

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

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

Aude Nicolas et al.

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1. SAMPLE DESCRIPTION

Demographics of the different case-control studies are fully described in the supplementary Table 1

The European Alzheimer & Dementia Biobank dataset (EADB)

This consortium groups together 20,464 Alzheimer's disease (AD) cases and 22,244 controls after quality controls from 17 European countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, The Netherlands and the UK). These samples were genotyped using the ILLUMINA GSA array in three independent centers (France, Germany and the Netherlands) leading to define three nodes: EADB-France, EADB-Germany and EADB-Netherlands.

EADB-France

In the France node, samples were collected from nine countries (39 centers/studies), and after quality controls (QCs), we obtained 13,867 AD cases and 15,310 controls. All these samples were genotyped at the Centre National de Recherche en Génomique Humaine (CNRGH, Evry, France).

Belgium: The participants were part of a large prospective cohort¹ of Belgian AD patients and healthy elderly control individuals. The patients were ascertained at the memory clinic of Middelheim and Hoge Beuken (Hospital Network Antwerp, Belgium) and at the memory clinic of the University Hospitals of Leuven, Belgium. The control individuals were the partners of the patients or volunteers from the Belgian community. The study protocols were approved by the ethics committees of the Antwerp University Hospital and the participating neurological centers at the different hospitals of the BELNEU consortium and by the University of Antwerp.

Czech Republic: The Czech Brain Aging Study (CBAS)² is a longitudinal memory-clinic-based study recruiting subjects at risk of dementia (subjects referred for cognitive complaints-SCD, MCI). The CBAS+ study is a cross-sectional study of patients in the early stages of dementia. All subjects signed informed consent and both studies were approved by the local ethics committee.

Denmark: The Copenhagen General Population Study (CGPS) is a prospective study of the Danish general population initiated in 2003 and still recruiting. Individuals were selected randomly based on the national Danish Civil Registration System to reflect the adult Danish population aged 20-100. Data were obtained from a self-administered questionnaire reviewed together with an investigator at the day of attendance, a physical examination, and from blood samples including DNA extraction.

Finland: *The ADGEN cohort*³: a clinic-based collection of AD patients from Eastern and Northern Finland examined in the Department of Neurology in Kuopio University Hospital and the Department of Neurology in Oulu University Hospital. All the patients were diagnosed with probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRD). The study was approved by the ethics committee of Kuopio University Hospital, Finland (420/2016). *The FINGER study*⁴: a Finnish multi-domain lifestyle RCT enrolling 1,260 older adults with an increased risk of dementia from the general population. The intensive lifestyle intervention lasted for two years, and follow-up extends currently up to seven years. The FINGER study was approved by the coordinating ethics committee of the Hospital District of Helsinki and Uusimaa (94/13/03/00/2009 and HUS/1204/2017), and all the participants gave written informed consent.

France: *The BALTAZAR multicenter (23 memory centers) prospective study*⁵: 1,040 participants from September 2010 to April 2015. They were classified as AD cases (n = 501) according to DSM IV-TR and NINCDS-ADRD criteria as well as amnesic mild cognitive impairment (MCI) cases (a MCI, n = 417) and non-amnesic MCI cases (na MCI, n = 122)

according to Petersen's criteria. A comprehensive battery of cognitive tests was performed, including MMSE, verbal fluency, and FCSRT. All the participants or their legal guardians gave written informed consent. The study was approved by the Paris ethics committee (CPP Ile de France IV Saint Louis Hospital). *MEMENTO*: a clinic-based study⁶ aimed at better understanding the natural history of AD, dementia, and related diseases. Between 2011 and 2014, 2,323 individuals presenting either recently diagnosed MCI or isolated cognitive complaints were enrolled in 26 memory centers in France. This study was performed in accordance with the guidelines of the Declaration of Helsinki. The MEMENTO study protocol has been approved by the local ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre Mer III; approval number 2010-A01394-35). All the participants provided written informed consent. *The CNRMAJ-Rouen study*⁷: early onset AD patients (n = 870). The patients or their legal guardians provided written informed consent. This study was approved by the ethics committee of CPP Ile de France II.

Italy: The AD cases and controls were collated through Italy in different centers: Brescia, Cagliari, Florence, Milan, Rome, Perugia, San Giovanni Rotondo and Torino. AD cases were diagnosed according to DSM III-R, IV and NINCDS-ADRD criteria. Controls were defined as subjects without DSM-III-R dementia criteria and with integrity of their cognitive functions (MMSE > 25).

Spain: The Dementia Genetic Spanish Consortium (DEGESCO) is a national consortium comprising 23 research centers and hospitals across the country, that holds the institutional coverage of The Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED). Created in 2013, DEGESCO's objective is the promotion and conduction of genetic studies aimed at understanding the genetic architecture of neurodegenerative dementias in the Spanish population and participates in coordinated actions in national and international frameworks. All DNA samples are in compliance with the Law of Biomedical Research (Law 14/2007) and the Royal Decree on Biobanks (RD 1716/2011). Patients included in the present study met clinical criteria for probable or possible disease established by the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRD). Cognitively healthy controls were unrelated individuals who had a documented MMSE in the normal range. Contributing centers in the France node genotyping were Centro de Biología Molecular Severo Ochoa (CSIC-UAM (Madrid), the Institute Biodonostia, University of Basque Country (EHU-UPV, San Sebastián), Institut de Biomedicina de Valencia CSIC (València), and Sant Pau Biomedical Research Institute (Barcelona).

Sweden: *Uppsala*. The Swedish AD patients were ascertained at the Memory Disorder Unit at Uppsala University Hospital. For all patients, the diagnosis was established according to the National Institute on Neurological Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRD) guidelines⁸. Healthy control subjects were recruited from the same geographic region following advertisements in local newspapers and displayed no signs of dementia upon Mini Mental State Examination (MMSE). *Swedish National Study on Aging and Care in Kungsholmen (SNAC-K)* data was collected. The original SNAC-K population consisted of 4590 living and eligible persons who lived on the island of Kungsholmen in Central Stockholm, belonged to pre-specified age strata, and were randomly selected to take part in the study. Between 2001 and 2004, 3363 persons participated in the baseline assessment. They belonged to the age cohorts 60, 66, 72, 78, 81, 84, 87, 90, 93, and 96 years and 99 years and older. The examination consists of three parts: a nurse interview, a medical examination, and a neuropsychological testing session. Altogether, the examination takes about six hours. The participants are reexamined each time they reach the next age cohort. All parts of the SNAC-K project have been approved by the ethical committee at Karolinska Institutet or the regional ethical review board. Informed consent was collected from all the participants or, if the person was severely cognitively impaired, from their next of kin.

The UK: *MRC*. The sample set comprises individuals with AD and healthy controls recruited across the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK; Institute of Psychiatry, London, UK; University of Cambridge, Cambridge, UK. The collection of the samples was through multiple channels, including

specialist NHS services and clinics, research registers and Join Dementia Research (JDR) platform. The participants were assessed at home or in research clinics along with an informant, usually a spouse, family member or close friend, who provided information about and on behalf of the individual with dementia. Established measures were used to ascertain the disease severity: Bristol activities of daily living (BADL), Clinical Dementia Rating scale (CDR), Neuropsychiatric Inventory (NPI) and Global Deterioration Scale (GDS). Individuals with dementia completed the Addenbrooke's Cognitive Examination (ACE-r), Geriatric Depression Scale (GeDS) and National Adult Reading Test (NART) too. Control participants were recruited from GP surgeries and by means of self-referral (including existing studies and Joint Dementia Research platform). For all other recruitment, all AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the Mini Mental State Examination (MMSE) or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Control samples were chosen to match case samples for age, gender, ethnicity and country of origin. Informed consent was obtained for all study participants, and the relevant independent ethical committees approved study protocols. *SOTON, University of Southampton, Southampton, UK.* All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. *Nottingham and Manchester, University of Nottingham, Nottingham, UK and Manchester Brain Bank.* All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. *KCL, London Neurodegenerative Diseases Brain Bank.* All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. *PRION,* All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. *CFAS Wales,* The Cognitive Function and Ageing Study Wales (CFAS-Wales) is a longitudinal population-based study of people aged 65 years and over in rural and urban areas of Wales that aims to investigate physical and cognitive health in older age and examine the interactions between health, social networks, activity, and participation. Individuals aged 65 years and over were randomly sampled from general medical practice lists between 2011 and 2013, stratified by age to ensure equal numbers in two age groups, 65-74 years and 75 and over. The baseline sample included 3593 older people and included those living in care homes as well as those living at home. Those who provided written consent to join the study were interviewed in their own homes by trained interviewers and could choose to have the interview conducted through the medium of either English or Welsh. Participants were followed up 2 years later. All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or CAMCOG, and were determined to be free from dementia. *UCL-DRC.* the UCL Alzheimer's disease cohort of the Dementia Research Centre (UCL - EOAD DRC) included patients seen at the Cognitive Disorders Clinics at The National Hospital for Neurology and Neurosurgery (Queen Square), or affiliated hospitals. Individuals were assessed clinically and diagnosed as having probable Alzheimer's disease based on contemporary clinical criteria in use at the time, including imaging and neuropsychological testing where appropriate.

EADB-Germany

In the German node, samples were collected from seven countries (11 centers/studies) and after QCs, we obtained 4,159 AD cases and 4,545 controls. All these samples were genotyped at Life&brain (Bonn, Germany).

Germany: DELCODE (the multicenter DZNE-Longitudinal Cognitive Impairment and Dementia Study). This is an observational longitudinal memory clinic-based multicenter study in Germany comprising 400 subjects with Subjective cognitive decline (SCD), 200 mild cognitive impairment (MCI) patients, 100 AD dementia patients, 200 control subjects without subjective or objective cognitive decline, and 100 first-degree relatives of patients with a documented diagnosis of AD dementia. All patient groups (SCD, MCI, AD) are referrals, including self-referrals, to the participating memory centers. The control group and the relatives of AD dementia patients are recruited by standardized public advertisement. Ten university-based memory centers are participating, all being collaborators of local DZNE sites. All patient groups (SCD, MCI, AD) were assessed clinically at the respective memory centers before entering DELCODE. The assessments include medical history, psychiatric and neurological examination, neuropsychological testing, blood laboratory work-up, cerebrospinal fluid (CSF) biomarkers, and routine MRI, all according to the local standards. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery was applied at all memory centers to measure cognitive function. German age, sex, and education-adjusted norms of the CERAD neuropsychological battery are available online (www.memoryclinic.ch). Detail description of recruitment protocol is reported elsewhere. *The VOGEL study:* The VOGEL study is a prospective, observational, long-term follow-up study with three time points of investigation within 6–8 years. This cohort includes dementia and healthy subjects. Residents of the city of Würzburg born between 1936 and 1941 were recruited. Every participant underwent physical, psychiatric, and laboratory examinations and performed intense neuropsychological testing as well as VSEP and NIRS according to the published procedures. A total of 604 subjects were included. *The Heidelberg/Mannheim memory clinic sample:* This cohort includes 61 subjects from whom 40 MCI patients were recruited and assessed between 2012 and 2016. Some of those patients converted to dementia by AD or other dementias. *The PAGES study:* This study includes 301 subjects. AD patients were recruited at the memory clinic of the Department of Psychiatry, University of Munich, Germany. Participants in whom dementia associated with AD was diagnosed fulfilled the criteria for probable AD according to the NINCDS–ADRDA. The control group included participants who were randomly selected from the general population of Munich. Controls who had central nervous system diseases or psychotic disorders or who had first-degree relatives with psychotic disorders were excluded. *The Technische Universität München study:* This cohort includes 359 healthy, AD, and other dementias patients recruited from the Centre for Cognitive Disorders. All the participants provided written informed consent. A biobank was submitted to the ethics committee of the Technical University of Munich, School of Medicine (Munich, Germany), which raised no objections and approved the biobank (reference number 347-14). *The Göttingen Universität study:* This study includes 111 in- and outpatients with a healthy or AD dementia status from the Department of Psychiatry of the University of Göttingen. The study's ethical statement was provided locally at the Göttingen University Medical Centre. *The German Dementia Competence Network (DCN) cohort:* Individuals from the DCN cohort were recruited from 14 university hospital memory clinics across Germany between 2003 and 2005⁹. The study was approved by the respective ethics committees, and written informed consent was obtained from all the participants prior to inclusion. *The German Study on Aging, Cognition, and Dementia (AgeCoDe):* The AgeCoDe study is a general practice (GP) registry-based longitudinal study in elderly individuals that recruited patients aged 75 years and above in six German cities from 2003 to 2004¹⁰. The study was approved by the respective ethics committees, and written informed consent was obtained from all the participants prior to inclusion.

Greece/Bulgaria: *the HELIAD study*, comprising 49 AD cases and 1,150 controls. HELIAD is a population-based, multidisciplinary, collaborative study designed to estimate, in the Greek population over the age of 64 years, the prevalence and incidence of MCI, AD, other forms of dementia, and other neuropsychiatric conditions of aging and to investigate associations between nutrition and cognitive dysfunction or age-related neuropsychiatric diseases. The participants were selected through random sampling from the records of two

Greek municipalities, Larissa and Marousi. All the participants signed informed consent in Greek.

Portugal: *the Lisbon study* from Portugal, totaling 78 AD cases and 74 controls. This cohort was recruited in 2008–2009 to investigate the connections between oxidative stress and lipid dyshomeostasis in AD. The project includes 190 subjects and was approved by the local ethics committee, and all the participants provided written informed consent. This study includes healthy and dementia-by-AD subjects. The Ethics Committee of *Centro Académico de Medicina de Lisboa* (CAML) approved the study.

Spain: Those samples are part of DEGESCO. DEGESCO Centers from whom DNA samples were genotyped in the German node (1,778 cases and 470 controls) were the Alzheimer Research Center and Memory Clinic, Fundació ACE, Institut Català de Neurociències Aplicades (Barcelona), the Neurology Service at University Hospital Marqués de Valdecilla (Santander), the Alzheimer's disease and other cognitive disorders, Neurology Department, at Hospital Clínic, IDIBAPS (Barcelona), the Molecular Genetics Laboratory, at the Hospital Universitario Central de Asturias (Oviedo), and Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mútua de Terrassa (Barcelona).

Switzerland/Austria: Two datasets from Switzerland and Austria were combined, totaling 182 AD cases and 388 controls. *The Lausanne study:* This study includes 137 community-dwelling participants aged 55+ years with cognitive impairment (memory clinic patients with MCI, dementia) or normal cognition (recruited by advertisement, word of mouth). The study's ethical statement was provided locally at the Department of Psychiatry, Geneva University Centre, Switzerland. *The VITA study:* This is a longitudinal study of 606 individuals (Vienna, Austria) who were 75 years old in 2000, followed up every 30–90 months. This cohort includes dementia and healthy subjects. All the participants gave written informed consent. The study conformed to the latest version of the Declaration of Helsinki and was approved by the ethics committee of the City of Vienna, Austria

EADB-Netherlands

In the Dutch node, samples were collected from six organizations in the Netherlands and after QCs, we obtained 2,438 AD cases and 2,389 controls. All these samples were genotyped at the Erasmus Medical University (Rotterdam, The Netherlands). The Medical Ethics Committee (METC) of the local institutes approved the studies. All the participants and/or their legal guardians gave written informed consent for participation in the clinical and genetic studies. Samples from the following institutes were included. 1) *Erasmus Medical Center:* most individuals were selected from population studies from the epidemiology department and accounted for most of the controls, while a smaller subset of samples originated from the neurology department, where AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD¹¹. 2) *The Amsterdam Dementia Cohort (ADC)*¹²: This cohort comprises patients who visit the memory clinic of the VU University Medical Centre, the Netherlands. The diagnosis of probable AD is based on the clinical criteria formulated by the NINCDS–ADRDA and based on the NIA–AA. Diagnosis of MCI was made according to Petersen and NIA-AA. Controls presented with subjective cognitive decline at the memory clinic, but performed within normal limits on all clinical investigations. 3) *The 100-Plus study:* This study includes Dutch-speaking individuals who (i) can provide official evidence for being aged 100 years or older, (ii) self-report to be cognitively healthy, which is confirmed by a proxy, (iii) consent to the donation of a blood sample, (iv) consent to (at least) two home visits from a researcher, and (v) consent to undergo an interview and neuropsychological test battery¹³. 4) *Parelsnoer Institute:* a collaboration between 8 Dutch University Medical Centers in which clinical data and biomaterials from patients suffering from chronic diseases (so called "Pearls") are collected according to harmonized protocols. The Pearl Neurodegenerative Diseases¹⁴ includes individuals diagnosed with dementia, mild cognitive impairment, and controls with subjective memory complaints. 5) *The Netherlands Brain Bank:* a non-profit organization that collects human brain tissue of donors with a variety of neurological and

psychiatric disorders, but also of non-diseased donors. A clinical diagnosis of AD is based on the clinical criteria of probable AD^{8,15}. The selected AD patients for this study all received a definitive diagnosis which was based on autopsy. 6) *Maastricht University Medical Center*: a subset of individuals that were referred to the memory clinic for cognitive complaints were included if they participated in the BioBank-Alzheimer Centrum Limburg (BB-ACL)¹⁶. Diagnosis of MCI was made according to the criteria of Petersen, and diagnosis of AD-type dementia was made according to the criteria of the DSM-4¹⁷, and the NINCDS-ADRDA⁸. The Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting VUmc fonds. The clinical database structure was developed with funding from Stichting Dioraphte. Genotyping of the Dutch case-control samples was performed in the context of EADB (European Alzheimer DNA biobank) funded by the JPco-fuND FP-829-029 (ZonMW projectnumber 733051061).

GR@ACE

The GR@ACE study¹⁹ recruited Alzheimer's disease (AD) patients from Ace Alzheimer Center Barcelona (Barcelona, Spain), and control individuals from three centers: Ace Alzheimer Center Barcelona (Barcelona, Spain), Valme University Hospital (Seville, Spain), and the Spanish National DNA Bank–Carlos III (University of Salamanca, Spain) (<http://www.bancoadn.org>). Additional cases and controls were obtained from dementia cohorts included in the Dementia Genetics Spanish Consortium (DEGESCO)²⁰. At all sites, AD diagnosis was established by a multidisciplinary working group—including neurologists, neuropsychologists, and social workers—according to the DSM-IV criteria for dementia and the National Institute on Aging and Alzheimer's Association's (NIA-AA) 2011 guidelines for diagnosing AD. In our study, we considered as AD cases any individuals with dementia diagnosed with probable or possible AD at any point in their clinical course.

Genotyping was conducted using the Axiom 815K Spanish biobank array (Thermo Fisher) at the Spanish National Centre for Genotyping (CeGEN, Santiago de Compostela, Spain). The genotyping array not only is an adaptation of the Axiom biobank genotyping array but also contains rare population-specific variations observed in the Spanish population.

The Rotterdam Study

The Rotterdam Study is a prospective population-based middle-aged and elderly cohort that started in 1990 in the district of Ommoord, in Rotterdam, The Netherlands. The study includes 14,926 participants and has three subcohorts²¹. At start of the study, all inhabitants of the district of Ommoord who were aged 55 years and older were invited to participate. At baseline, in 1990-1993, of the 10,215 invited inhabitants, 7,983 agreed to participate in the baseline examination (response rate 78%). In 2000, the cohort was extended with 3,011 participants (67% of invitees). This extension consisted of all persons living in the study district who had become 55 years and older or had moved into the study district. A second extension was initiated in 2006, in which 3,932 participants (65% of invitees) who were 45 years and older were included. Study rounds consist of a home interview and visits with extensive investigations at the dedicated research centre. Rounds are repeated every 4-6 years. Participants are continuously monitored for diseases and mortality through linkage of the medical records from the general practitioners and municipality records. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of The Netherlands. All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

A total of 11,496 participants from the three subcohorts who were genotyped passed genotyping quality control (92% of all subjects with genotyping)²². Exclusion criteria were a call rate <98%, Hardy–Weinberg p-value <10⁻⁶, minor allele frequency <0.01%, excess autosomal heterozygosity >0.336, sex mismatch, and outlying identity-by-state clustering estimates. Imputations were performed using the Haplotype Reference Consortium (HRC) panel²³.

Dementia ascertainment involved cognitive screening at the study research centre. We further assessed individuals with a Mini-mental state examination (MMSE) score <26 or Geriatric Mental State Schedule organic level >0²⁴, by administering the Cambridge Mental Disorders

of the Elderly Examination by a research physician. We also interviewed spouses or informants. A consensus panel headed by a consultant neurologist established the final diagnosis according to standard criteria. We studied the outcomes of all-cause dementia (DSM-III-R), and Alzheimer's disease (NINCDS-ADRDA). For the assessment of dementia, and type of dementia, the latest follow-up information with available data was used to determine the disease state. Follow-up for dementia was near complete until 1st January 2016. Within this period, participants were censored at date of dementia diagnosis, death, or loss to follow-up. For this study, we included participants from the first, second and third subcohort (N=11,070).

European Alzheimer's Disease Initiative (EADI) Consortium

EADI is composed of several case-control studies and one population-based cohort, the 3C study^{25,26}. Case-control studies are comprised of AD cases and cognitively normal controls across France. The population-based cohort, the 3C study, is a prospective study of the relationship between vascular factors and dementia carried out in the three French cities Bordeaux, Montpellier and Dijon. The AD status was defined based on 12 years follow-up for Dijon participants, 14-15 years follow-up for Montpellier participants and 17-18 years follow-up for Bordeaux participants. All other non-demented subjects of 3C were included as controls. All AD cases, both in the case-control studies and the 3C study, were ascertained by neurologists and the clinical diagnosis of probable AD was established according to the DSM-III-R and NINCDS-ADRDA criteria. Samples that passed DNA quality control were genotyped with Illumina Human 610-Quad BeadChips.

Genetic and Environmental Risk in AD (GERAD) Consortium/Defining Genetic, Polygenic, and Environmental Risk for Alzheimer's Disease (PERADES) Consortium

The GERAD/PERADES sample comprises 3,177 Alzheimer's disease cases and 7,277 controls with available age and gender data²⁷. Cases and elderly screened controls were recruited by the Medical Research Council (MRC) Genetic Resource for Alzheimer's disease (Cardiff University; Institute of Psychiatry, London; Cambridge University; Trinity College Dublin), the Alzheimer's Research Trust (ART) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen's University Belfast; the Oxford Project to Investigate Memory and Ageing (OPTIMA), Oxford University); Washington University, St Louis, United States; MRC PRION Unit, University College London; London and the South East Region Alzheimer's disease project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany; the National Institute of Mental Health (NIMH) Alzheimer's disease Genetics Initiative. 6129 population controls were drawn from large existing cohorts with available GWAS data, including the 1958 British Birth Cohort (1958BC) (<http://www.b58cgene.sgul.ac.uk>), the KORA F4 Study and the Heinz Nixdorf Recall Study. All Alzheimer's disease cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) Alzheimer's disease. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Genotypes from all cases and 4617 controls were previously included in the AD GWAS by Harold and colleagues²⁷. Genotypes for the remaining 2660 population controls were obtained from WTCCC2.

The Norwegian DemGene Network

This is a Norwegian network of clinical sites collecting cases from memory clinics based on a standardized examination of cognitive, functional, and behavioral measures and data on the progression of most patients. The Norwegian DemGene Network includes 2,224 cases and 3,089 healthy controls from different studies described elsewhere²⁸. The cases were diagnosed according to recommendations from the NIA-AA, the NINCDS-ADRDA criteria, or the ICD-10 research criteria. The controls were screened with a standardized interview and cognitive tests. Additional controls from blood donors of the Oslo University Hospital, Ullevål Hospital, were included (n=4992, age between 18-65 years, 48% female). They were

thoroughly screened for diseases and medication, and provided blood for DNA analysis, in line with approval from the Regional Committee for Medical and Health Research Ethics. Individuals from the DemGene study and blood donors were genotyped using either the Human Omni Express-24 v1.1 chip (Illumina Inc., San Diego, CA) or the DeCodeGenetics_V1_20012591_A1 chip at deCODE Genetics (Reykjavik, Iceland).

The Neocodex–Murcia study (NxC)

This study includes 324 sporadic AD patients and 754 controls of unknown cognitive status from the Spanish general population collected by Neocodex^{29,30}. AD patients were diagnosed as having possible or probable AD in accordance with the NINCDS–ADRDA criteria.

Bonn studies

DietBB: The DietBB sample included in this GWAS is a subsample extracted from the AgeCoDe cohort in the context of an ongoing genome-wide methylation analysis for dementia. In addition to methylation, the DietBB samples has genome-wide genotype data which was included in this study. The German study on aging, cognition and dementia (AgeCoDe)^{10,31} study is a general practice (GP) registry-based longitudinal study in elderly individuals on the identification of predictors of dementia. Participants were recruited in six German cities (Bonn, Dusseldorf, Hamburg, Leipzig, Mannheim, and Munich) with a total of 138 GPs connected to the study sites. The inclusion criteria for this study were an age of 75 years and older, absence of dementia according to GP judgment, and at least one contact with the GP within the past 12 months. Exclusion criteria were GP consultations by home visits only, living in a nursing home, severe illness with an anticipated fatal outcome within 3 months, language barrier, deafness or blindness, and lack of ability to provide informed consent. Baseline recruitment was performed in 2002 and 2003. The study was approved by the local ethical committees of the Universities of Bonn, Hamburg, Dusseldorf, Heidelberg/Mannheim, and Leipzig, and the Technical University of Munich. A total of 3327 subjects provided informed consent for participation after being provided with a complete description of the study protocol. The study assessments were performed by trained interviewers at the subjects' home. Seventy individuals were excluded after baseline interview because of the presence of dementia according to standard assessment, and 40 subjects were excluded for age less than 75 years. In AgeCoDe, dementia was diagnosed according to the criteria set of DSM-IV in a consensus conference with the interviewer and an experienced geriatrician or geriatric psychiatrist. The etiological diagnosis of dementia in AD was established according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD⁸. Mixed dementia was diagnosed in cases of cerebrovascular events without temporal relationship to cognitive decline. Mixed dementia and dementia in AD were combined. Dementia diagnosis in subjects who were not interviewed personally was based on the Global Deterioration Scale³² (score ≥ 4 points). In these cases, an etiological diagnosis was established only if the information provided was sufficient to judge etiology according to the criteria just described. For DietBB, cohort participants were included if they were dementia-free at baseline and available biomaterial for DNA analysis is available. This criterion led to the selection of 320 participants. In 120 of these participants, dementia of the AD-type occurred at any follow up. The additional 200 remain free of dementia until last follow up of AgeCoDe.

Bonn OMNI cohort: the Bonn OMNI cohort consists of AD patients and controls derived from a larger German GWAS cohort which was recruited from the following three sources: (i) the German Dementia Competence Network; (ii) the German study on Aging, Cognition, and Dementia in primary care patients (AgeCoDe); and (iii) the interdisciplinary Memory Clinic at the University Hospital of Bonn. The control sample comprised of individuals from the population-based study Heinz Nixdorf Recall (HNR) study cohort. This sample was previously used for replication in Lambert et al.³³. *The German study on aging, cognition and dementia (AgeCoDe):* see description above. *The German competence network cohort (DCN):* The DCN cohort includes 1,095 patients with mild cognitive impairment (MCI) and 648 cases with mild Alzheimer's disease (AD) clinical dementia syndrome that were recruited from 14 university

hospital memory clinics across Germany between 2003 and 2005⁹. Exclusion criteria were substance abuse or dependence, insufficient German language skills, multi-morbidity, comorbid condition with excess mortality, circumstances that would have made regular attendance at follow-up visits questionable and lack of an informant. The diagnosis of mild dementia according to ICD-10 criteria required a decline of cognitive ability (at least 1 SD) from a previous level in at least 2 domains as evidenced by age-corrected standardized tests, impairment in activities of daily living (i.e. B-ADL > 6), changes in personality, drive, social behavior or control of emotion but no clouding of consciousness. These changes must have persisted for at least 3 months. The etiological diagnosis of AD was assigned according to NINCDS-ADRDA criteria⁸. *Memory clinic Bonn*: The interdisciplinary Memory Clinic of the Department of Psychiatry and Department of Neurology at the University Hospital in Bonn provided further patients. Diagnoses were assigned according the NINCDS/ADRDA criteria⁸ and on the basis of clinical history, physical examination, neuropsychological testing (using the CERAD neuropsychological battery, including the MMSE), laboratory assessments, and brain imaging. *Control sample*: In the Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) study, participants were randomly sampled in three cities in Germany. The study design has previously been described^{34,35}. Briefly, 4814 participants aged 45 to 75 years were enrolled between 2000 and 2003 (t0, baseline). Cognitive performance of participants was evaluated at follow up scheduled 5 years after baseline (t1, n = 4157, 2005–2008) and then again at follow up 5 years after t1 (t2, n = 3087, 2010–2015). Controls sample was selected if participant did not present cognitive impairment as reported at the last available evaluation. Cognitive evaluation has been described extensively previously^{36,37}. Herein, cognitive impairment at t1 was defined as a performance of one standard deviation (SD) below the age- and education-adjusted mean except for the clock-drawing test, where a performance ≥ 3 was rated as impaired (for a detailed description, see the study by Winkler et al.³⁶). The study was approved by the University of Duisburg-Essen Institutional Review Board and followed established guidelines of good epidemiological practice.

Sub Saharan Africa (EPIDEMCA)

Between 2011 and 2012, a population-based study of dementia prevalence and its associated factors in Central Africa (EPIDEMCA) was carried out³⁷. Around 2,000 participants aged 65 and above living in Central African Republic (CAR) and Republic of Congo (ROC) were interviewed. The full protocol of the EPIDEMCA study (including data collection, variable definition and dementia diagnosis) has been described elsewhere¹⁷. An annual follow-up (EPIDEMCA-FU) was carried out over 3 years (2013-2015) only in ROC. Dementia diagnosis was made according to the DSM-IV criteria and AD was diagnosed according to the clinical criteria proposed by the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association). The severity of dementia was evaluated by the CDR (Clinical Dementia Rating Scale). Mild cognitive impairment (MCI) was diagnosed according to Petersen criteria and MCI cases were excluded from controls. An experienced neurologist reviewed all clinical assessments, evaluation of dependence (Instrumental Activities of Daily Living adapted to the African context, leisure, other social and occupational activities), and test performances (the Free and Cued Selective Reminding Test (oral version with image), Zazzo's cancellation task and Isaac's Set Test of verbal fluency) for all the participants assessed at the second stage of the baseline study / during follow-up studies to reach a consensus. In case of insufficient information to reach a diagnosis, the participant was coded unclassifiable. These samples were genotyped using the ILLUMINA GSA array in the EADB-France node. Ethics committees, "Comité d'Ethique de la Recherche en Sciences de Santé" in ROC (reference: 00000204/DGRST/CERSAA for EPIDEMCA and reference: 0000200/MRSIT/DGRST/CERSSA for EPIDEMCA-FU), as well as the "Comité de la Protection des Personnes Sud-Ouest Outre-Mer" in France (SOOM4-CE-3) approved the study protocol.

Tunisia

DNA samples from 254 subjects (58 AD patients and 196 healthy controls) were recruited from the Department of Neurology, University Hospital of Fattouma Bourguiba, Monastir, Tunisia; the Department of Neurology, University Hospital of Mahdia, Tunisia; and the Alzheimer Family Assistance Center in Tunisia (AFA center) as previously described³⁸. Written informed consent was obtained from all participants or their representatives according to the ethical standards of the Ethics Committee for Research in Life Sciences and Health of the ISBM (CER-SVS/ISBM) and the 1964 Helsinki Declaration. For each participant, age, demographic information, and family and medical histories were collected. All participants were unrelated over three generations. In addition, for AD patients, a detailed clinical assessment was carried out, including a Mini Mental State Examination (MMSE), a standard brain MRI, neuropsychological tests, and laboratory studies. All AD patients were included after at least 2 years of follow-up. Diagnoses of AD were made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for possible or probable AD. Controls were selected after passing an MMSE test and according to the following criteria: no family member with AD or any type of dementia or psychiatric disorder, a mentally healthy status, and no history of alcohol or drug use. This retrospective chart study involving human participants was in accordance with the ethical standards of the Ethics Committee for Research in Life Sciences and Health of the ISBM (CER-SVS/ISBM) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All procedures performed in the present work were approved by Ethics Committee for Research in Life Sciences and Health of the ISBM (CER-SVS/ISBM), Monastir, Tunisia. The Axiom 815K Spanish biobank arrays (Thermo Fisher) at the Spanish National Centre for Genotyping (CeGEN, Santiago de Compostela, Spain) were used for genotyping.

Argentina.

The Argentinian samples were recruited in the context of the Alzheimer's Genetics in Argentina – ALzheimer ARgentina consortium (AGA-ALZAR) from the following centers: Medical Research Institute A. Lanari (C1427ARO, Buenos Aires City), Hospital de Clínicas José de San Martín (C1120AAF, Buenos Aires City), Hospital HIGA-Eva Perón (B1650NBN, General San Martín), Hospital El Cruce (B1888AAE, Florencio Varela), and several geriatric centers across Jujuy and Mendoza provinces, organized and coordinated by their respective Public Ministry of Health. The study (protocol CBFIL#22) was approved by the ethical committee (HHS IRB#00007572, IORG#006295, FWA00020769), and all participants and/or family members gave their informed consent. Diagnosis of AD followed diagnostic criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA). Peripheral blood or saliva samples were processed to obtain DNA using the QIAmp DNA mini kit (Qiagen) and genotyped using the Illumina Infinium Global Screening Array (GSA) v.1.0 combined to a GSA shared custom content³⁹.

Chile

The Chilean samples recruited correspond to patients with AD and control subjects, from different studies. Control individuals were recruited from Alexandros longitudinal study⁴⁰ of community dwelling older adults (≥ 60 years old) of different demographic origin and socioeconomic level, mainly in the study of healthy life expectancy, free of disability and dementia. All participants were randomly selected from 18 Primary Health Care Centers and signed an informed consent on enrolment after they had received written and verbal information about the study. The ethical committee of Institute of Nutrition and Food Technology (INTA), University of Chile (Acta 23, 2012) approved the study protocol (FONDECYT n°1130947). Cognitive status was determined through the Mini-mental State Examination (MMSE) test with a cut-off point of 21/22, previously validated in Chile⁴¹. AD patients were recruited at Biomedica Research Group in Santiago. Subjects were comprehensively studied and diagnosed following the NINCDS-ADRDA criteria for AD. The GWAS study was approved by the Ethics Committee "Servicio de Salud Metropolitano Oriente"

(SSMO). Additional AD cases and control individuals (32 AD and 20 controls) from Santiago were recruited from the GERO⁴² (Geroscience Center for Brain Health and Metabolism) study at the Memory and Neuropsychiatric Center of the Hospital del Salvador and Faculty of Medicine of the University of Chile. The FONDAP GERO project n°15150012 was also approved by the Ethics Committee of the SSMO. A total of 934 samples (n=800 DNA and n=134 frozen blood) were sent to Ace Alzheimer Center Barcelona (Barcelona, Spain) for processing. DNA was extracted from peripheral blood according to standard procedures using the Chemagic system (Perkin Elmer). For the starting DNA samples, a re-extraction protocol using the Chemagic system was also followed in order to purify the DNA samples. Only samples reaching DNA concentrations of >10 ng/μL and presenting high integrity were included for genotyping. Finally, AD cases (n=123) and controls (n=252) were randomized across sample plates to avoid batch effects. The Axiom 815K Spanish biobank arrays (Thermo Fisher) at the Spanish National Centre for Genotyping (CeGEN, Santiago de Compostela, Spain) were used for genotyping.

Brazil

Individuals were recruited at the geriatric outpatient clinic, University Hospital of the Federal University of Minas Gerais (UFMG). This Clinic serves as a Reference Center for the diagnosis and treatment of dementia as well as the diagnosis and treatment of frail older adults. The study was approved by the local ethics committee, and written informed consent was obtained from all the participants prior to inclusion. All participants underwent the same research protocol, which consisted of assessment of sociodemographic characteristics, medical comorbidities, medication history and lifestyle habits as well as memory complaints. The cognitive assessment protocol included the following instruments: MMSE, Clinical Dementia Rating Scale, Verbal Fluency Test, CERAD battery word list, Brief Cognitive Screening, clock drawing test, Neuropsychiatric Inventory, functional activities questionnaire, diagnostic criteria for depression (DSM-5), Geriatric Depression Scale 15 items version (GDS).

The neuropsychological battery used was previously validated for assessing older adults with low formal education⁴³. All tests were validated for use with Brazilian elderly and cutoff points were considered according to their education level. Patients also underwent routine blood tests (e.g., hematology, biochemistry, thyroid-stimulating hormone, vitamin B12 and folate levels, syphilis, and HIV serology) and neuroimaging studies (computerized tomography or nuclear magnetic resonance). The inclusion criteria consisted of older adults aged 60 or over, with a clinical diagnosis of probable Alzheimer's disease dementia and cognitively unimpaired older adults who agreed to take part in the project and signed the consent form. The exclusion criteria included cognitive impairment due to causes other than AD dementia, patients with moderate to severe mental disorders, hydrocephalus and intracranial mass documented by CT scan or NMR, abnormalities in serum folate and/or vitamin B12, serology for syphilis or thyroid hormone levels, and individuals with severe sensory impairment, that made it difficult to administer and respond to the cognitive assessment instruments and those who failed to attend the appointment for the application of the clinical and cognitive protocols. The samples were genotyped by Life & Brain (Bonn, Germany) using the Illumina Infinium Global Screening Array (GSA) v.1.0.

Colombia

The study sample consisted of 241 AD patients and 254 control subjects for a total of 495 individuals from the cundiboyacense region of Colombia. All of the participants were recruited and evaluated at neurology and neuropsychology services by the Neuroscience Group of the National University of Colombia. Diagnosis of AD was determined following the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). The control group consisted of individuals with no personal or family history of neurodegenerative and/or psychiatric diseases. All patients and controls signed an informed consent to participate in the study.

ADSP. Alzheimer's Disease Sequencing Project (ADSP) is a collaborative project aiming at identifying new variants, genes, and therapeutic targets in AD⁴⁴. The joint-called whole-genome sequencing data from the Alzheimer's Disease Sequencing Project (ADSP) accession id NG00067.v10 were downloaded from the NIAGADS DSS website (<https://dss.niagads.org/datasets/ng00067/>), with 36,361 whole-genome genomes⁴⁵. The global ancestry of each individual genome was determined with SNPweights v.2.1⁴⁶ using a set of ancestry-weighted variants computed on reference populations from the 1000 Genomes Project as in⁴⁷. By applying a global ancestry percentage cutoff of >75%, the samples were assigned to the 5 super-populations: South-Asians, East-Asians, Americans, Africans, and Europeans, and classified as Admixed ancestries otherwise. Indian samples were selected using their Identifying code "G-LSID" and a percentage of South-Asian genetic ancestry > 50. The African Americans or Native Americans were selected with an African ancestry above 75% or a Native American ancestry above 75%. As the Hispanic/Latinos group is based on a self-report, samples with African, Native American, South Asian or South East Asian genetic ancestries above 50% were filtered out. Then, in each genetic ancestry super-population, PC outliers of one of the first 4 PCs were excluded. The 83 independent variants were extracted from the individual genomes with vcftools v0.1.17⁴⁸. The PCs significantly associated with the disease status, were selected as covariates, in the logistic regressions. The 83 independent variants were extracted from the individual genomes with vcftools v0.1.17⁴⁸. Technical duplicates or twins were identified using KING v2.2.5 (Kinship-based INFERENCE for Gwas)⁴⁹ and only one genome among the set of identical pairs was retained for further analysis. The phenotype cognitively unimpaired or Alzheimer's disease case was obtained from the ADSP, and participants who did not fall in either of these two categories were excluded from further analysis (see cohorts descriptions at <https://dss.niagads.org/datasets/ng00067/>). Principal components accounting for genetic ancestry were computed per ancestry group using smartpca⁵⁰.

Japan

Participants of Japanese ancestry were recruited by the Japanese Genetic Study Consortium of Alzheimer's Disease⁵² composed of 48 medical institutes and the Japanese Alzheimer's Disease Neuroimaging Initiative⁵³ composed of 38 clinical sites across Japan. Probable AD cases were ascertained on the basis of the criteria of the National Institute of Neurological and Communicative Disorders, and Stroke-Alzheimer's Disease and Related Disorders (NINCDS/ADRD). The Mini-Mental State Examination, Clinical Dementia Rating, and/or Function Assessment Staging were primarily used for evaluation of cognitive impairment. Elders living in an unassisted manner in the local community with no signs of dementia were used as controls. DNA was extracted from peripheral blood leukocytes using standard protocols. GWAS genotyping was performed using Illumina Infinium Asian Screening Array.

Korea (GARD)

Participants of Korean ancestry were recruited from 34 referral hospitals in the Republic of Korea. Participants were diagnosed with AD dementia based on detailed neuropsychological test results⁵⁴. The participants' diagnoses was those of at the latest assessment point. AD dementia was defined in accordance with the core clinical criteria for probable AD dementia according to the National Institute on Aging-Alzheimer Association. Participants were excluded when they had (1) a causative genetic mutation for AD in known genes, such as PSEN1, PSEN2, or APP; (2) structural abnormalities detected on brain magnetic resonance imaging, such as severe cerebral ischemia, territorial infarction, or brain tumors; or (3) other medical or psychiatric diseases that may cause cognitive impairment. DNA samples were genotyped using the Asian screening array (ASA) chip (Illumina). A subset of 125 samples was genotyped using a customized Korea Biobank array (KBA) chip (Affymetrix). Quality control for SNV data was conducted using the PLINK software and imputation was conducted using the Minimac4 software at the University of Michigan Imputation Server⁵⁴.

CHINA

The Chinese AD WGS cohort (N = 1239 comprising 453 patients with AD and 786 HCs) have been previously described⁵⁵. Patients with AD were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The phenotypic data of the participants analyzed in this study were based on the participants' most recent diagnostic records (as of December 2019). The study was approved by the Clinical Research & Ethics Committees of Joint Chinese University of Hong Kong-New Territories East cluster for Prince of Wales Hospital (CREC Ref no. 2015.461), Kowloon Central Cluster/Kowloon East Cluster for Queen Elizabeth Hospital (KC/KE-15-0024/FR-3), and Human Participants Research Panel of the Hong Kong University of Science and Technology (CRP#180 and CRP#225). All participants provided written informed consent for both study participation and sample collection. We sent genomic DNA to Novogene for library preparation and WGS. The genomic DNA libraries were sequenced using an Illumina NovaSeq 6000 System, which generated 150-bp paired-end reads. We performed quality control by examining the G/C content and per-base sequencing quality statistics. We subjected raw sequencing data to fastp for quality control, read trimming, and filtration⁵⁶. We used BWA-mem to align clean reads to the GRCh37 human reference genome and then subjected the reads to GATK for duplicate removal and base quality score recalibration^{57,58}. We performed variant calling and filtering of SNPs and INDELs by using GATK's germline joint calling as well as variant quality score recalibration with 95% and 90% sensitivity-level cutoffs for SNPs and INDELs, respectively⁷. Finally, we subjected filtered SNPs and INDELs to Beagle 4.0 for genotype refinement⁵⁹. After variant calling, we performed standard quality control analysis. All participants showed consistent sex according to their genotypes and phenotypes. We calculated relatedness by performing KING analysis using plink2 and applied a kinship coefficient cutoff of 0.08 to remove second-degree relatives⁶⁰. We performed principal component analysis and removed outliers according to the bigsnpr instruction manual⁶¹. After sample-level quality control, we further filtered genetic variants by Hardy–Weinberg equilibrium test P-values $>1 \times 10^{-6}$.

MVP

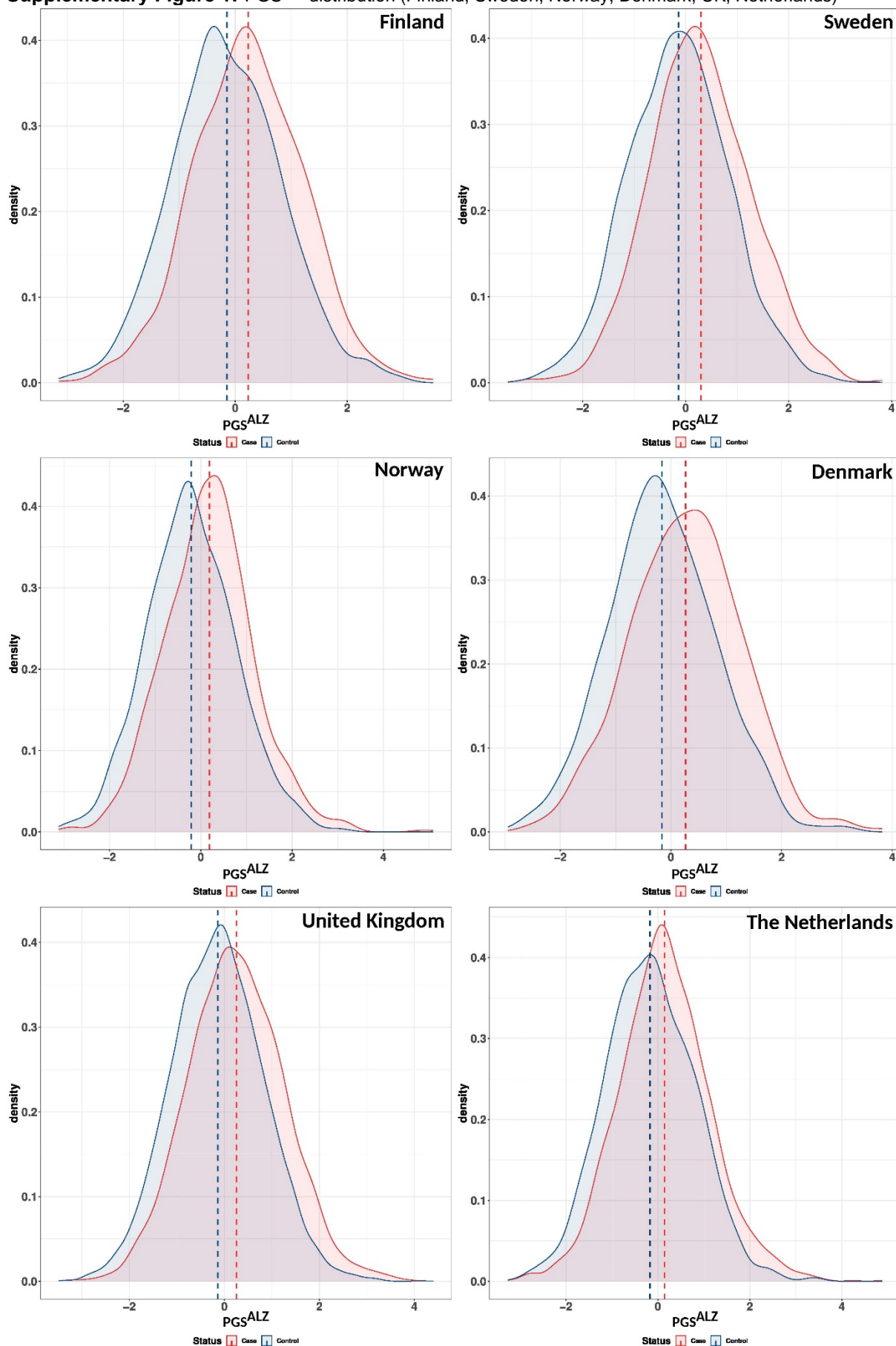
The Million Veteran Program is a United States Office of Veterans Affairs (VA) Office of Research and Development-funded effort to identify factors that impact the health of US Veterans⁶². MVP volunteers are US Veterans who donate a blood sample for genetic analysis, agreed to have their electronic medical record (EMR) accessed for research purposes and in many cases complete surveys covering a wide range of health conditions and lifestyle factors⁶³. Genome-wide genotype data are currently available for approximately 650K MVP participants (MVP Phase 4 genotype release). The generation of MVP genotype data for MVP participants is described in detail elsewhere⁶⁴. Briefly, genotypes were assessed using the custom-designed MVP 1.0 custom Axiom array. QC procedures include relatedness, sex-concordance checks, and advanced marker filtering. Imputation was performed using TOPMed reference data. The ancestry of MVP participants was determined using the harmonized ancestry and race/ethnicity (HARE) method⁶⁵, 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 FlashPCA25. Similar to several recent MVP publications⁶⁶, we utilized an International Classification of Diseases (ICD)-code-based method for classifying subjects as being AD, AD and related dementias (ADRD), or all-cause Dementia cases and controls. MVP participants were identified as a case at one of these levels if they had two or more qualifying ICD codes, with the first occurring after age 60. Controls were drawn from MVP participants age 65 or greater who had no ICD codes for any type of dementia or mild cognitive impairment, had not been prescribed AD medication, and who did not report AD/dementia in either parent on the MVP Baseline survey⁶⁷.

American CSF samples

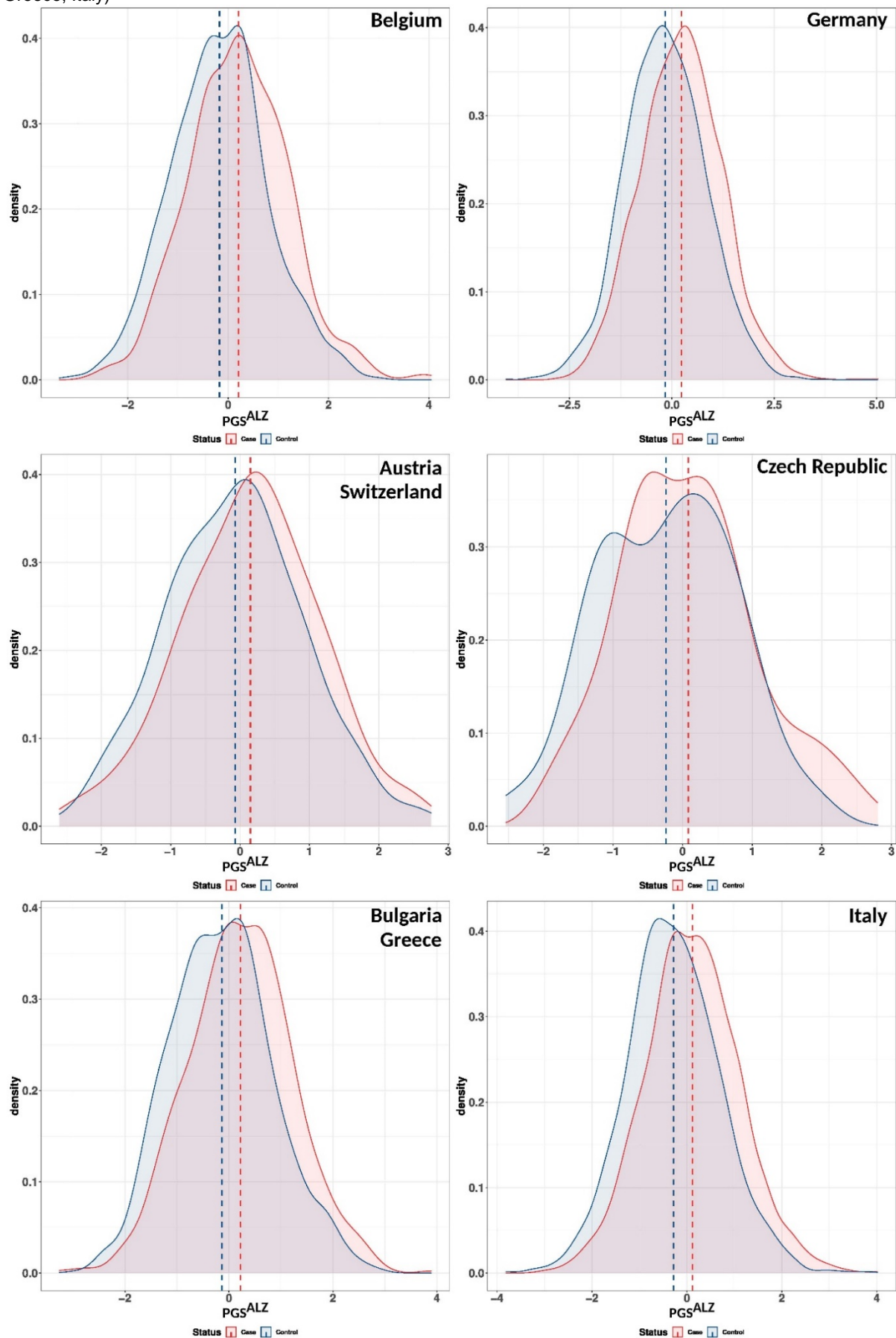
Samples included in this study are from 23 different American cohorts⁶⁸. Genotyping QC was performed within each cohort and involved stringent filtering criteria as previously described⁶⁹. Prior to analysis, all related samples were removed, and only non-Hispanic white population

were kept. In total, 7229 samples were included of which 3701 (51.20%) were males. The average of samples included was 68.67 (± 11.39) years.

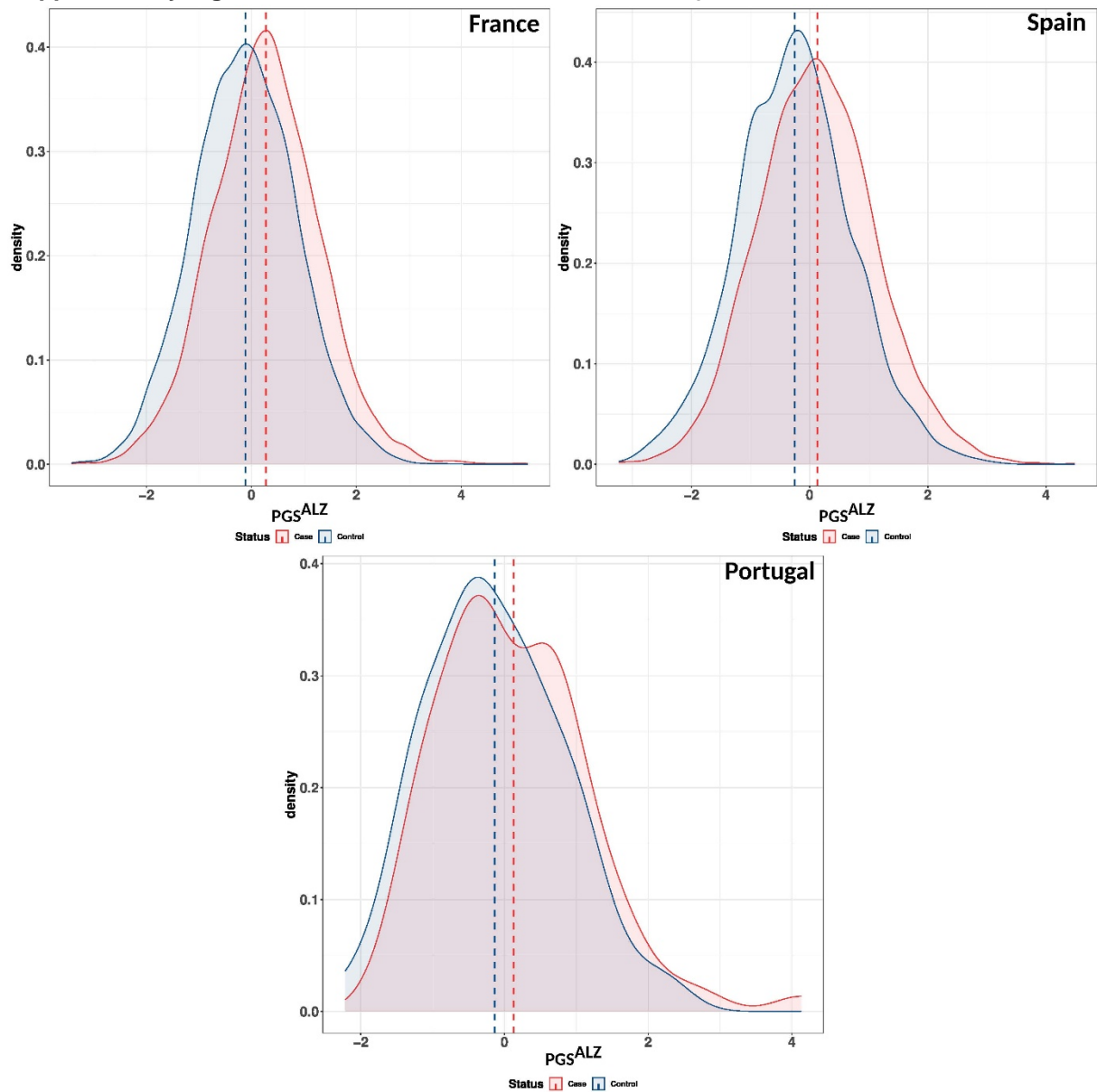
Supplementary Figure 1: PGS^{ALZ} distribution (Finland, Sweden, Norway, Denmark, UK, Netherlands)



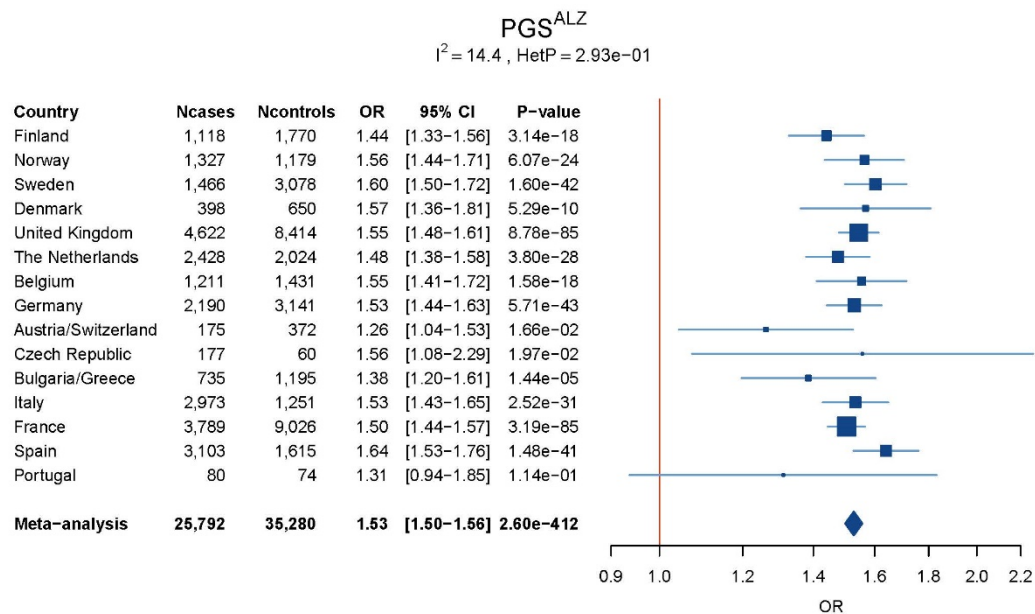
Supplementary Figure 2: PGS^{ALZ} distribution (Belgium, Germany, Austria/Switzerland, Czech Republic, Greece, Italy)



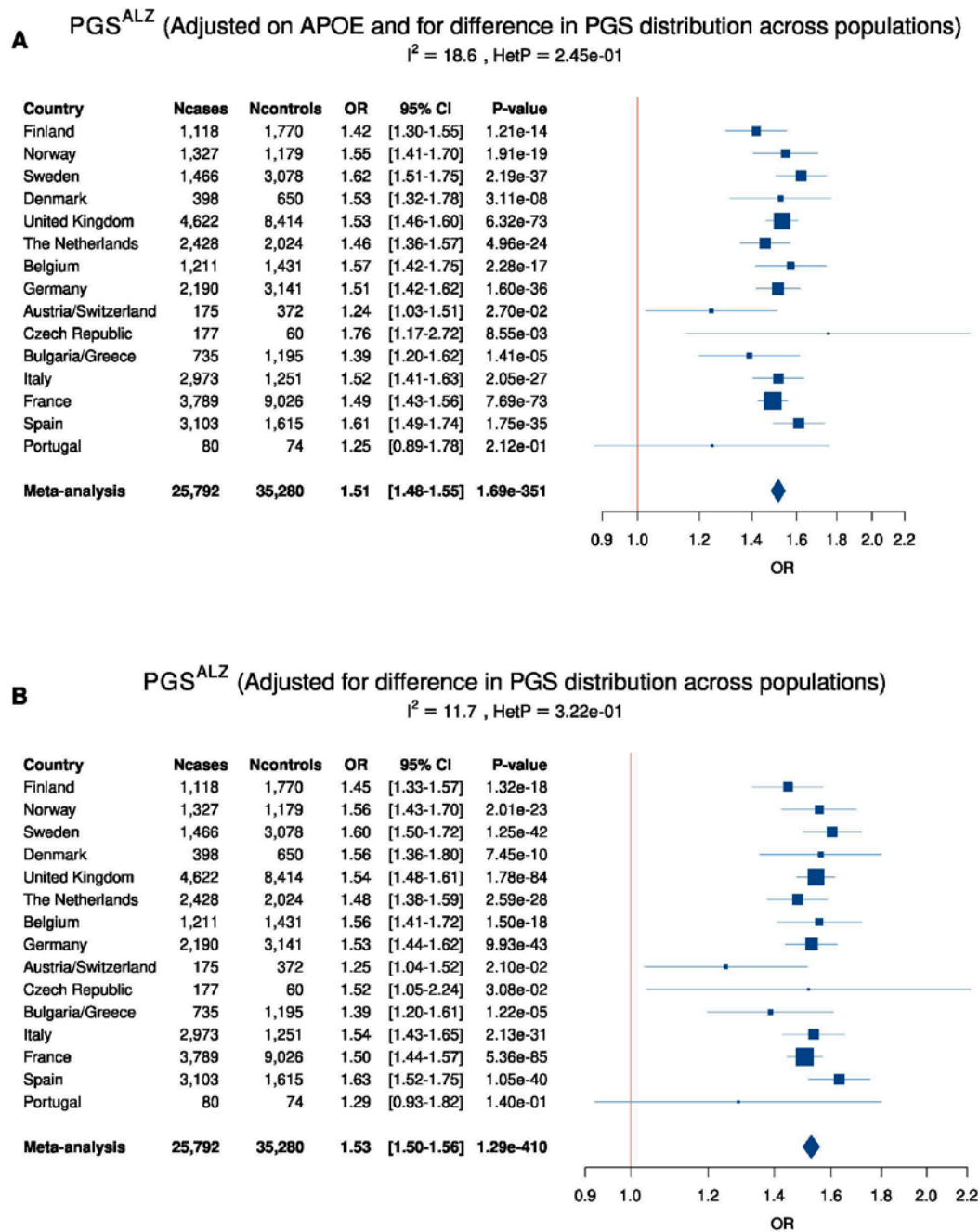
Supplementary Figure 3: PGS^{ALZ} distribution (France, Spain, Portugal)



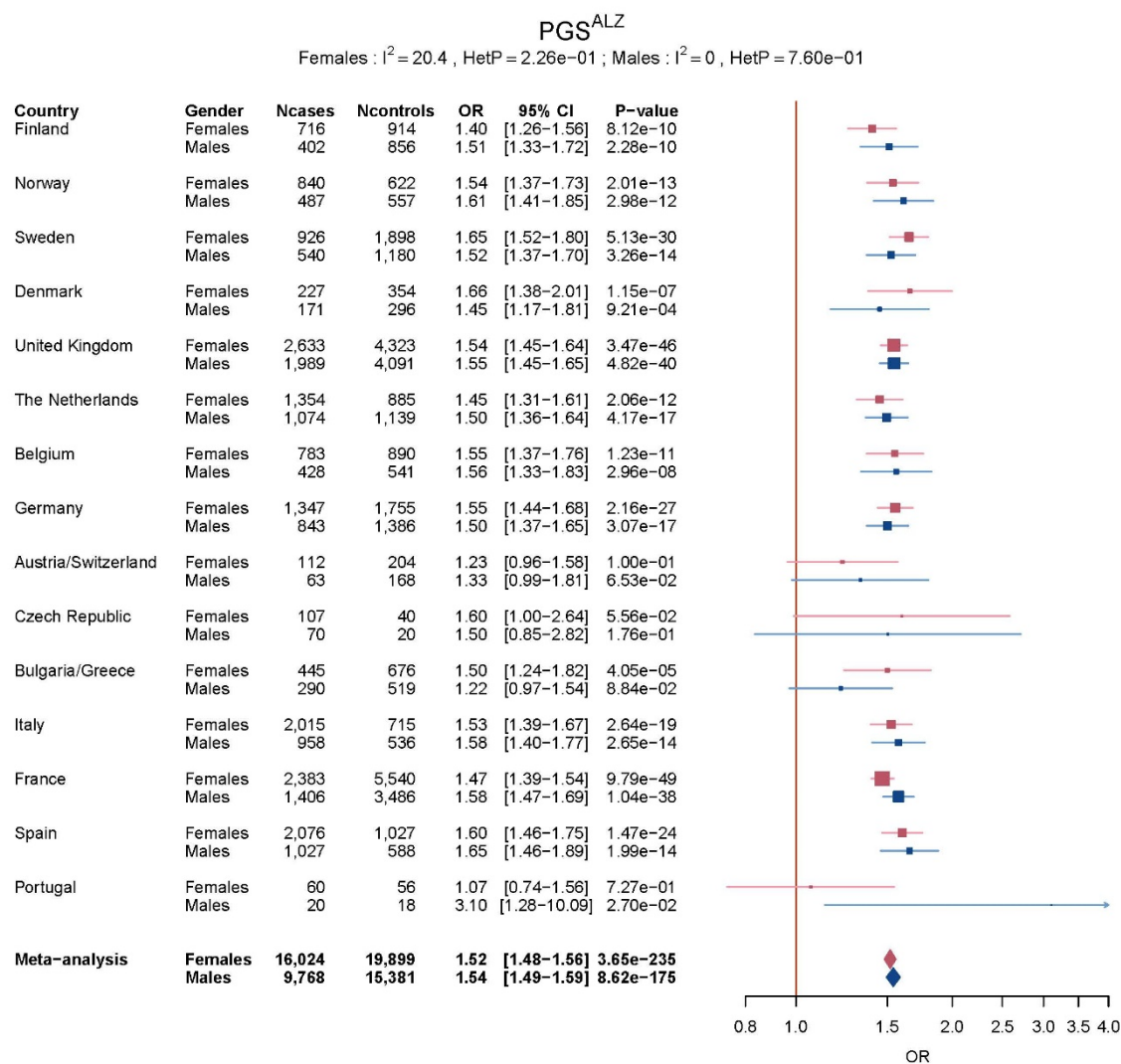
Supplementary Figure 4: PGS^{ALZ} association with AD risk across Europe. Ncases, number of cases; Ncontrols, number of controls; OR, Odds ratio. The lines in the Forrest plots indicate the 95% confidence interval for the ORs.



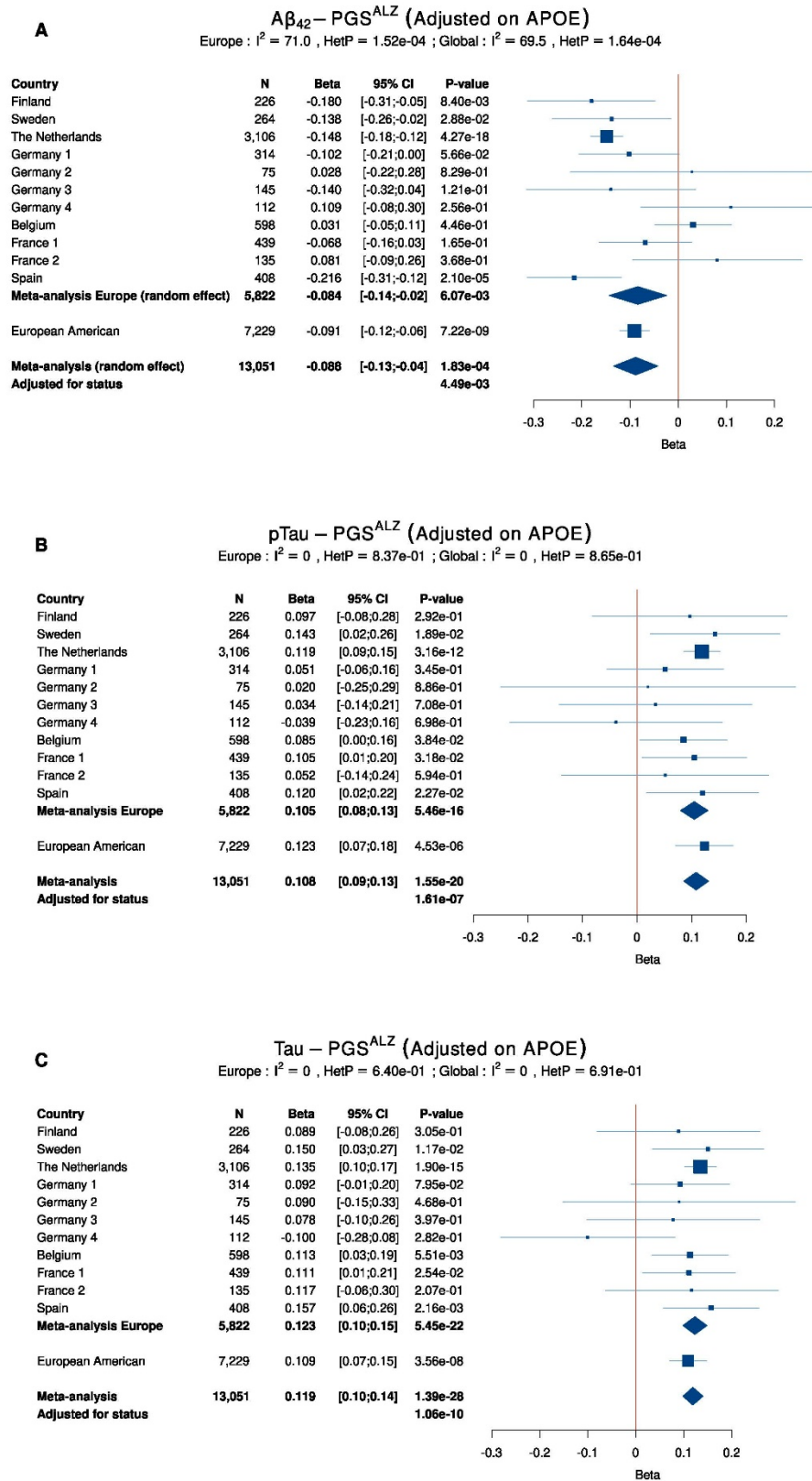
Supplementary Figure 5: PGS^{ALZ} association with AD risk across Europe adjusted for difference in distributions across populations. Ncases, number of cases; Ncontrols, number of controls; OR, Odds ratio. The lines in the Forrest plots indicate the 95% confidence interval for the ORs.



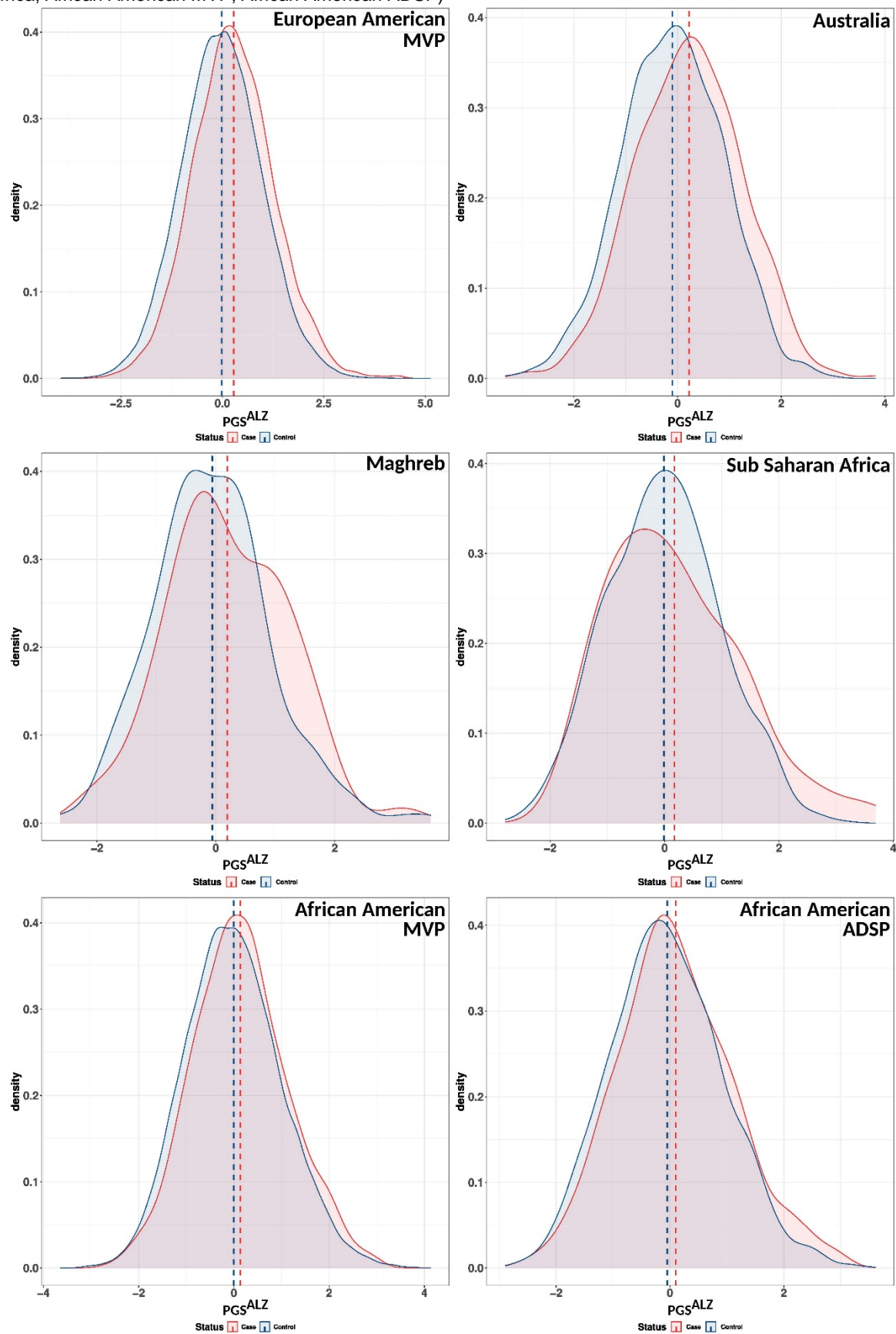
Supplementary Figure 6: PGS^{ALZ} association with AD risk in Men and Women. Ncases, number of cases; Ncontrols, number of controls; OR, Odds ratio. The lines in the Forrest plots indicate the 95% confidence interval for the ORs.



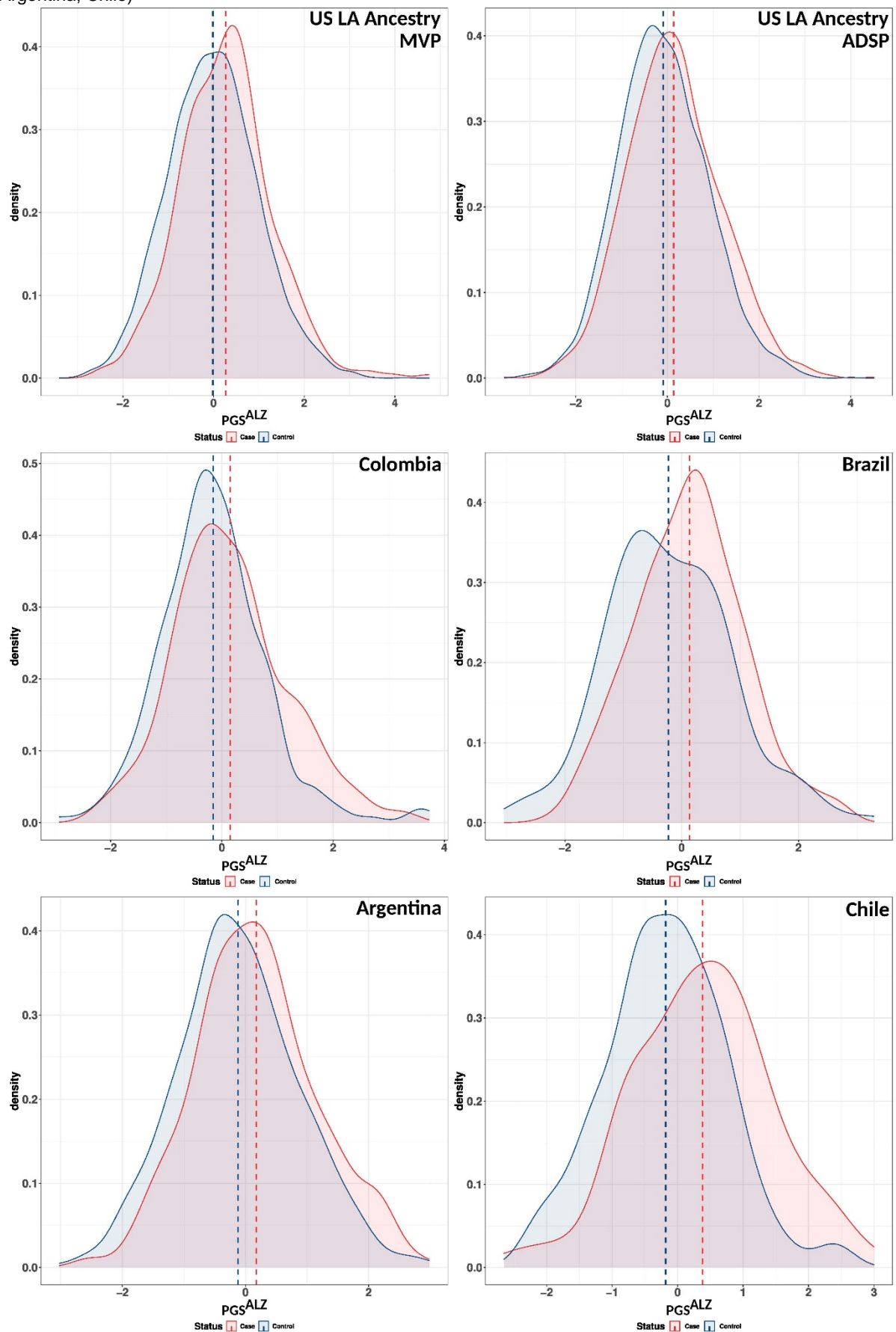
Supplementary Figure 7: Association of PGS^{ALZ} with the level of A β 42, Tau and p-TAU in the cerebrospinal fluid in European-ancestry populations. Ncases, number of cases; Ncontrols, number of controls, OR, Odds ratio. The lines in the Forrest plots indicate the 95% confidence interval for the ORs. If HetP < 0.05, random-effect is shown for the meta-analysis results.



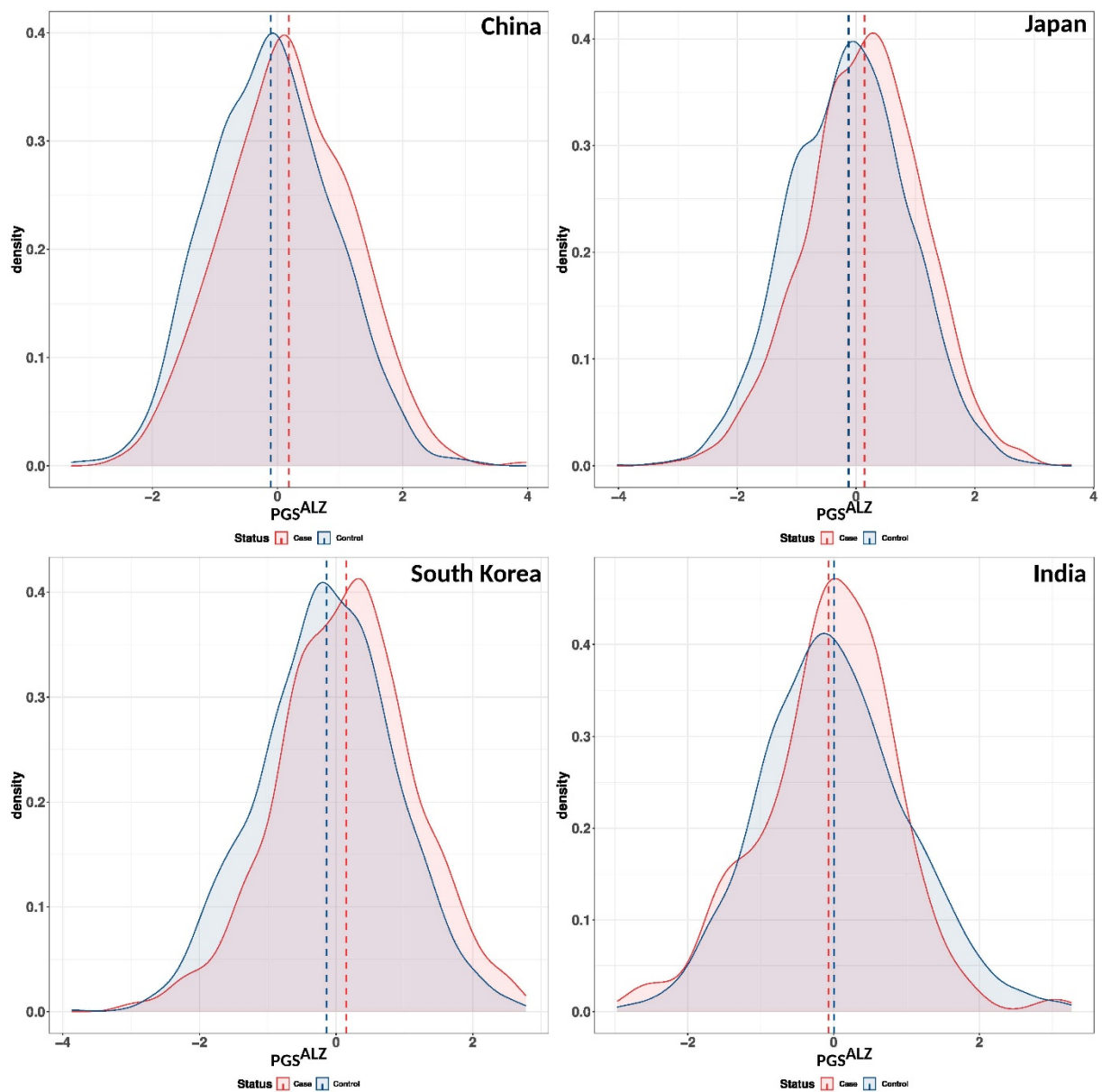
Supplementary Figure 8: PGS^{ALZ} distribution (European American MVP, Australia, Maghreb, Sub Saharan Africa, African American MVP, African American ADSP)



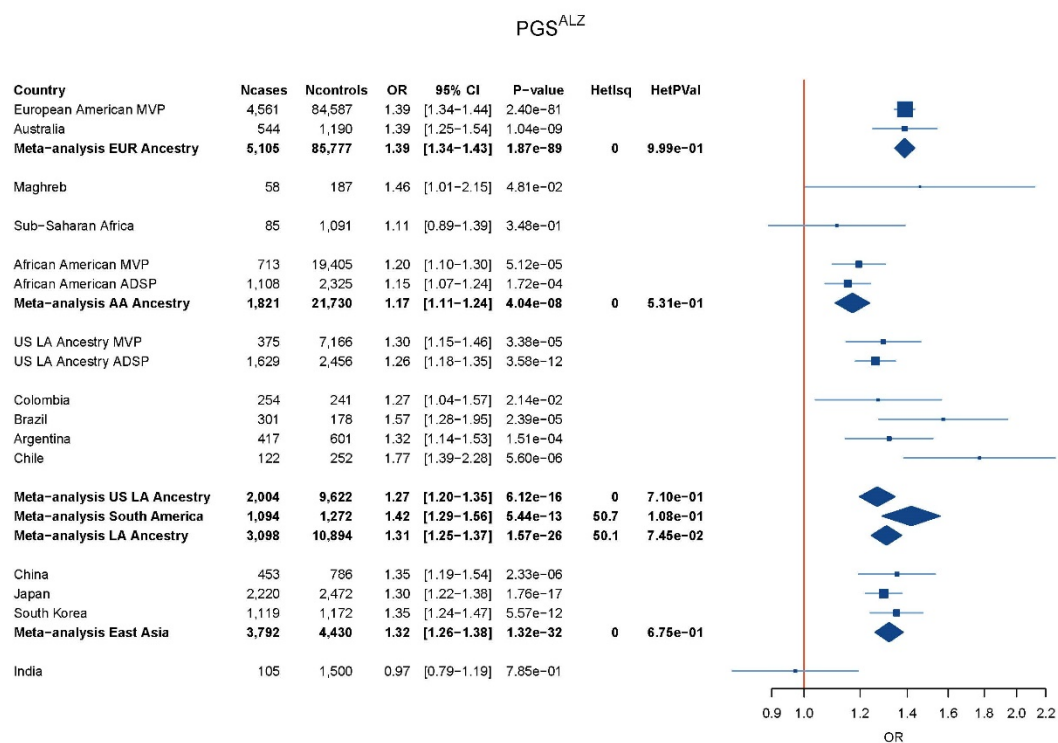
Supplementary Figure 9: PGS^{ALZ} distribution (US LA ancestry MVP, US LA ancestry ADSP, Colombia,, Brazil, Argentina, Chile)



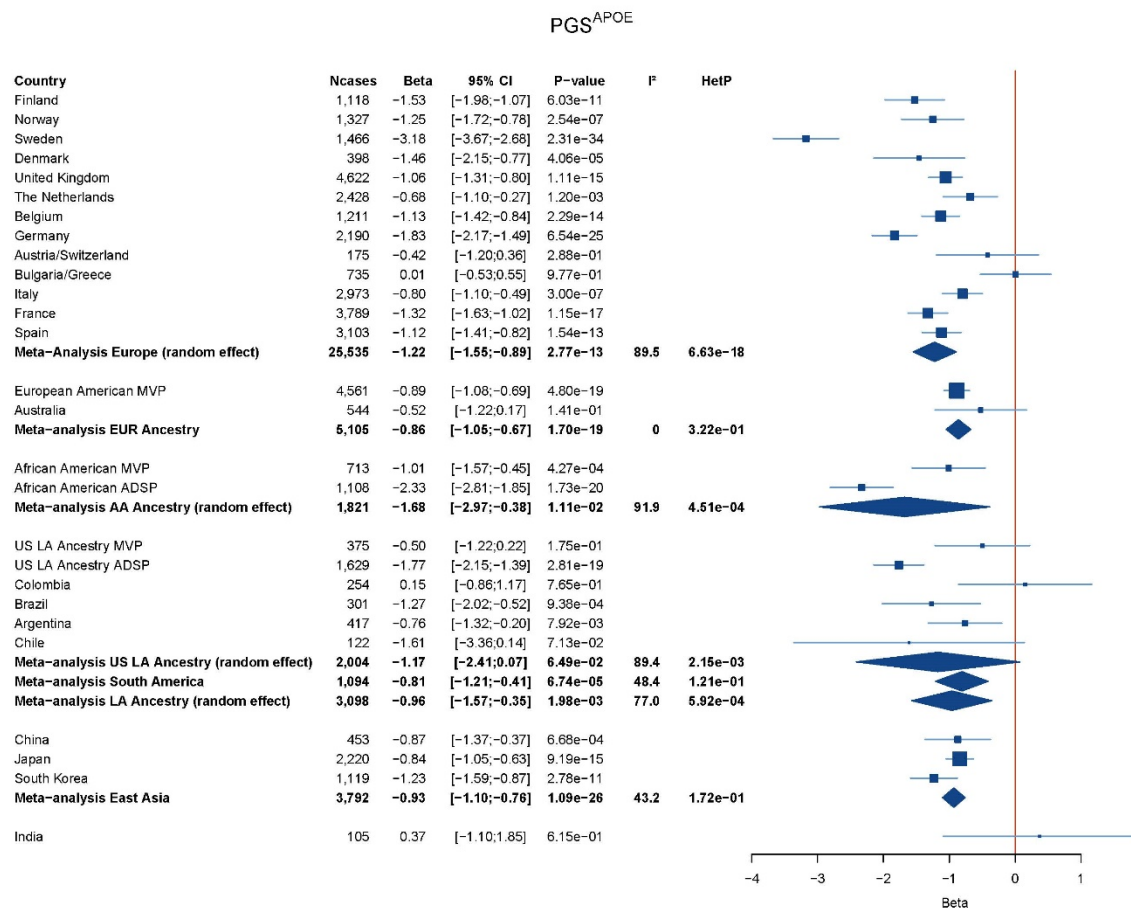
Supplementary Figure 10: PGS^{ALZ} distribution (China, Japan, South Korea, India)



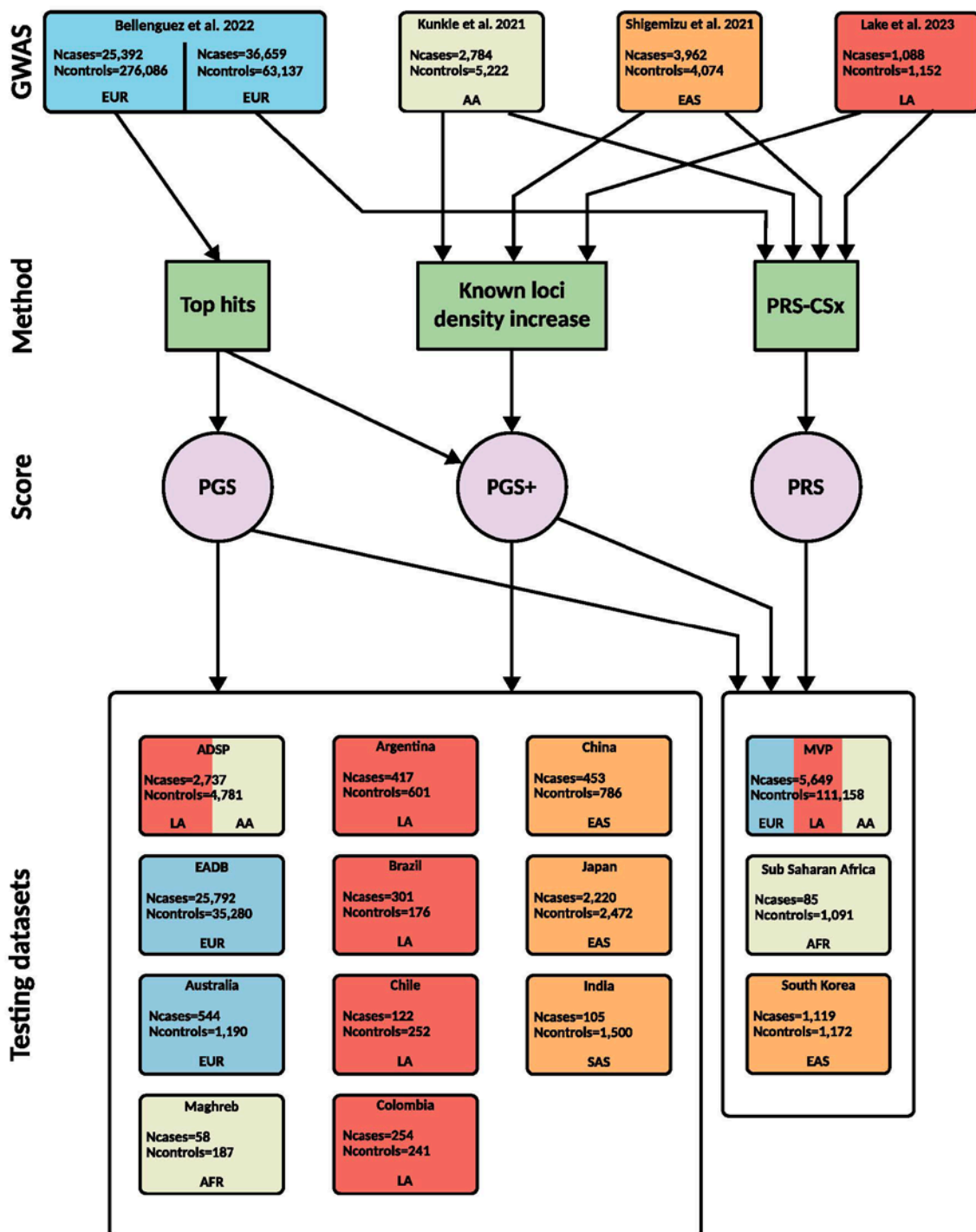
Supplementary Figure 11: Association of PGS^{ALZ} with the risk of developing AD in multi-ancestry populations. European ancestry meta-analysis includes MVP and Australia. African-American-ancestry (more than 75% AA ancestry) meta-analysis includes MVP and ADSP. East-Asia meta-analysis includes China, Korea and Japan. Latino-American ancestry (self-reporting) meta-analysis includes MVP, ADSP and Salsa. South-America meta-analysis includes Argentina, Brazil, Chile and Colombia. Ncases, number of cases; Ncontrols, number of controls, OR, Odds ratio. The lines in the Forrest plots indicate the 95% confidence interval for the ORs. If HetP <0.05, random-effect is shown for the meta-analysis results.



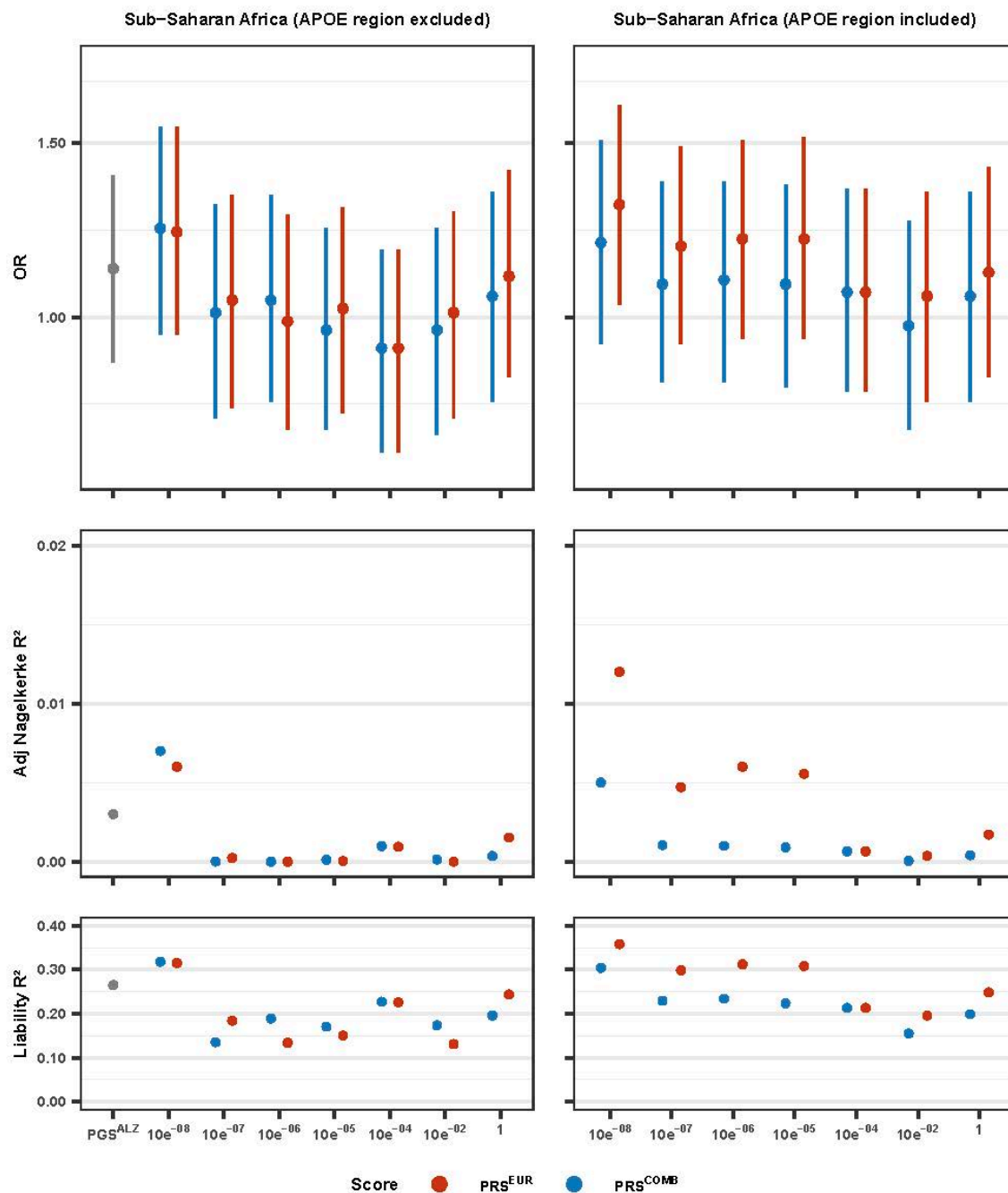
Supplementary Figure 12. Association of PGS^{APOE} with age at onset in multi-ancestry populations. European ancestry meta-analysis includes MVP and Australia. African-American-ancestry (more than 75% AA ancestry) meta-analysis includes MVP and ADSP. East-Asia meta-analysis includes China, Korea and Japan. Latino-American ancestry (self-reporting) meta-analysis includes MVP, ADSP and Salsa. South-America meta-analysis includes Argentina, Brazil, Chile and Colombia. Ncases, number of cases. The lines in the Forrest plots indicate the 95% confidence interval for the ORs. If HetP < 0.05, random-effect is shown for the meta-analysis results.



Supplementary Figure 13: Workflow indicating the summary statistics and populations used to develop and test PGS^{ALZ}, PGS^{ALZ+} and PRS.



Supplementary Figure 14: Comparison of the association of PGS^{ALZ} or PRS (excluding APOE region) with AD risk and the corresponding predictive values (adjusted Nagelkerke R² and Liability R²) in EPIDEMCA. 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.



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