Transferability of European-derived Alzheimer's Disease Polygenic Risk Scores across Multi-Ancestry Populations.

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A polygenic score (PGS) for Alzheimer's disease (AD) was recently derived 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 AD risk, age at onset, and cerebrospinal fluid levels of AD biomarkers, independently of apolipoprotein E *(APOE)*. This PGS was also associated with the AD risk in many other populations of diverse ancestries. A cross-ancestry polygenic risk score (PRS) improved the association with AD risk in most of the multi-ancestry populations tested when the *APOE* region was included. Lastly, we found that the PGS/PRS, 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, but studies of more diverse populations are still needed for a better characterization of the AD genetics.

Over the last 15 years, genome-wide association studies (GWASs) have fostered the development of powerful approaches for characterizing disease processes and proposed diagnostic/prognostic tools such as polygenic scores (PGS)[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 and their associations with AD risk or related phenotypes have been almost systematically reported[4,5,6,7,8,9,10]. However, comparisons across studies are complicated by marked differences in the populations analyzed, 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 PGS performance in populations of different ancestries[12,13,14,15].

In this manuscript, we first generated a PGS ($PGS^{ALZ)}$ including 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. We next extended PGS^{ALZ} study to populations of diverse ancestries from Asia, Africa, Latin and North America. Finally, as already developed in other complex human diseases[17,18,19,20], we generated a cross-ancestry polygenic risk score (PRS) by integrating GWAS summary statistics from multiple populations to potentially improve PGS^{ALZ} predictive performance[21,22].

We first evaluated the association between PGS^{ALZ} and the risk of developing AD in case-control studies of European countries (see Supplementary Table 2 for population description and adjustments used per population; Supplementary Fig. 1-3 for PGS^{ALZ} distributions). PGS^{ALZ} was significantly associated with AD risk irrespective of *APOE* adjustment (Extended Fig. 1A and Supplementary Fig. 4). PGS^{ALZ} was similarly associated with AD risk in men and in women (Extended Fig. 1B and Supplementary Fig. 6) and with a younger age at onset (Extended 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 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 respectively associated with a more than 2-fold decrease in the AD risk and a more than 3-fold increase in the AD risk compared with the 40-60% stratum (Fig. 1A and Supplementary Table 3).

Since these results suggested an association for PGS^{ALZ} independently of *APOE*, we took advantage of our mega-analysis to determine how PGS^{ALZ} interacts with the *APOE* genotypes. We found a limited interaction between PGS^{ALZ} and the number *APOE* ε4 alleles on the risk of

developing AD ($p=3x10^{-4}$). We next stratified the mega-analysis into four *APOE* genotype groups (ε2ε2/ε2ε3, ε3ε3, ε2ε4/ε3ε4, and ε4ε4) and assessed the association between PGS^{ALZ} and the AD risk per quintile (0-20%, 20-40%, 60-80%, and 80-100%) for each subpopulation (reference: 40-60% stratum). PGS^{ALZ} was similarly associated with the AD risk in all the strata, even if 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 of CSF levels of Aβ42, tau and p-tau (n=13,051 individuals) as previously described[23]. PGS^{ALZ} was associated with a decrement in $A\beta_{42}$ levels and an increment in tau and p-tau levels whatever the adjustment on *APOE* (Fig. 2A,B and Supplementary Fig. 7). We also checked the available samples 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 a 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 (USA, 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-, Native- and Latino American ancestry populations from US studies (i.e. more than 75% African or Native American ancestry or self-reporting for Latino American populations; Extended Fig. 3A; supplementary Table 2 for population description). With the exception of the analyses for Korea and Japan (where respectively 72 and 74 SNPs were available), most PGSs were constructed from 78 to 85 SNPs (including APOE variants; Supplementary Table 1; Supplementary Fig. 8-10 for PGS^{ALZ} distributions). The strength of the *APOE* ε4-AD association differed by population, as previously described in the literature[24,25]. ORs ranged from 1.36 in sub-Saharan Africa to 5.46 in Maghreb (Extended Fig 3B).

As expected, the PGS^{ALZ} association with AD risk was strongest in European-ancestry populations in the USA or Australia. PGS^{ALZ} was also significantly associated with the AD risk in Maghreb, East Asia, Latino American and African American populations (Fig. 3A and Supplementary Fig. 11). Lastly, 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 Fig. 4). It is noteworthy that the APOE ε2/ε3/ε4 alleles influenced age at onset in the two latter populations (Supplementary Fig. 12).

To refine our analysis of these populations of diverse ancestries, we calculated the association between AD and PGS^{ALZ} quintile (0-20%, 20-40%, 60-80%, and 80-100%; reference: 40-60% stratum) and meta-analyzed them per ancestry (Fig. 3B and C, Supplementary Table 6 and Supplementary Table 7). The Indian, Maghreb 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 Latino American populations to the African American population, in that order (Fig. 3B and supplementary Table 6). PGS^{ALZ} generated from European-ancestry population GWAS performed poorly in African-ancestry populations.

This 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 the AD risk in populations in whom more than 90% of the members were of African ancestry had an OR of 1.09 (95%CI 0.98-1.21, $P=1.4x10^{-1}$, adjusted on *APOE*). It is noteworthy that a similar pattern was observed in the Alzheimer Disease Sequencing Project (ADSP) Native American population: the strength of the association decreased as the Native American-

ancestry percentage increased from OR=1.21 (95%CI 1.12-1.32), P=5.3x10^{-6} and OR=1.14 (95%CI 1.05-1.25), P=2.6x10^{-3} to OR=1.12 (95%CI 1.02-1.24, P=1.4x10^{-2} in the populations with more than 50%, 75% and 90% of individuals of Native American-ancestry, respectively; adjusted for *APOE*. A similar finding was seen in Chilean and Argentinian populations: the PGS^{ALZ} association weakened as the proportion of Native American ancestry rose[14].

We next checked whether we had fully captured the genetic information within the GWAS-defined loci in the non-European admixed populations. To this end, we developed a PGS (PGS^{ALZ+}) that included other SNPs associated with AD risk in non-European ancestry populations (p<10^{-3}) at the European-GWAS-defined loci (for details, see Online Methods). We used the summary statistics generated by Kunkle et al.[26], Lake et al.[27] and Shigemizu et al.[28], and added 30, 13 and 47 variants to the initial 83 PGS^{ALZ} variants for Latino American, East Asian and African American ancestries, respectively (Supplementary Table 8). We did not detect any increment in the strength of the PGS^{ALZ+} association with the AD risk or in PGS^{ALZ+} predictive performance, relative to PGS^{ALZ} (Supplementary Table 9).

By initially restricting our analyses to the genome-wide significant loci from European ancestry AD GWAS, we likely excluded genetic information associated with the risk of developing AD in these European populations and (especially) non-European multi-ancestry 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 population differences. To deal with these various questions, we used the Bayesian polygenic modeling method PRS-CSx to build a cross-ancestry PRS (PRS)[20] which re-estimates variant effect sizes, by coupling diverse summary statistics with external ancestry-matched allele frequencies and local Linkage Disequilibrium structure, according to a sparseness parameter 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), Latino American (1,088 AD cases and 1,152 controls) and East Asian (3,962 AD cases and 4,074 controls) populations[26,27,28]. Polygenic Risk Scores (PRS), all adjusted for population structure, were generated in multi-ancestry populations from the Million Veteran Program (MVP; European, Latino American and African American ancestries), EPIDEMCA (Sub-Saharan Africa ancestry) and GARD studies (East Asian ancestry; Supplementary Fig. 13).
We assessed potential increment of PRS association with AD risk and predictive performance when the summary statistics of the European, African American, Latino American or East Asian populations were used independently (respectively, PRS^{EUR}, PRS^{AA}, PRS^{LA}, PRS^{EA}), or when they were combined (PRS^{COMB}) at multiple sparseness parameter (10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-2} and 1). We initially excluded the APOE *region* to enable a comparison with PGS^{ALZ}. We did not observe any increases in the association with AD risk or predictive performance in the different multi-ancestry populations (Fig. 4, supplementary Figure 14, supplementary Table 10) with the exception of the Latin American MVP population. However, we cannot exclude the possibility that this improvement is due to overfitting. Next, we included the *APOE* region when generating the different PRSs. While no impact was observed in European-ancestry populations when comparing PRS^{EUR} and PRS^{COMB}), we detected a potential increment in both the strength of association with the AD risk and predictive performance when comparing PRS^{EUR} and PRS^{COMB} for all other populations, indicating 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 global shrinkage parameter used; Fig. 5, supplementary Figure 14, supplementary Table 10).

Lastly, we leveraged the MVP data to determine how the association between PGS^{ALZ} or PRS^{COMB} (APOE region excluded) and the risk of AD changed in multi-ancestry populations as a function of diagnostic specificity. That is, we looked at how a PGS^{ALZ}/ PRS^{COMB} derived from AD case/control performed when the applied to cohorts when the diagnosis was broadened to dementia. In all the multi-ancestry population studied, the association between PGS^{ALZ}/

PRS^{COMB} and the AD risk weakened as the diagnosis became less specific (Fig. 6 and Supplementary Table 11).

Several major points can thus be highlighted from our work: (i) In European populations, the associations of PGS^{ALZ} with AD risk are potentially slightly impacted by the *APOE* genotype (suggesting two independent genetic entities for sporadic AD; *APOE* ε4-associated sporadic AD, and *APOE* ε4-unassociated sporadic AD as previously proposed[29]); (ii) this simple PGS^{ALZ} based on the largest GWAS from European populations and the resulting European GWAS-defined loci appears to be enough to detect AD genetic risk in most of the different ancestry populations. Our results thus suggest that most of the different ancestry populations are likely to be affected by shared pathophysiological processes driven in part by genetic risk factors; (iii) Conversely, it is observed in the genetics of complex traits[30] and other multifactorial diseases[17,31,32], a cross-ancestry PRS built with a Bayesian polygenic modelling method did not systematically outperform a simple PGS^{ALZ} (when the APOE locus is excluded). The small population size of GWAS for the different ancestry populations can significantly limit the power of the PRS-CSx approach, potentially explaining this observation. However, this may also indicate that a high proportion of AD genetic risk is already accounted for by the European ancestry GWAS-defined loci; (iv) When PRS includes the *APOE* region, this region appears to likely contain additional multi-ancestry genetic variability as already proposed[33,34,35,36]; (v) Finally, the PGS/PRS associations mainly captures genetic information related to AD as their association 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 devastating disease and to evaluate AD risk assessments in various populations. However, the field of AD genetics is still limited by the size of GWASs in these diverse ancestry populations. In addition, it is likely that the different ancestry populations will differ strongly regarding rare/very rare variants associated with the AD risk. this could clearly impact PRSs association with AD risk and their predictive performances[37]. Both GWAS and sequencing studies of more diverse populations are thus needed for a better characterization of AD genetics.

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Author contributions

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Competing Interests Statement

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METHODS Online

Sample and variant quality controls

To ensure that the βs were completely independent of the summary statistics, all samples from ADGC, CHARGE and FinnGen GWASs were filtered out. In addition, Sample overlap was systematically assessed and there was no sample overlap between any of the non-US studies analyzed. Overlap between ADSP and MVP is likely to be negligible (no more than a few cases). For biomarker analysis, there is overlap of 460 samples 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 for the PGS^{ALZ}). However, this overlap is limited (less than 2.5%) and in addition, we only analyzed in these samples the association of PGS^{ALZ} with quantitative traits (p-tau, tau and Aβ42 CSF concentrations), limiting the risk of inflated results. After it met the conventional GWAS gold standard of sample quality control, each sample was included in the analyses[16]. If a discordance in the variant dose or covariate or a discordance between imputed and genotyped (if available) APOE status was observed, the sample was discarded. After the quality control, a demographic description of each study is shown in Supplementary Table 1[38]**.** Genotyped variants had to meet the gold standard GWAS variant quality control[16]. All the studies including genotyping data were imputed with the TOPmed reference panel[39,38]. If the variants were imputed, those with a Rsq 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 individual in the ADSP samples was determined with SNPweights v.2.1[40] using a set of ancestry-weighted variants computed on reference populations from the 1000 Genomes Project as in[41]. 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[42], which is similar to other genotype-based ancestry calling methods, except that concordance is checked between self-report and genetically inferred ancestry, and those with discrepant ancestry groups are not assigned a HARE category. Within-group PCs for ancestry were computed using FlashPCA2[43].

European mega-analysis methods

For the mega-analysis of European countries, we merged samples from five datasets: EADB-core, GERAD, EADI, Demgene, and Bonn. To adjust for the population structure, we computed principal components using the following procedure. From the list of 146,705 variants used in the principal component analysis of EADB-core[43], we extracted TOPMed imputed variants having 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 was higher than 0.8. Lastly, we merged all the datasets and removed variants for which the proportion of missing genotypes was above 0.02. Ultimately, 90,471 variants were fed into the principal component analysis (performed with FlashPCA2). The analyses were adjusted for the first 14 principal components, the genotyping chip, and the center.

PGS and PRS Computations

The equation used to calculate the PGSs and the coPRSs is as follow:

$$PGS^{ALZ}_{sample} \text{ or } coPRS_{sample} = \sum_{i=1}^{n} (\beta_i * genotype_{i,\,sample})$$

where the PGS^{ALZ}/PRS 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.

The PGS^{ALZ} includes the 83 independent signals associated with AD[13], 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). The PGS^{APOE} includes only these two last SNPs. The stage I meta-analysis of EADB studies[13] without the UK Biobank samples, contained 39,106 clinically diagnosed AD cases versus 25,392 in the

stage II meta-analysis (including the ADGC, CHARGE and FinnGen data)[13]. To respect the independence between the samples and the GWAS summary statistics, in the PGS analyses, the European summary statistics used are from stage II or (for APOE variants only). In the PGS^{ALZ}/PRS analyses adjusted for difference in distribution between populations, the European more powerful summary statistics, *i.e.* stage I meta-analysis of EADB were preferred.

The PGS^{ALZ+} score was developed to include additional SNPs within the GWAS-defined loci to capture more genetic information in non-European-ancestry populations. Firstly, each locus's "start and end positions" (as specified in the GRCh38 assembly) were defined manually by looking at the regional plots and extracting (i) recombination rate peak positions, (ii) starts/ends of chromosomes, (iii) specific variant positions, or (iv) start/end positions of regions containing no variants. Next, insertions and deletions were excluded. Variants that were non ambiguous (i.e. 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 of 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 Latino American, East Asian and African-American ancestries, respectively[27,28,26]. 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 (v2.27.5) and restricting the process to variants with a minor allele frequency above 0.01. In order to remove variants in LD with the sentinel variant of each locus, we computed the LD between each sentinel variant and all other variants within the locus by using the 1000GP3 data restricted to samples representing European ancestries (EUR super-population), Latino American ancestries (AMR super-population plus IBS population), Japanese ancestries (JPT population) and African-American ancestries (AFR super-population). Since one of the sentinel variant (chr9:104903697:C:G) was not present in the 1000GP3 data, we replaced it with a proxy variant (chr9:104903754:G:GC, R^2=1 in the EUR super-population). 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. Lastly, we performed a clumping procedure on the remaining variants in each of the three ancestries by using plink v1.9, a p-value threshold of $1x10^{-3}$, a R^2 of 0.05 (as estimated in the corresponding 1000GP3 data samples, as described above), and a distance of 1Mb. For the PGS^{ALZ+}, this led us to select 30, 13 and 47 variants (in addition to the initial 85 PGS variants) for the Latino American, East Asian and African-American ancestries, respectively.

PRS-CSx[20,44] was, by the time of analysis, one of the most performing cross-ancestry PRS model method[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[13,26,27,28], and external ancestry-matched allele frequencies and local Linkage Disequilibrium structure, according to a global shrinkage parameter. This global shrinkage parameter provides the sparseness of the genetic architecture of AD, by avoiding over-shrinkage of true signals and by shrinking noisy signals. This 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. Then, new ancestry-specific or joint-ancestry effect size estimates were obtained with PRS-CSx, leading to a maximal number of 1,292 532 variants in the joint-ancestry summary statistics, potentially included in the PRS computations. The coPRSs were computed per chromosome, with 1- joint-ancestry and 2- European ancestry and 3- ancestry-specific PRS-CSx-effect size estimates, using PLINK (v.2.0.a) software[47] and its --score option, then summed across all chromosomes.

Adjustment for difference in PGS^{ALZ}/PRS distribution across populations

To account for population structure, PRS_{raw} and PGS^{ALZ}_{raw} were adjusted for difference in distributions across populations[48]. The adjustment was performed with a selection of 84,035

765 variants, common to all studies, independent and well-imputed variants (R > 0.8). With this list
766 of variants, FlashPCA2 projected the samples into the 1000G Phase 3 PC-space and
767 calculated the projected PCs. For each study, the raw score was fit in a linear model, in
768 controls, according to the 5 first projected PCs. This model was used to compute a predicted
769 score in all the samples. The resulting adjusted score was the difference between the raw
770 score and the predicted score.
771
772 **Statistical analyses**
773 The different scores (PGS or coPRS) were standardized in a standard normal distribution,
774 using the mean and the standard deviation, calculated over all the samples. The associations
775 between AD status and the different scores were tested in logistic regression, named according
776 to the score and the covariates. The name "ALZinclAPOE" was attributed, if the score included
777 variants in the APOE region (from 43Mb to 47Mb). The other covariates included age, sex, in
778 addition to covariates specific to each study (Supplementary Table 2).
779 - Model PGS^{ALZ}: AD ~ PGS^{ALZ} + COV
780 - Model PGS^{ALZ}: AD ~ PGS^{ALZ} + COV + the count of APOE ε2 alleles + the count
781 of APOE ε4 alleles (when adjusted on *APOE*)
782 - Model PRS: AD ~ PRS + COV
783 - Model PRS: AD ~ PRS + COV + the count of APOE ε2 alleles + the count of
784 APOE ε4 alleles (when adjusted on *APOE*)
785 - Model $PRS^{ALZinclAPOE}$: AD ~ $PRS^{ALZinclAPOE}$ + COV

786 To estimate the proportion of phenotypic variance explained by the variance of the score, we
787 computed the Nagelkerke's *Pseudo*-R^2_{Full} using the function Nagelkerke implemented in the
788 package *rcompanion* in R[49,50]. A *Pseudo*-R^2_{Null} was computed including only the covariates.
789 The adjusted *Pseudo*-R^2 is the difference between *Pseudo*-R^2_{Full} and the tied *Pseudo*-R^2_{Null}.
790 This adjusted Pseudo-R^2 corresponds to the phenotypic variance explained by the genetic
791 score only. The adjusted *Pseudo*-R^2 was also transformed into a liability scale, for ascertained
792 case-control studies[51], using a prevalence value of 0.15.
793 We chose a prevalence of 15%, which we consider to be consistent for populations with an
794 average age over 75. However, this prevalence is different in multi-ethnic populations of the
795 same average age. Furthermore, the AD prevalence increases with age, so the genetic liability
796 is not homogeneous across all age groups. AD heritability cannot be expressed as a single
797 number because it depends on the ages of the cases and controls[52].
798
799 **Quantile or percentile analyses**
800 Depending on the value of the corresponding PGS^{ALZ}, the samples were classified into the
801 reference group or into one of the test groups. In the mega-analysis, the reference group
802 corresponded to the 40-60% percentile and was tested across different percentiles (0-2%, 2-
803 5%, 5-10%, 10-20%, 20-40%, 60-80%, 80-90%, 95-98%, and 98-100%). In the *APOE*-stratified
804 analysis and in the multi-ancestry analyses, the reference group was defined as the 40-60%
805 percentile and was tested across different quintiles (0-20%, 20-40%, 60-80%, 80-100%). The
806 multi ancestry analyses were performed for each population and then meta-analyzed per
807 genetic ancestry using the inverse variance method, as implemented in METAL[53]. It should be
808 noted that the Indian, North African and sub-Saharan African populations were excluded
809 because of their small sample size.
810 - Model PGS^{ALZ}: AD ~ $Group_{0/1}(PGS^{ALZ})$ + COV
811 - Model PGS^{ALZ}: AD ~ $Group_{0/1}(PGS^{ALZ})$ + COV + number of APOE ε2 alleles +
812 number of APOE ε4 alleles (when adjusted on *APOE*)
813 - Model $PGS^{ALZinclAPOE}$: AD ~ $Group_{0/1}(PGS^{ALZinclAPOE})$ + COV

814
815 **Data Availability**

1000GP3:
http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/1000_genomes_project/release/20190312_biallelic_SNV_and_INDEL/)
ADSP: https://dss.niagads.org/datasets/ng00067/

Code availability

The sets of scripts are available upon request.

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Figure 1: Associations between the various PGSs and the risk of developing AD, as a function of *APOE* status. **(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 the *APOE* genotype (by grouping together the ε2ε2/ε2ε3, ε3ε3, ε2ε4/ε3ε4, ε4ε4 carriers). The 40-60% PGS^{ALZ} stratum was used as the reference.

Figure 2: Association of PGS^{ALZ} with the level of $A\beta_{42}$ and p-tau in the cerebrospinal fluid **(A)** across European-ancestry populations and **(B)** according to PGS^{ALZ} strata (0-20%, 20-40%, 60-80% and 80-100%). The 40-60% PGS^{ALZ} stratum was used as the reference. Ncases, number of cases; Ncontrols, number of controls, OR, Odds ratio per standard deviation. The lines in the Forest plots indicate the 95% confidence interval for the ORs. If HetP <0.05, random-effect is shown for the meta-analysis results.

Figure 3: Association of PGS^{ALZ} across multi-ancestry populations. **(A)** Association of PGS^{ALZ} with the risk of developing AD in multi-ancestry populations. European-ancestry meta-analysis includes MVP and Australia. African-American-ancestry (more than 75% AA ancestry) meta-analysis includes MVP and ADSP. East-Asia meta-analysis includes China, Korea and Japan. Latino-American ancestry (self-reporting) meta-analysis includes MVP and ADSP. South-America meta-analysis includes Argentina, Brazil, Chile and Colombia. **(B)** Risk of developing AD according to PGS^{ALZ} (adjusted or not for *APOE* or included *APOE* variants) strata (0-20%, 20-40%, 60-80% and 80-100%) in multi-ancestry populations. The 40-60% PGS^{ALZ} stratum was used as the reference in each population and results were meta-analyzed. European-ancestry meta-analysis includes MVP and Australia. African-American ancestry meta-analysis includes MVP and ADSP. East-Asia meta-analysis includes China, Korea and Japan. Latin-American ancestry meta-analysis includes MVP and ADSP. South-America meta-analysis includes Argentina, Brazil, Chile and Colombia.
Ncases, number of cases; Ncontrols, number of controls; OR, Odds ratio per standard deviation. The lines in the Forest plots indicate the 95% confidence interval for the ORs. If HetP <0.05, random effect is shown for the meta-analysis results. EUR, European; LA, Latino-American; AA, African American.

Figure 4: Comparison of the association of PGS^{ALZ} or PRS (excluding *APOE* region) with AD risk and the corresponding predictive values (adjusted Nagelkerke R^2 and Liability R^2). All PGS^{ALZ} and PRS were adjusted for difference in distribution between populations; OR, Odds ratio per standard deviation; PRS^{EUR} were generated by using only European ancestry summary statistics; PRS^{COMB} were generated by combining European, African American (AA), Latin-American (LA) and East Asian ancestry summary statistics. Sparseness parameter at 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} or 1.

Figure 5: Association of PRS (including *APOE* region) with AD risk and the corresponding predictive values (adjusted Nagelkerke R^2 and Liability R^2). All PGS^{ALZ} and PRS were adjusted for difference in distribution between populations; OR, Odds ratio per standard deviation; PRS^{EUR} were generated by using only European ancestry summary statistics; PRS^{COMB} were generated by combining European, African American (AA), Latin-American (LA) and East Asian ancestry summary statistics. Sparseness parameter at 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} or 1.

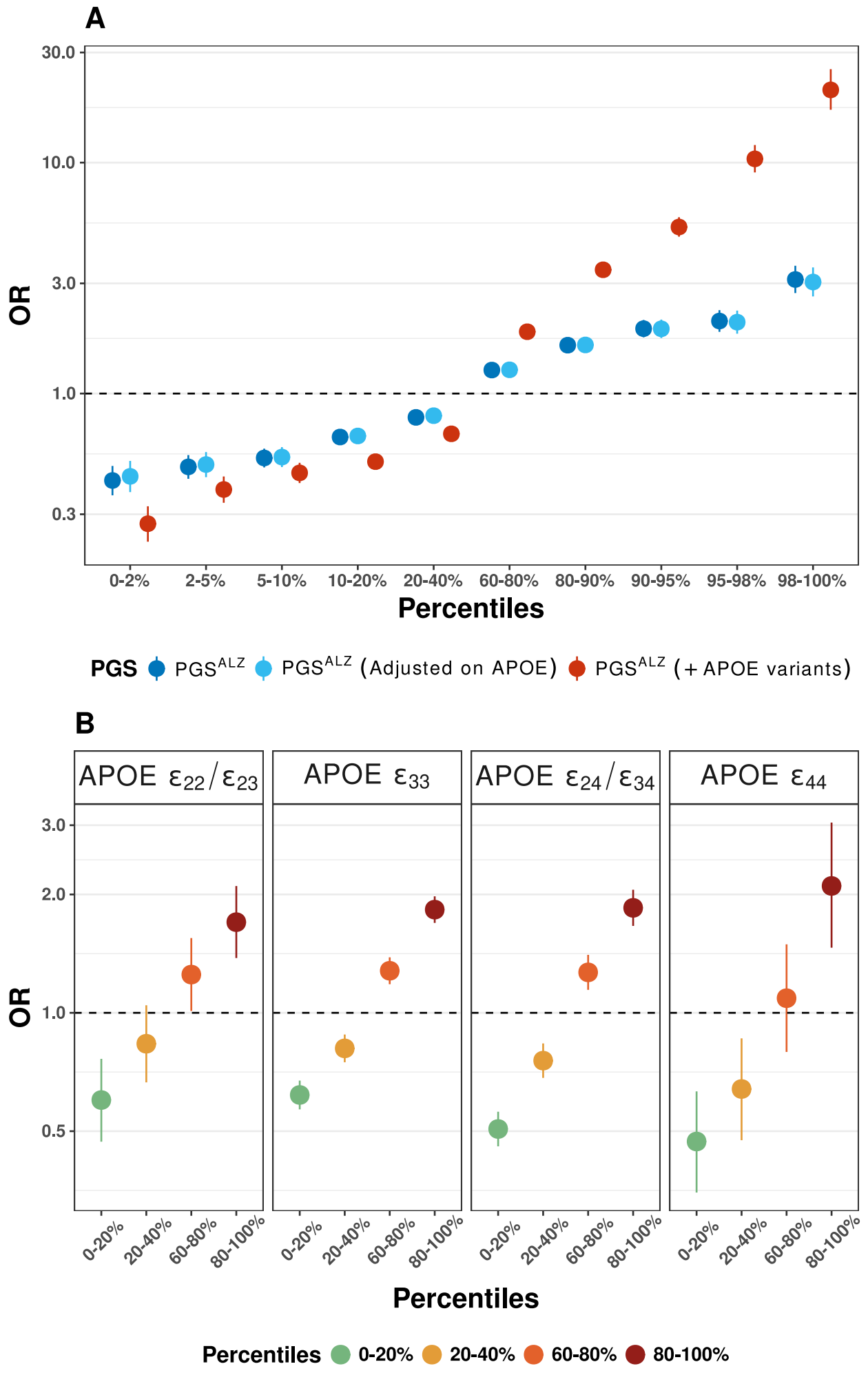
Figure 6: Association of PGS^{ALZ} or PRS^{COMB} (excluding the *APOE* region) with AD, AD and related dementia (ADRD) and dementia in MVP and the corresponding predictive values (adjusted Nagelkerke R^2 and Liability R^2). PGS^{ALZ} and PRS were adjusted for *APOE* and for difference in distribution between populations; OR, Odds ratio per standard deviation; PRS-CSx were generated by combining European (EUR), African American (AA) and Latin-American (LA) and East Asian ancestry summary statistics. Sparseness parameter at 10^{-8} and 10^{-6}.

Extended Figure 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. The lines in the Forest plots indicate the 95% confidence interval for the ORs.

Extended Figure 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.

Extended Figure 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.

Extended Figure 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.


A
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10.0
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OR
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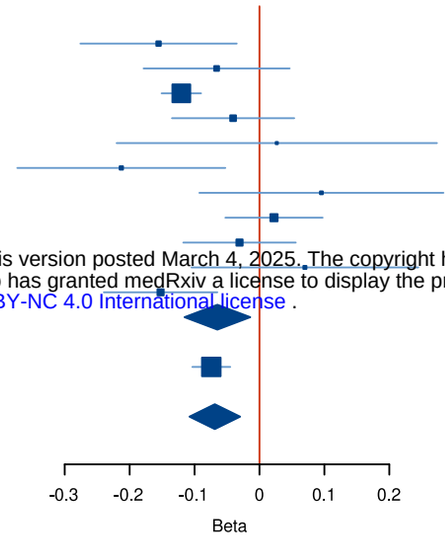
10-20%
20-40%
60-80%
80-90%
90-95%
95-98%
98-100%
Percentiles
PGS
PGS^ALZ
PGS^ALZ (Adjusted on APOE)
PGS^ALZ (+ APOE variants)
B
APOE ε22/ε23
APOE ε33
APOE ε24/ε34
APOE ε44
3.0
2.0
1.0
0.5
OR
0-20%
20-40%
60-80%
80-100%
Percentiles
Percentiles
0-20%
20-40%
60-80%
80-100%

A

$A\beta_{42} - PGS^{ALZ}$ (Adjusted on APOE)

Europe : I^2 = 65.1 , HetP = 1.43e-03 ; Global : I^2 = 62.6 , HetP = 1.94e-03

Country	N	Beta	95% CI	P-value
Finland	226	-0.155	[-0.28;-0.04]	1.22e-02
Sweden	264	-0.066	[-0.18;0.05]	2.52e-01
The Netherlands	3,106	-0.120	[-0.15;-0.09]	1.22e-14
Germany 1	314	-0.041	[-0.13;0.05]	3.99e-01
Germany 2	75	0.027	[-0.22;0.27]	8.33e-01
Germany 3	145	-0.213	[-0.37;-0.05]	1.04e-02
Germany 4	112	0.095	[-0.09;0.28]	3.23e-01
Belgium	598	0.022	[-0.05;0.10]	5.59e-01
France 1	439	-0.031	[-0.12;0.06]	4.87e-01
France 2	135	0.070	[-0.10;0.24]	4.34e-01
Spain	408	-0.152	[-0.24;-0.06]	7.04e-04
Meta-analysis Europe (random effect)	**5,822**	**-0.065**	**[-0.12;-0.01]**	**1.22e-02**
European American	7,229	-0.074	[-0.10;-0.04]	6.56e-07
Meta-analysis (random effect)	**13,051**	**-0.069**	**[-0.11;-0.03]**	**5.56e-04**
Adjusted for status				**3.50e-03**

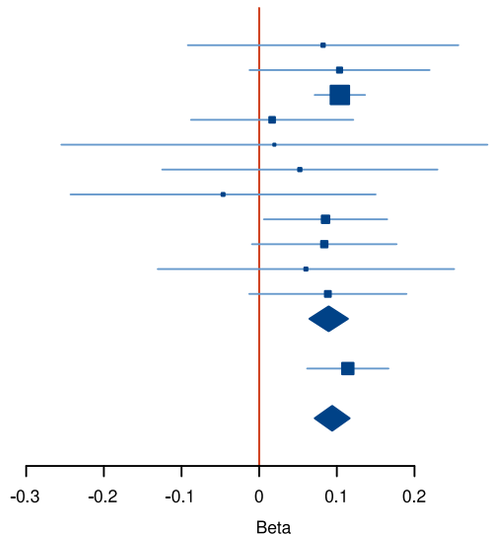


B

pTau – PGS^{ALZ} (Adjusted on APOE)

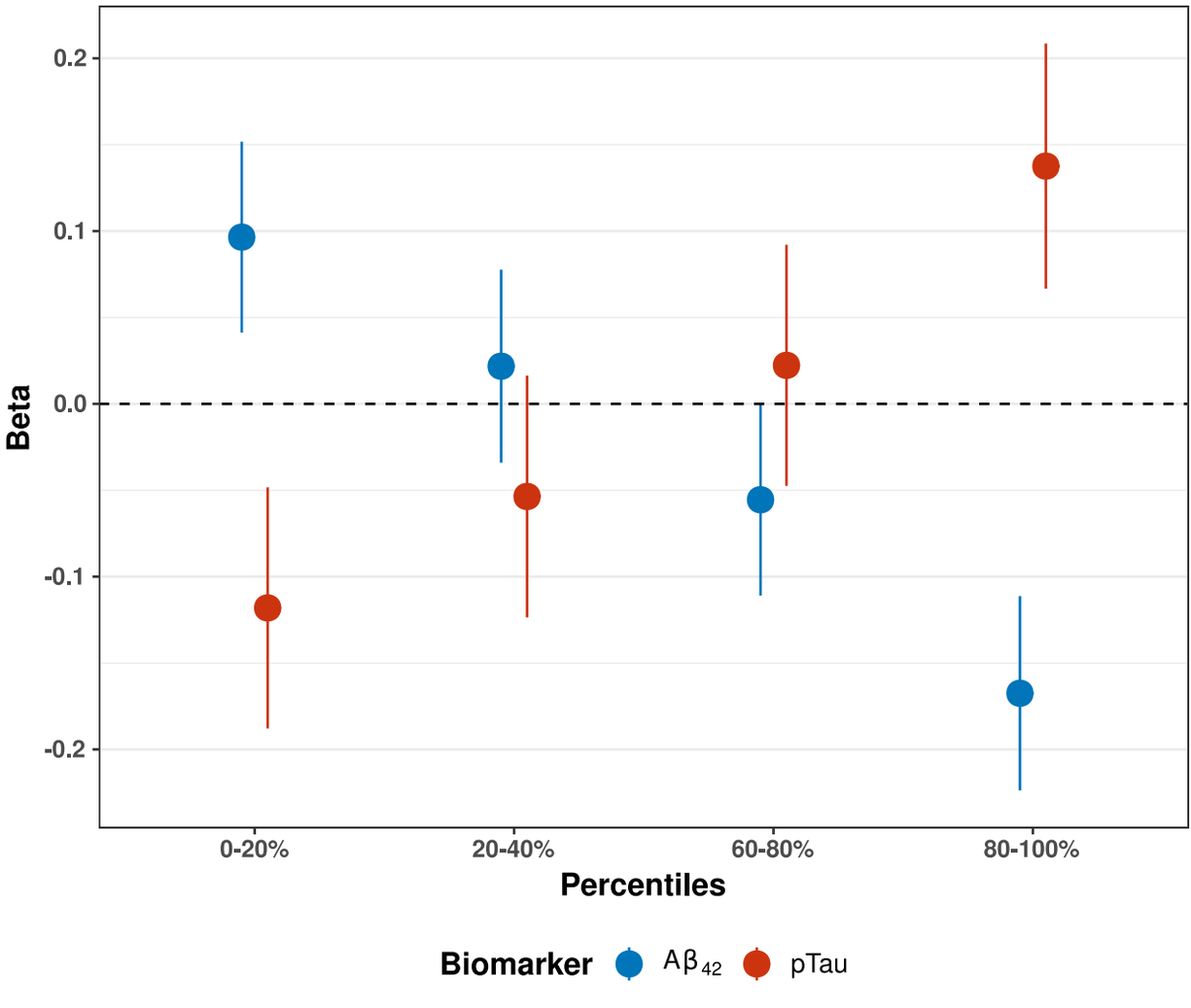
Europe : I^2 = 0 , HetP = 8.87e-01 ; Global : I^2 = 0 , HetP = 8.89e-01

Country	N	Beta	95% CI	P-value
Finland	226	0.082	[-0.09;0.26]	3.56e-01
Sweden	264	0.104	[-0.01;0.22]	8.14e-02
The Netherlands	3,106	0.104	[0.07;0.14]	4.22e-10
Germany 1	314	0.017	[-0.09;0.12]	7.55e-01
Germany 2	75	0.020	[-0.25;0.29]	8.89e-01
Germany 3	145	0.052	[-0.12;0.23]	5.64e-01
Germany 4	112	-0.046	[-0.24;0.15]	6.44e-01
Belgium	598	0.085	[0.01;0.16]	3.54e-02
France 1	439	0.084	[-0.01;0.18]	7.84e-02
France 2	135	0.060	[-0.13;0.25]	5.38e-01
Spain	408	0.088	[-0.01;0.19]	8.77e-02
Meta-analysis Europe	**5,822**	**0.089**	**[0.06;0.11]**	**1.82e-12**
European American	7,229	0.114	[0.06;0.17]	2.02e-05
Meta-analysis	**13,051**	**0.094**	**[0.07;0.12]**	**2.50e-16**
Adjusted for status				**7.05e-07**



C

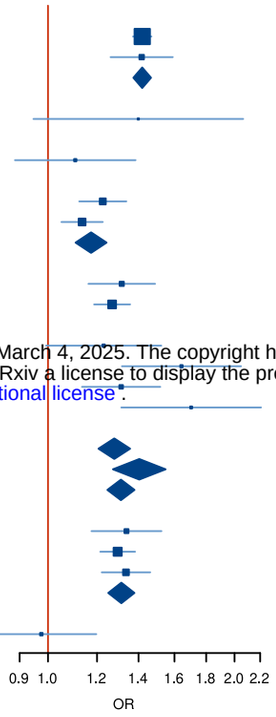
PGS^{ALZ} (Adjusted on APOE)



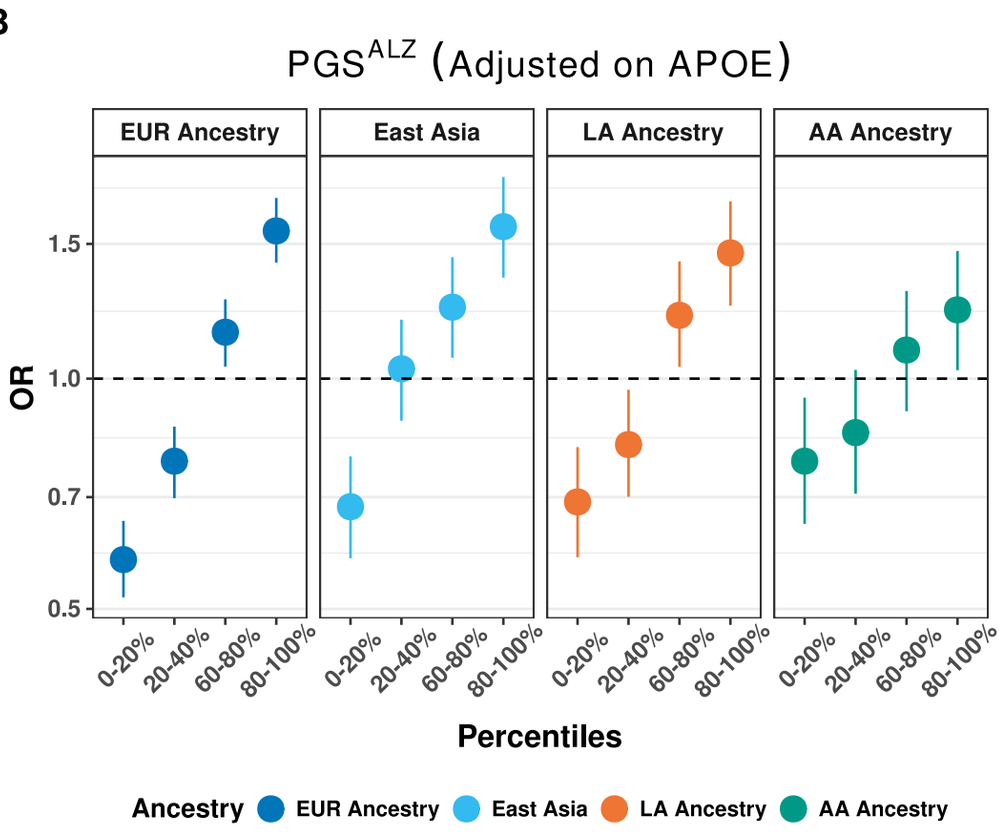
A

PGS^{ALZ} (Adjusted on APOE)

Country	Ncases	Ncontrols	OR	95% CI	P-value	HetIsq	HetPVal
European American MVP	4,561	84,587	1.42	[1.37-1.47]	1.73e-88		
Australia	544	1,190	1.42	[1.26-1.59]	3.71e-09		
Meta-analysis EUR Ancestry	**5,105**	**85,777**	**1.42**	**[1.37-1.47]**	**4.68e-96**	**0**	**9.72e-01**
Maghreb	58	187	1.40	[0.95-2.09]	9.15e-02		
Sub-Saharan Africa	85	1,091	1.11	[0.88-1.38]	3.76e-01		
African American MVP	713	19,405	1.23	[1.12-1.34]	5.38e-06		
African American ADSP	1,108	2,325	1.14	[1.05-1.23]	1.23e-03		
Meta-analysis AA Ancestry	**1,821**	**21,730**	**1.17**	**[1.11-1.24]**	**5.68e-08**	**40.1**	**1.97e-01**
US LA Ancestry MVP	375	7,166	1.32	[1.16-1.49]	1.47e-05		
US LA Ancestry ADSP	1,629	2,456	1.27	[1.19-1.36]	3.31e-12		
Colombia	254	241	1.23	[0.99-1.53]	5.84e-02		
Brazil	301	178	1.64	[1.32-2.06]	1.12e-05		
Argentina	417	601	1.31	[1.14-1.52]	2.54e-04		
Chile	122	252	1.70	[1.32-2.22]	5.96e-05		
Meta-analysis US LA Ancestry	**2,004**	**9,622**	**1.28**	**[1.21-1.36]**	**2.68e-16**	**0**	**6.19e-01**
Meta-analysis South America	**1,094**	**1,272**	**1.40**	**[1.27-1.55]**	**1.16e-11**	**52.6**	**9.66e-02**
Meta-analysis LA Ancestry	**3,098**	**10,894**	**1.31**	**[1.25-1.38]**	**7.50e-26**	**45.1**	**1.05e-01**
China	453	786	1.34	[1.18-1.53]	1.12e-05		
Japan	2,220	2,472	1.30	[1.21-1.38]	4.88e-15		
South Korea	1,119	1,172	1.34	[1.22-1.46]	3.01e-10		
Meta-analysis East Asia	**3,792**	**4,430**	**1.31**	**[1.25-1.38]**	**6.71e-28**	**0**	**8.21e-01**
India	105	1,500	0.98	[0.79-1.20]	8.13e-01		



B



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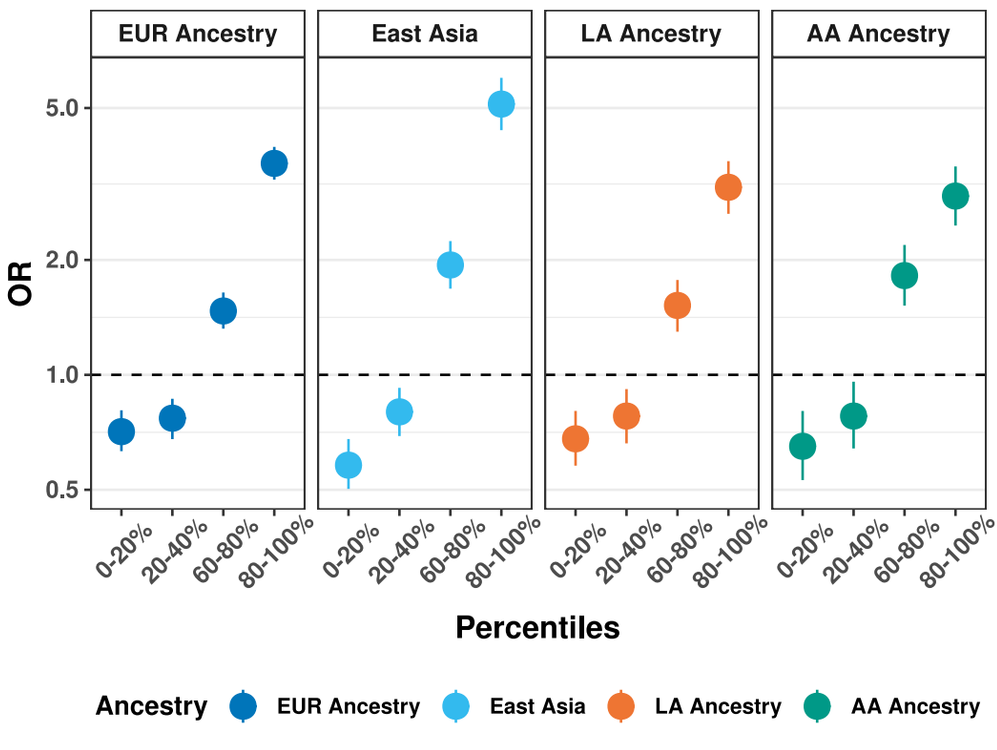
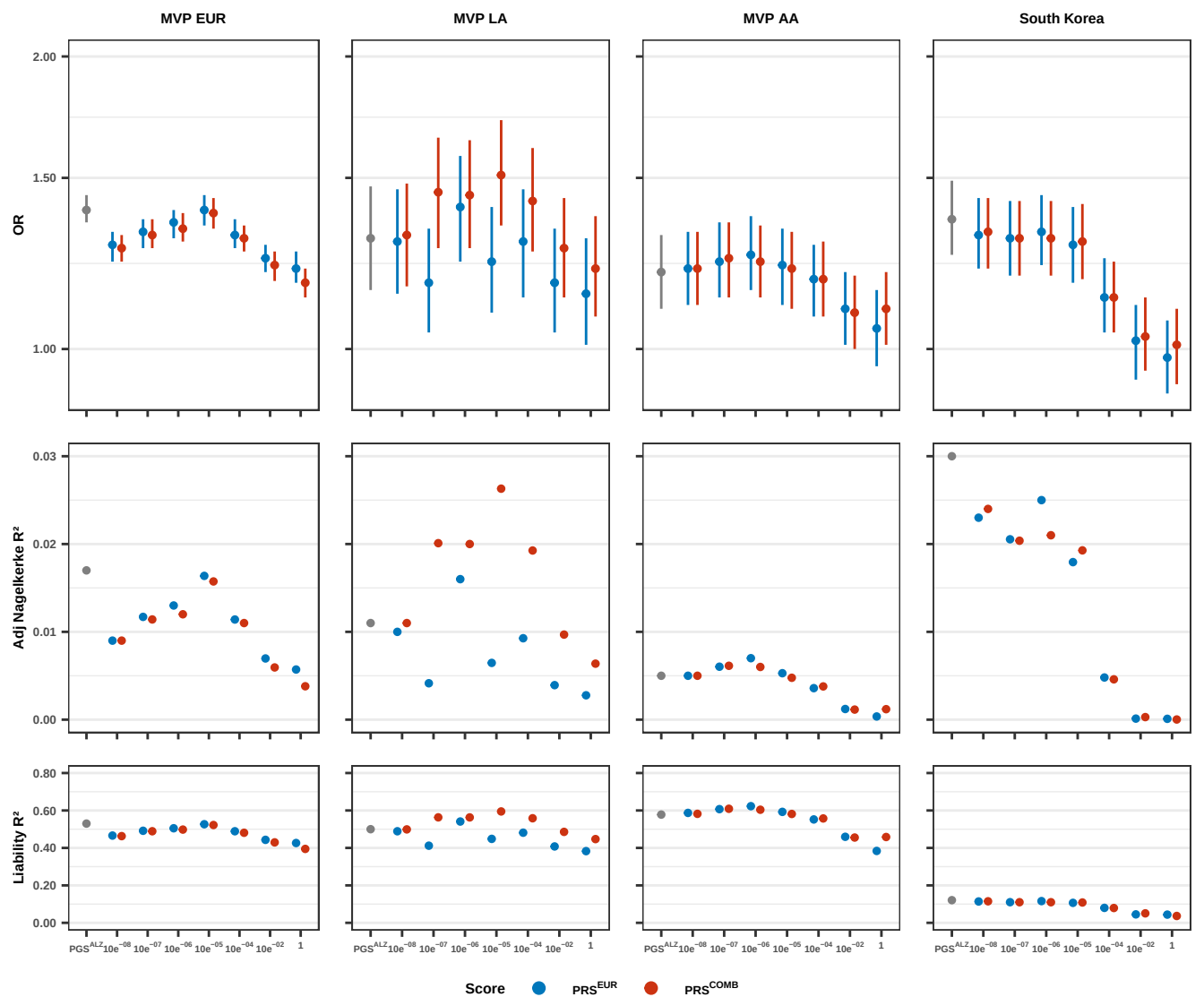
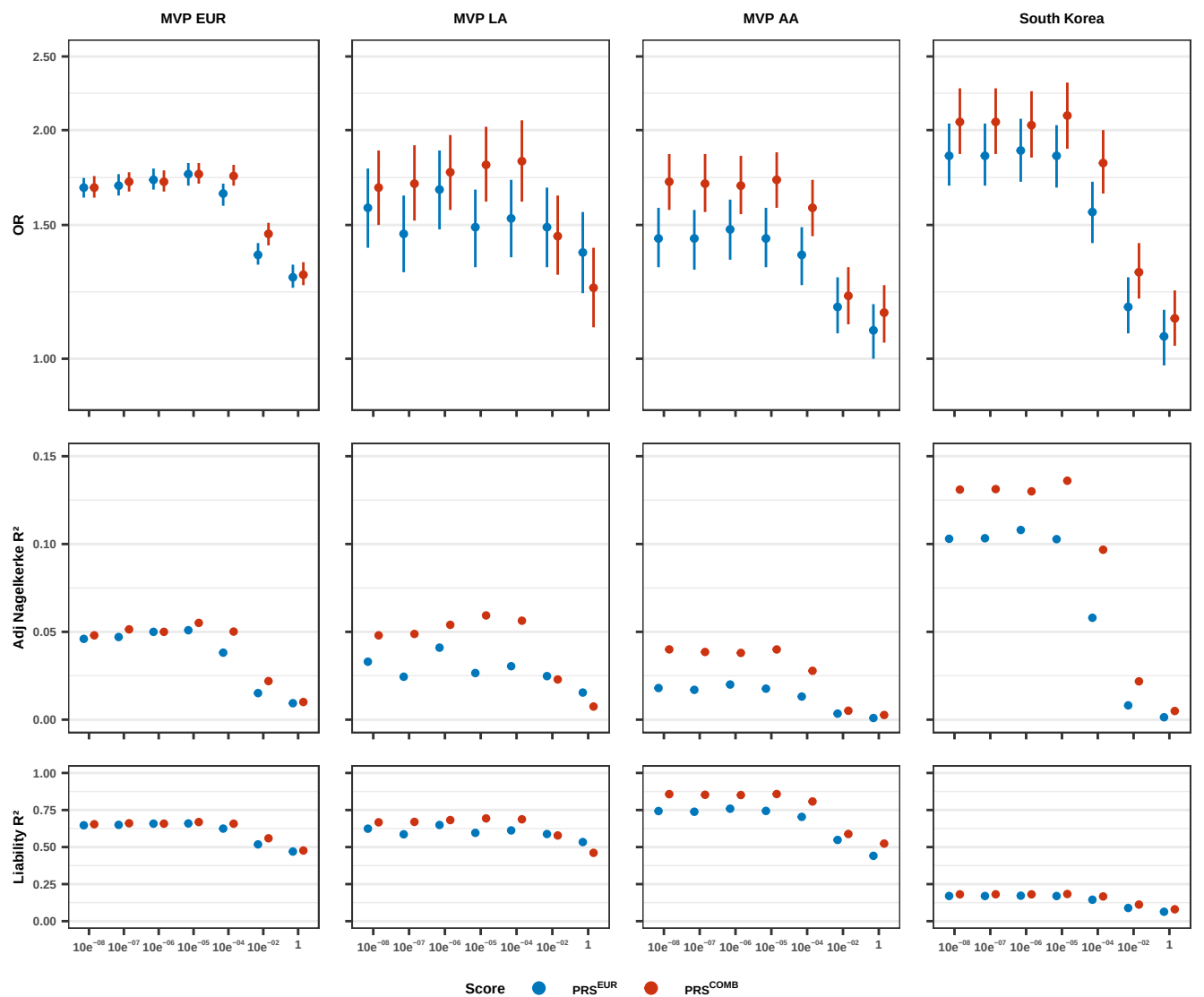
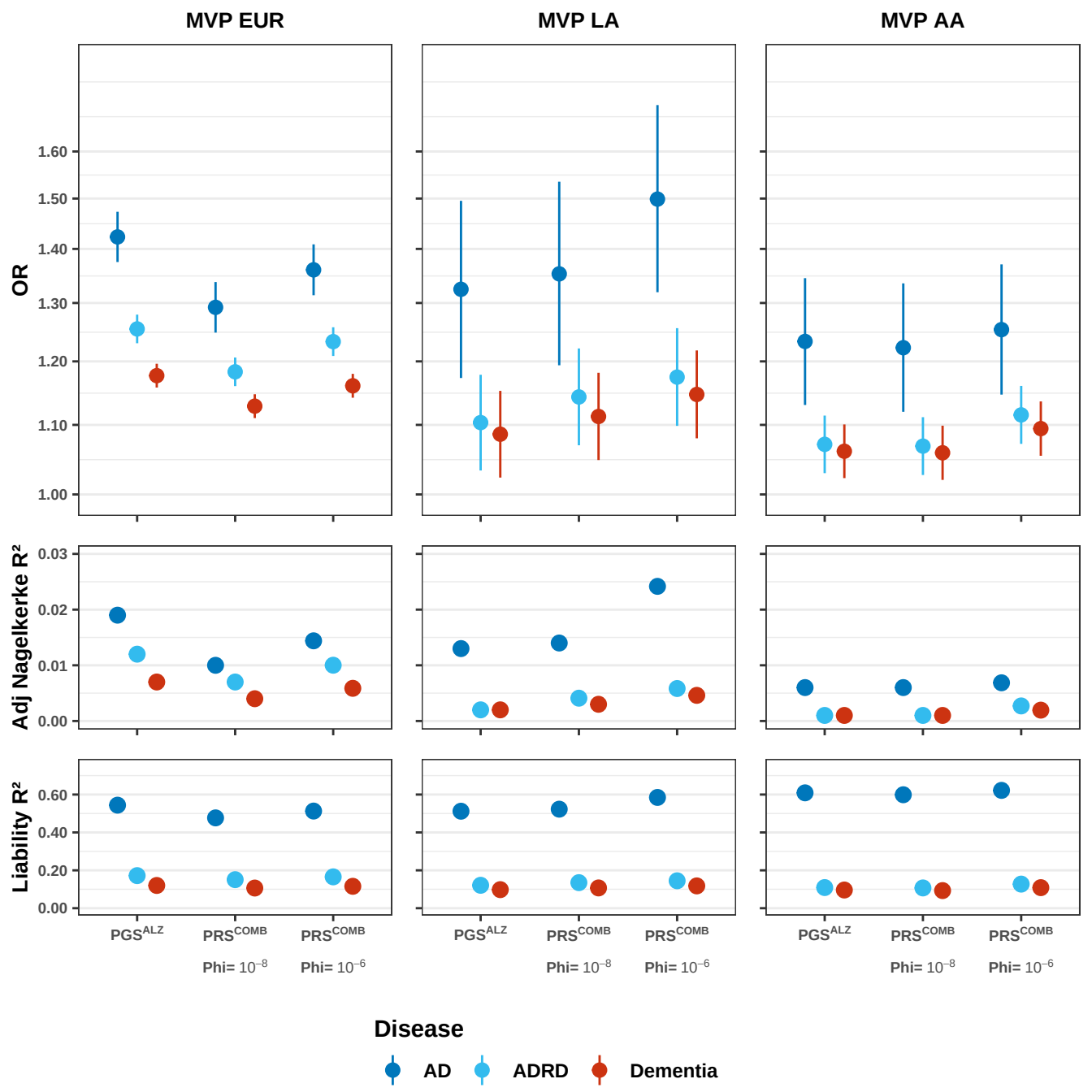



MVP EUR
MVP LA
MVP AA
South Korea
OR
2.00
1.50
1.00
Adj Nagelkerke R²
0.03
0.02
0.01
0.00
Liability R²
0.80
0.60
0.40
0.20
0.00
PGS^ALZ
10e^−08
10e^−07
10e^−06
10e^−05
10e^−04
10e^−02
1
Score
PRS^EUR
PRS^COMB


MVP EUR
MVP LA
MVP AA
South Korea
OR
2.50
2.00
1.50
1.00
Adj Nagelkerke R²
0.15
0.10
0.05
0.00
Liability R²
1.00
0.75
0.50
0.25
0.00
10e⁻⁰⁸ 10e⁻⁰⁷ 10e⁻⁰⁶ 10e⁻⁰⁵ 10e⁻⁰⁴ 10e⁻⁰² 1
Score
PRS^EUR
PRS^COMB

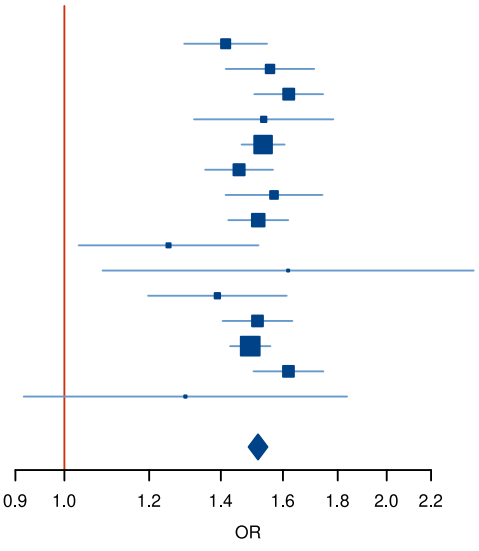

MVP EUR
MVP LA
MVP AA
OR
1.60
1.50
1.40
1.30
1.20
1.10
1.00
Adj Nagelkerke R²
0.03
0.02
0.01
0.00
Liability R²
0.60
0.40
0.20
0.00
PGS^ALZ
PRS^COMB
Phi= 10^−8
PRS^COMB
Phi= 10^−6
Disease
AD
ADRD
Dementia

A

PGS^{ALZ} (Adjusted on APOE)

I^2 = 17.8 , HetP = 2.54e-01

Country	Ncases	Ncontrols	OR	95% CI	P-value
Finland	1,118	1,770	1.41	[1.29-1.55]	2.32e-14
Norway	1,327	1,179	1.56	[1.42-1.71]	8.43e-20
Sweden	1,466	3,078	1.62	[1.51-1.75]	2.27e-37
Denmark	398	650	1.54	[1.32-1.79]	2.08e-08
United Kingdom	4,622	8,414	1.53	[1.46-1.61]	3.13e-73
The Netherlands	2,428	2,024	1.46	[1.35-1.57]	6.50e-24
Belgium	1,211	1,431	1.57	[1.42-1.74]	2.20e-17
Germany	2,190	3,141	1.52	[1.42-1.62]	9.18e-37
Austria/Switzerland	175	372	1.25	[1.03-1.52]	2.32e-02
Czech Republic	177	60	1.62	[1.10-2.45]	1.81e-02
Bulgaria/Greece	735	1,195	1.39	[1.20-1.61]	1.52e-05
Italy	2,973	1,251	1.51	[1.41-1.63]	2.15e-27
France	3,789	9,026	1.49	[1.43-1.56]	4.69e-73
Spain	3,103	1,615	1.62	[1.50-1.75]	2.91e-36
Portugal	80	74	1.30	[0.92-1.86]	1.42e-01
Meta-analysis	**25,792**	**35,280**	**1.52**	**[1.49-1.55]**	**4.93e-353**

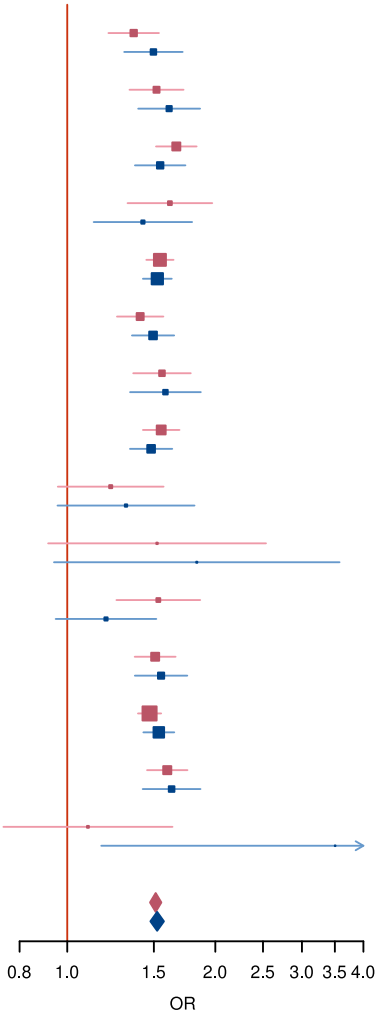


B

PGS^{ALZ} (Adjusted on APOE)

Females : I^2 = 20.1 , HetP = 2.29e-01 ; Males : I^2 = 0 , HetP = 7.58e-01

Country	Gender	Ncases	Ncontrols	OR	95% CI	P-value
Finland	Females	716	914	1.36	[1.21-1.54]	2.57e-07
	Males	402	856	1.50	[1.31-1.72]	7.73e-09
Norway	Females	840	622	1.52	[1.34-1.73]	9.49e-11
	Males	487	557	1.61	[1.40-1.87]	1.12e-10
Sweden	Females	926	1,898	1.67	[1.52-1.83]	6.79e-26
	Males	540	1,180	1.54	[1.37-1.74]	5.46e-13
Denmark	Females	227	354	1.62	[1.33-1.98]	2.02e-06
	Males	171	296	1.42	[1.13-1.80]	2.59e-03
United Kingdom	Females	2,633	4,323	1.54	[1.45-1.65]	1.62e-40
	Males	1,989	4,091	1.52	[1.43-1.63]	1.98e-34
The Netherlands	Females	1,354	885	1.41	[1.26-1.57]	7.29e-10
	Males	1,074	1,139	1.49	[1.35-1.65]	1.59e-15
Belgium	Females	783	890	1.56	[1.36-1.79]	1.11e-10
	Males	428	541	1.58	[1.34-1.87]	5.37e-08
Germany	Females	1,347	1,755	1.55	[1.43-1.69]	7.79e-24
	Males	843	1,386	1.48	[1.34-1.64]	7.78e-15
Austria/Switzerland	Females	112	204	1.23	[0.96-1.57]	1.07e-01
	Males	63	168	1.32	[0.96-1.82]	9.27e-02
Czech Republic	Females	107	40	1.52	[0.93-2.59]	1.06e-01
	Males	70	20	1.83	[0.97-3.76]	7.55e-02
Bulgaria/Greece	Females	445	676	1.53	[1.26-1.87]	2.04e-05
	Males	290	519	1.20	[0.95-1.52]	1.31e-01
Italy	Females	2,015	715	1.51	[1.37-1.66]	3.40e-17
	Males	958	536	1.55	[1.37-1.76]	2.31e-12
France	Females	2,383	5,540	1.47	[1.39-1.55]	5.28e-44
	Males	1,406	3,486	1.54	[1.43-1.65]	3.74e-31
Spain	Females	2,076	1,027	1.60	[1.45-1.76]	3.04e-22
	Males	1,027	588	1.63	[1.43-1.87]	1.45e-12
Portugal	Females	60	56	1.10	[0.75-1.66]	6.31e-01
	Males	20	18	3.50	[1.34-12.77]	2.48e-02
Meta-analysis	**Females**	**16,024**	**19,899**	**1.51**	**[1.47-1.55]**	**3.49e-203**
	Males	**9,768**	**15,381**	**1.52**	**[1.48-1.57]**	**3.71e-149**

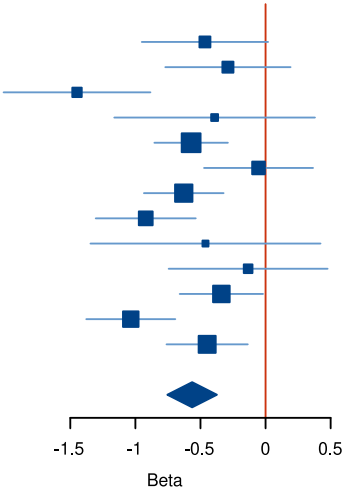


A

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 (random effect)	**25,535**	**-0.56**	**[-0.75;-0.37]**	**6.87e-09**

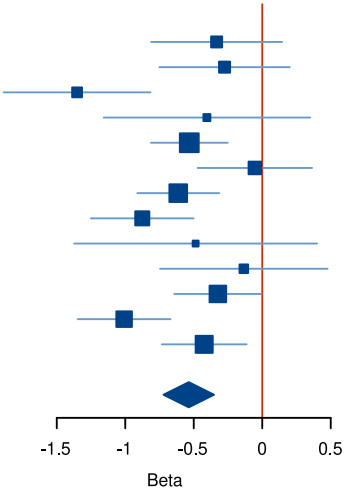


B

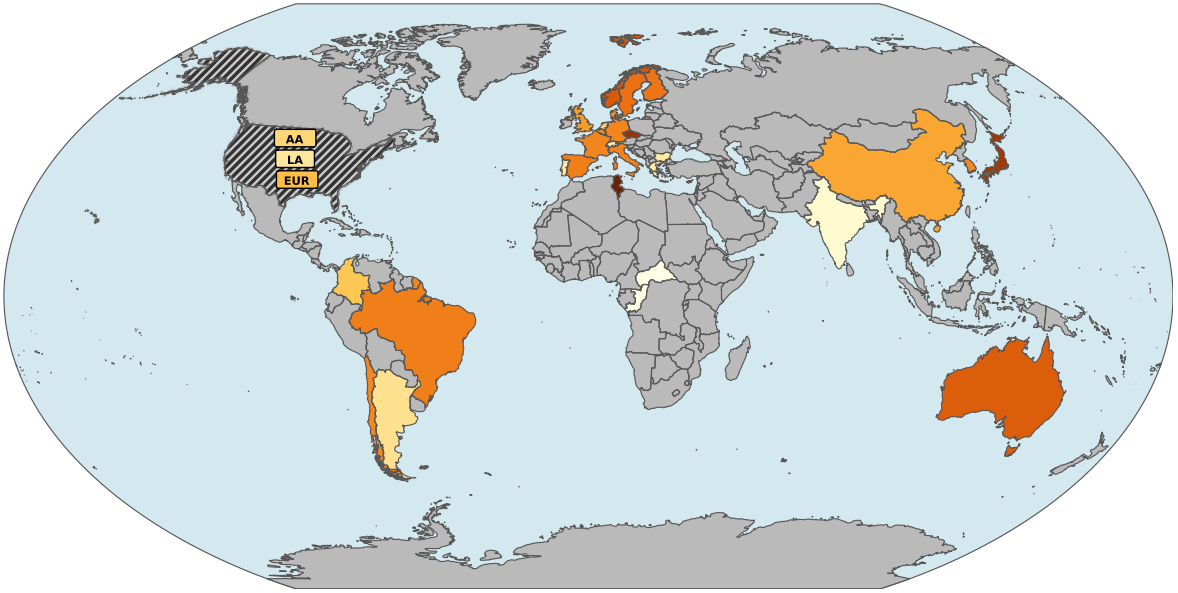
PGS^{ALZ} (Adjusted on APOE)

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 (random effect)	**25,535**	**-0.54**	**[-0.72;-0.35]**	**1.27e-08**



A



B

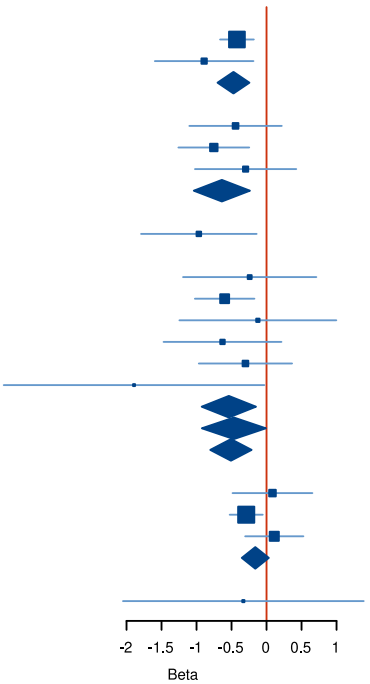
Country	Cases			Controls			OR ε_4
	ε_4	ε_3	ε_2	ε_4	ε_3	ε_2	
Finland	0.42	0.56	0.02	0.16	0.79	0.05	3.85 [3.33-4.46]
Norway	0.43	0.54	0.03	0.17	0.76	0.08	4.23 [3.62-4.95]
Sweden	0.41	0.57	0.03	0.16	0.77	0.08	3.90 [3.47-4.39]
Denmark	0.34	0.60	0.07	0.15	0.76	0.09	3.51 [2.71-4.53]
United Kingdom	0.33	0.63	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]

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