding	The analysts were blinded to the status of the individuals when running the different PGS/PRS codes

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Methods

n/a	Involved in the study
☒	☐ ChIP-seq
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Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*