A genome-wide association meta-analysis of all-cause and vascular dementia

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Supplementary File 2

Study Description and Acknowledgments

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Introduction

This project was conducted within the neurology working group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (*CHARGE*) Consortium. The CHARGE cohorts are supported in part by the National Heart, Lung, and Blood Institute (NHLBI) infrastructure grants R01HL105756 (Psaty), RC2HL102419 (Boerwinkle) and the neurology working group is supported by the National Institute on Aging (NIA) R01 grant AG033193.

1 – Study Description

1 – 1. AGES-Reykjavik Study (AGES)

The AGES-Reykjavik Study is a single center prospective cohort study based on the Reykjavik Study. The Reykjavik Study was initiated in 1967 by the Icelandic Heart Association to study cardiovascular disease and risk factors. The cohort included men and women born between 1907 and 1935 who lived in Reykjavik at the 1967 baseline examination. Reexamination of surviving members of the cohort was initiated in 2002 as part of the AGES-Reykjavik Study. AGES is designed to investigate aging using a multifaceted comprehensive approach that includes detailed measures of brain function and structure. All cohort members were European Caucasians. The study design has been described previously.1 Briefly, as part of a comprehensive examination, all participants answered a questionnaire, underwent a clinical examination, multiple digital measurements were acquired, and blood was drawn.

All-cause and vascular dementia ascertainment.

The dementia case finding was based on a 3-step procedure. All participants were screened on the Mini-Mental State Examination and DSST. Screen positives on either of the tests were administered another more complete diagnostic test battery. Those screening positive on the Trails A and B or the Rey Auditory Verbal Learning Test went for a final assessment that included a

proxy interview and a neurologic examination. The diagnosis of dementia and subtypes was made during a consensus conference that included a geriatrician, a neurologist, a neuropsychologist, and a neuroradiologist who provided a clinical reading of MRI. Dementia was diagnosed according to the guidelines of the DSM-IV. Alzheimer disease (AD) was diagnosed according to the criteria of the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association. Vascular dementia (VaD) was diagnosed following the criteria of the State of California AD Diagnostic and Treatment Centers; Clinical medical history and MRI were used in the diagnosis. It was possible to diagnose a subject with possible AD and possible VaD if the 2 pathologies were thought to contribute to dementia.

Genotyping, quality control and imputation.

Within the AGES cohort, 3219 individuals were genotyped with the Illumina hu370CNV array, and 2,705 individuals genotyped with the Illumina Infinium Global Screening Array. Data from both genotype arrays underwent quality control procedure, separately, removing variants with call rate <95% and HWE P-value $< 1 \times 10{-}6$. Both arrays were imputed against the Haplotype Reference Consortium imputation panel r1.1 with the Minimac3 software.[1] Post-imputation quality control consisted of filtering out variants with imputation quality $R2 < 0.7$, $MAF < 0.01$, as well as monomorphic and multiallelic variants for each platform separately. Genotypes for remaining variants, with matching location and alleles between platforms, were merged to create a dataset with 7,506,463 variants for 5656 individuals (268 individuals were genotyped on both platforms, with a 99% match of genotypes for the final set of variants between platforms). The quality control procedure was performed using bcftools (v1.9) and PLINK 1.9.[2,3] All positions are based on genome assembly GRCh37

Association testing.

Association testing was performed with PLINK 1.9 adjusting for age, sex and the first five principal components.[3]

Funding.

AGES is funded by the National Institute on Aging (NIA) (N01-AG-12100), Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament), with contributions from

the Intramural Research Programs at the NIA and at the National Heart, Lung, and Blood Institute (Z01 HL004607-08 CE). The study was approved by the Icelandic National Bioethics Committee (VSN: 00-063) and the MedStarResearch Institute (project 2003-145).

1 – 2. The Atherosclerosis Risk in Communities Study (ARIC)

The ARIC study is a prospective population-based study of atherosclerosis and clinical atherosclerotic diseases in 15,792 men and women, including 11,478 white participants, drawn from four United States communities (Suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi). In the first three communities, the sample reflects the demographic composition of the community. Since the baseline exam, there have been five subsequent follow-up visits with neurocognitive functioning assessed in visit 2 (1990-1992), visit 4 (1996-1998), visit 5 (2011-2013), and visit 6 (2016 – 2017). In Jackson, only black residents were enrolled. Participants were between age 45 and 64 years at their baseline examination in 1987-1989 when blood was drawn for DNA extraction and participants consented to genetic analysis.

All-cause and vascular dementia ascertainment.

Cognitive diagnoses were adjudicated at the fifth visit using cognitive, neurologic, and brain imaging assessments (comprehensive diagnostic details are available elsewhere[4]). Cognitive status was not available on the whole sample at the third visit. The ARIC study has been approved by the Institutional Review Board at each field center, including Wake Forest Baptist Medical Center (Forsyth County, NC), University of Mississippi Medical Center (Jackson, MS), University of Minnesota (suburban Minneapolis, MN), and Johns Hopkins University (Washington County, MD). Participants provided written informed consent prior to each examination.

Genotyping, quality control and imputation and association testing.

At baseline, blood was drawn for DNA extraction and participants consented to genetic testing. Genome-wide genotyping was conducted at the Broad Institute using the Affymetrix 6.0 SNP Array. Genotyping calling was performed using Birdseed for 9,747 European Americans.

Imputation was performed on the QCed data on the Michigan Imputation Server in two steps: pre-phasing with EAGLE and imputation with MiniMac3, using the HRC r1.1 data reference panel.

Funding.

ARIC is funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). The authors thank the staff and participants of the ARIC study for their important contributions. Funding support for "Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium" was provided by the NIH through the American Recovery and Reinvestment Act of 2009 (ARRA) (5RC2HL102419). This project was funded from R01-NS087541 to Myriam Fornage and Eric Boerwinkle.

1 – 3. The ASPirin in Reducing Events in the Elderly (ASPREE)

The ASPirin in Reducing Events in the Elderly (ASPREE) trial was a randomised placebo-controlled clinical trial of daily 100mg low-dose aspirin versus placebo in healthy older people. The design, recruitment, and baseline characteristics of the ASPREE study have been published previously.[5,6] At enrolment, ASPREE participants had no previous history or current diagnosis of atherothrombotic cardiovascular disease, dementia, loss of independence with basic activities of daily living, or life-threatening illness. Participants passed a global cognition screen at enrollment (>77 on the Modified Mini-Mental State (3MS) Examination). Informed consent for genetic analysis was obtained from all participants who provided a biospecimen to the ASPREE Healthy Ageing Biobank, with ethical approval from the Alfred Hospital Human Research Ethics Committee (390/15) and site-specific Institutional Review Boards (US).

All-cause and vascular dementia ascertainment.

After standardized cognition and functional measures, ASPREE participants reporting memory or cognitive problems were assessed by specialists or prescribed dementia medication (in Australia). Following identification of dementia triggers (3MS<78 or a drop of >10.15 points from the participant's baseline 3MS score, accounting for age and education), additional assessments were conducted, with brain imaging and laboratory analyses collected for adjudication. Each dementia trigger case was reviewed according to the ASPREE protocol for clinical adjudication[5,6] by an adjudication committee consisting of geriatricians, neurologists and neuropsychologists. Dementia was diagnosed using Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria. Diagnosis date was recorded as date of trigger. Dementia cases were sub-classified into either 'probable AD', 'possible AD'or 'non-AD dementia', using the 2011 NIA-Alzheimer's Association core clinical criteria [7].

Genotyping, quality control, imputation, and association testing.

Genotyping of DNA samples provided by ASPREE participants was performed on the Axiom 2.0 Precision Medicine Diversity Research Array (Thermo Fisher Scientific (TFS), Waltham, MA, USA) following standard protocols. Variants were aligned to the human genome reference GRCh38. Participants with European ancestry were included to minimize the effect of population stratification. To estimate population structure, we performed principal component analysis using the 1000 Genomes reference population (Figure S2)[8,9]. Imputation was performed using the haplotype reference consortium European panel[1]. Post-imputation quality control removed variants r2<0.3. *APOE* genotype was measured using two directly genotyped variants (rs7412, rs429358) extracted using plink v1.9[3]. Association analysis was performed following the pre-defined CHARGE dementia GWAS analysis plan.

Funding.

This work was supported by an ASPREE Flagship cluster grant (including the Commonwealth Scientific and Industrial Research Organization, Monash University, Menzies Research Institute, Australian National University, University of Melbourne); and grants (U01AG029824 and U19AG062682) from the National Institute on Aging and the National Cancer Institute at the National Institutes of Health, by grants (334047 and 1127060) from the National Health and Medical Research Council of Australia, and by Monash University and the Victorian Cancer Agency. Paul Lacaze is supported by a National Heart Foundation Future Leader Fellowship (102604).

1 – 4. The Cardiovascular Health Study (CHS)

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers in the United States: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Pittsburgh, Allegheny County, Pennsylvania. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African American cohort of 687 persons was enrolled for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

All-cause and vascular dementia ascertainment.

The Alzheimer's disease sample for this study included all prevalent cases identified in 1992 and incident events identified between 1992 and December 2006[10]. Briefly, persons were examined annually from enrollment to 1999, and the examination included a 30-minute screening cognitive battery. In 1992-94 and again in 1997-99, participants were invited to undergo brain MRI and detailed cognitive and neurological assessment as part of the CHS Cognition Study. Persons with

prevalent dementia were identified, and all others were followed until 1999 for the development of incident dementia and Alzheimer's disease. Since then, CHS participants at the Maryland and Pennsylvania centers have remained under ongoing dementia surveillance[11].

Beginning in 1988/89, all participants completed the Modified Mini-Mental State Examination (3MSE) and the DSST at their annual visits, and the Benton Visual Retention Test (BVRT) from 1994 to 1998. The Telephone Interview for Cognitive Status (TICS) was used when participants did not come to the clinic. Further information on cognition was obtained from proxies using the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE), and the dementia questionnaire (DQ). Symptoms of depression were measured with the modified version of the Center for Epidemiology Studies Depression Scale (CES-D). In 1991-94, 3608 participants had an MRI of the brain and this was repeated in 1997-98. The CHS staff also obtained information from participants and next-of-kin regarding vision and hearing, the circumstances of the illness, history of dementia, functional status, pharmaceutical drug use, and alcohol consumption. Data on instrumental activities of daily living (IADL), and activities of daily living (ADL) were also collected.

Persons suspected to have cognitive impairment based on the screening tests listed above underwent a neuropsychological and a neurological evaluation. The neuropsychological battery included the following tests: the American version of the National Reading test (AMNART), Raven's Coloured Progressive Matrices, California Verbal Learning Test (CVLT), a modified Rey-Osterreith figure, the Boston Naming test, the Verbal fluency test, the Block design test, the Trails A and B tests, the Baddeley & Papagno Divided Attention Task, the Stroop, Digit Span and Grooved Pegboard Tests. The results of the neuropsychological battery were classified as normal or abnormal (>1.5 standard deviations below individuals of comparable age and education) based on normative data collected from a sample of 250 unimpaired subjects. The neurological exam included a brief mental status examination, as well as a complete examination of other systems. The examiner also completed the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hachinski Ischemic Scale. After completing the neurological exam, the neurologist classified the participant as normal, having mild cognitive impairment (MCI), or dementia. International diagnostic guidelines, including the NINCDS-ADRDA criteria for probable and possible Alzheimer's disease and the ADDTC's State of California criteria for probable and possible vascular dementia (VaD) with or without Alzheimer's disease, were followed. CHS identified 3

subtypes: possible/probable Alzheimer's disease without VaD (categorized as pure Alzheimer's disease, included in all Alzheimer's disease) and mixed Alzheimer's disease (for cases that met criteria for both Alzheimer's disease and VaD, included in all-Alzheimer's disease), and, possible/probable VaD without Alzheimer's disease (excluded from current study). For this study, CHS contributed data on 450 Alzheimer's disease cases and 1,702 healthy controls with Alzheimer's disease-free status confirmed as of most recent follow- up.

Genotyping, quality control, imputation, and association testing.

Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS participants who consented to genetic testing and had DNA available using Illumina 370CNV BeadChip for European ancestry and Illumina HumanOmni1-Quad_v1 BeadChip for African ancestry. All African ancestry with available DNA and appropriate consent were genotyped. European ancestry participants with presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA were excluded from the GWAS study sample. Beyond laboratory genotyping failures, participants were excluded if they had a call rate<=95% or if their genotype was discordant with known sex or prior genotyping (to identify possible sample swaps). After quality control, genotyping was successful for 3,268 European ancestry and 823 African American participants. The following exclusions were applied to identify a final set of autosomal SNPs: call rate < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap. Imputation to the HRC r1.1 2016 panel was performed on the Michigan imputation server. SNPs were excluded for variance on the allele dosage ≤0.01.

Funding.

This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, 75N92021D00006; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and U01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629, R01AG20098,

R01AG15928, and R01AG033193 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

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1 – 5. European Alzheimer's Disease DNA BioBank (EADB)

The European Alzheimer's Disease Biobank (EADB)[12] dataset consortium groups together AD cases and controls from 15 European countries (Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, The Netherlands and the UK). These samples were genotyped in three independent centers (France, Germany and the Netherlands) as described below.

All-cause and vascular dementia ascertainment

This study was conducted within the Vascular Cognitive Impairment Genetics Consortium (VCIGC).

The Vascular Cognitive Impairment Genetics Consortium (VCIGC) was initially set up 2010-2013 by The Dementia Research Group, University of Bristol, to undertake pilot investigations into the genetic basis of forms of Vascular Cognitive Impairment (VCI).[13] The resultant collaborative collection consists of several thousand cases (vascular dementia, post-stroke dementia or mixed vascular dementia and Alzheimer's disease) and controls from a number of UK and International Centres with an intended use for further research into the genetic aetiology of VCI.

VCIGC cohort synopses:

COHORT: BED

PI: Prof. Malgorzata Bednarska-Makaruk; Institute of Psychiatry and Neurology, Department of Genetics, Warsaw, Poland

Clinical diagnostic criteria: AD: NINCDS-ADRDA; VaD: NINDS-AIREN; AD+VaD: NINCDS-ADRDA for AD + vascular changes in neuroimaging; vascular MCI: the Petersen criteria for MCI + vascular changes in neuroimaging

COHORT: BOR

PI: Prof. Regis Bordet; CHRU Lille, France

Resource: Clinical cohort study: Study of Factors Influencing Post-stroke Dementia **(STROKDEM)**

Description: The STROKDEM study is based on the 5-year prospective follow-up of a population of stroke patients without dementia, who were over 40 years old, displaying an hemorrhagic or an ischemic stroke, with a sus-tentorial localization, and included 72h before the onset of symptoms. At inclusion in the cohort, main antecedents and risk factors, previous treatment and lifestyle, initial severity and etiology are recorded. Clinical severity of stroke is assessed according to the National Institute of Health Stroke Scale (NIHSS). Biological samples (for standard and specialized analyses) and Magnetic Resonance Imaging (MRI) are performed at 72h after stroke occurrence. Thereafter, patients are regularly (6 months, 12 months, 36 months, 60 months) examined for clinical and cognitive assessment with biological samples and MRI. This study procedure was approved by the local ethics committee and registered on clinicaltrials.gov (NCT01330160). Patients gave written informed content.

Clinical diagnostic criteria: The cognitive functions of participants were assessed at M6, M12, M36, M60 post-stroke with a battery of neuropsychological tests, broadly classified into four cognitive domains (executive functions/attention, memory, language, visuospatial abilities). Tests used in the assessment of executive function/attention were Trail Making Test part A and B, a version of Stroop paradigm, and the subtest "code" from WAIS III. For the memory domain, total of the 3 free recalls trials and delayed free recall from the Free and Cued Selective Reminding Test (FCSR) and score of delayed recall from Rey complex figure test were used. The language domain score was built using scores from DO 80, semantic fluency (animal), phonemic fluency (p words) tests. Incomplete letter and number location subtests from VOSP and copy of Rey complex figure test were used in order to assess visuospatial abilities. For every subject, test-specific z-scores based on available norms corrected for age, sex, and education were calculated. We further obtained summary domain-specific z-scores by averaging the test-specific z-scores in each

domain. Following this neuropsychological assessment, participants were diagnosed for a cognitive impairment at 6- and 36-months post-stroke, using a summary z-score ≤1.5 in at least one of the four domains as diagnostic threshold.[14-17]

COHORT: CHE

PI: Prof. Christopher Chen; National University of Singapore

Resource: Clinical cohort study - The Memory Aging and Cognition Centre **(MACC,** *http://www.macc.sg/MACC-Publications-Memory-Problems-Dementia-Prevention***)**

Study description: The Memory Aging and Cognition Centre (MACC) cohort has a longitudinal case-control design. Cases were recruited from memory clinics in the National University Hospital and Saint Luke's Hospital, Singapore. Cognitively normal controls were recruited from both memory clinics and the community in the same catchment area. Ethics approval for this study was obtained from the National Healthcare Group Domain-Specific Review Board (DSRB) (DSRB reference: 2010/00017; study protocol number: DEM4233). Subjects are assessed annually for up to 5 years.

Clinical diagnostic criteria: The diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, whereas VaD was diagnosed using the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l' Enseignement en Neurosciences (NINDS-AIREN) criteria. Subjects who fulfilled the NINCDS-ADRDA criteria for AD but also showed significant cerebrovascular disease on neuroimaging scans (defined as the presence of cortical infarct and/or presence of >=2 lacunes and/or confluent white matter hypertension (ARWMC score >=8) were classified as AD with CVD. No cognitive impairment was diagnosed when subjects showed no objective cognitive impairment in any of the seven cognitive domains tested.[18]

Acknowledgements: This work is supported by the National Medical Research Council of Singapore (NMRC/CG/NUHS/2010, NMRC/CG/013/2013, NMRC/CIRG/1446/2016, NMRC/CSA-SI/0007/2016, NMRC/CG/M009/2017_NUH/NUHS, NMRC/CIRG/1485/2018 and MOH-000707-00).

COHORT: ERK

PI: Prof. Timo Erkinjuntti; Clinical Neurosciences, Neurology, University of Helsinki and Helsinki University Hospital, Finland

Resource: Clinical cohort study - Helsinki Stroke Aging Memory **(SAM)**

Description: The cohort consists of 486 ischemic stroke patients aged 55 to 85 years admitted consecutively to the Helsinki University Central Hospital (Finland) between December 1, 1993 - March 31, 1995. Cases were examined 3 months after the index stroke. Structured medical, neurological, and radiological (MRI or CT) examinations, mental status, and emotional examination, as well as the Mini-Mental State Examination and detailed clinical mental status examination of defined cognitive domains. Normative values for each cognitive domain were based on a random Finnish-speaking healthy community sample for those under and over 75 years of age. Prestroke and poststroke activities of daily living were assessed with five scales. Interview of a close informant was made also. Types of ischemic stroke were classified according to the TOAST criteria into large-artery atherosclerosis, cardioembolism, small-vessel occlusion (lacunar), and stroke of other determined or undetermined etiology. At 15 months the functional status and depression status were assessed. The patients were followed up to 12 years using hospital registers and mortality statistics.[19]

Clinical diagnostic criteria: The criteria for dementia were those of the Diagnostic and Statistical Manual of Mental Disorders (DSM) III

Acknowledgements: The study was supported by grants from the Clinical Research Institute, University of Helsinki and the Medical Research Fund of the Helsinki University Central Hospital.

COHORT: ESI

PI: Prof. Margaret Esiri; Nuffield Department of Clinical Neurosciences, Oxford University

Resource: Clinical Cohort study - Oxford Project to Investigate Memory and Ageing **(OPTIMA)**; Oxford Brain Bank (https://www.ndcn.ox.ac.uk/research/centre-prevention-stroke-dementia/resources/optima-oxford-project-to-investigate-memory-and-ageing)

Description: The Oxford project to investigate memory and ageing (OPTIMA) was a longitudinal study established by Professors David Smith (Pharmacology) and Margaret Esiri (Neuropathology) in 1988 with the prime purpose of advancing an understanding of the causes, treatment and prevention of dementia, and to develop methods of diagnosing the diseases

responsible for it. Professor Gordon Wilcock (Geratology) succeeded as director in 2008, and established the LEAD cohort, which undertook the final follow-up of the last participant in March 2015. Over the course of OPTIMA's existence, clinical, cognitive and imaging data along with tissue samples were collected annually from more than 1,100 patients with dementia, their spouses or carers, and age-matched controls. Most remarkably, over 500 of these subjects donated their brains for research after their deaths, making this an exceptional resource. Although it is not a population-based cohort, the OPTIMA cohort is ideally suited to case-control studies and a number of novel genetic and non-genetic risk factors have been discovered. The data continue to have great value for mechanistic and biomarker discovery and experimental medicine. More than 250 publications have made use of this resource.

Clinical diagnostic criteria: MCI was diagnosed using the Peterson criteria (Peterson RC et al Neurology 2001; 156: 1133-42; AD was diagnosed based on the NINCDS-ARDRA criteria, and the NINDS-AIREN criteria was used for the diagnosis of vascular dementia.

Acknowledgements: Oxford samples are part of the NIHR Oxford Biomedical Research Centre supported Oxford Project to Investigate Memory and Ageing (OPTIMA) study. We acknowledge the Oxford Brain Bank, supported by the Medical Research Council (MRC), Brains for Dementia Research (BDR) (Alzheimer Society and Alzheimer Research UK), Autistica UK and the NIHR Oxford Biomedical Research Centre.

COHORT: HOR

PI: Prof. Jakub Hort; Memory Clinic, Department of Neurology, Motol University Hospital, Prague, Czech Republic

Resource: The Czech Brain Aging Study **(CBAS,** www.cbas.cz**)**

Description: Longitudinal memory clinic based study recruiting subjects at risk of dementia (subjects referred for cognitive complaints - SCD, MCI), CBAS + study - crossectional study of patients in early stages of dementia.

Clinical diagnostic criteria: Cognitively healthy elderly with no significant memory complaint, recruited from patients and staff relatives, advertisement and among 3rd age University participants, age and education matched to CBAS cohort. McKhann 2011 - probable AD dementia

with intermediate or high evidence of AD pathophysiological process. bvFTD-Rascovsky 2011. Participants with objective cognitive decline classified as mild cognitive impairment (MCI) based National Institute on Aging and Alzheimer's Association guidelines by Albert et al 2011.[20]

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COHORT: KAL

PI: Prof. Raj Kalaria; Translational and Clinical Research Institute and The Newcastle Brain Tissue Resource, Newcastle University

Resource: Cognitive Function After Stroke **(CogFAST)** study comprising cohort study derived from North East UK Hospitals Stroke Registers

Description: Older stroke patients (n=706) ≥75 years were screened consecutively from hospital-based stroke registers in Tyneside and Wearside in the North East of England. Potential participants were evaluated at least 3 months after first stroke and to enable resolution of acute post stroke delirium with a standardized battery comprised of medical history, MMSE score, assessment of neurological deficits, a blood screen, and review of CT brain scan undertaken at the time of the stroke. Medical histories taken from the participants were supported by review of hospital charts for diagnoses of previous stroke (including whether there was any residual disability from previous stroke), hypertension (a documented history of blood pressure greater than 140/90 mm Hg or treatment of hypertension), atrial fibrillation (AF), ischaemic heart disease (IHD), peripheral vascular disease, hypercholesterolaemia, diabetes (documented or treated) and history of smoking prior to stroke. Follow up was for at least 20 years. As of December 2019, 96 brain donations were received.

Clinical diagnostic criteria: Stroke was defined according to the World Health Organization definition and classified according to the Oxford Community Stroke project classification.

Participants with a total CAMCOG score < 80 were defined as having cognitive impairment or dementia. The Clinical Dementia Rating (CDR) scale and IQCODE (informant) scores were obtained. Final dementia diagnosis was made when participant met the DSM IV criteria. The apolipoprotein genotype for each participant was determined.

Case selection criteria: All autopsies from post-stroke survivors were included. About ~50% developed dementia prior to death. 75% of the cases were diagnosed with VaD in the absence of any significant neurodegenerative pathology or disease.

Publication reference: Allan LM et al, Brain 2011; Allan LM et al, British Journal of Psychiatry 2013; Firbank MJ et al, Journal of Neurology Neurosurgery and Psychiatry 2012.

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COHORT: KEH

PI: Profs Patrick Gavin Kehoe & Seth Love; Dementia Research Group, Bristol Medical School (THS), University of Bristol, UK

Resource: Clinical cohort study - Memory Disorders Clinic **(MDC)**; South West Dementia Brain Bank **(SWDBB)**

Description: The former North Bristol NHS Trust Memory Disorders Clinic (MDC) at Blackberry Hill Hospital, Bristol (BRACE Clinic) collected data over a period of approximately twenty years (November 1985 through to July 2006) on those who attended for assessment and diagnosis. Data from patients who consented were collated in a comprehensive database, ©Bristol Dementia Research Group September 2006, for research use. Samples of DNA from patients of the now−closed BRACE Clinic were obtained and stored as part of the South West Dementia Brain Bank (SWDBB) Research Tissue Bank. The SWDBB also provided DNA samples for this study, under local Research Ethics Committee approval. The SWDBB began receipt of brain donations for dementia research in the mid-1980s and in 2010 became one of the recruitment centres and member brain banks in the ABBUK-funded Brains for Dementia Research (BDR) Network project.

Clinical diagnosis: MDC patients with a final clinical diagnosis of vascular dementia according to NINDS-AIREN criteria were selected for this study. The clinical diagnosis of dementia was made by experienced clinicians using standard criteria as specified in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV).

Post-mortem diagnosis: This was based on a combination of clinical history and neuropathological findings. National Institute on Aging-Alzheimer's Association guidelines (Montine et al., 2012) were utilised to ascertain the likelihood that Alzheimer's disease (AD) neuropathological changes were a sufficient explanation for the dementia. The pure vascular dementia cases had no more than occasional neuritic plaques, a Braak tangle stage of III or less, histopathological evidence of multiple infarcts/ischaemic lesions, moderate to severe atheroma and/or arteriosclerosis, and an absence of histopathological evidence of other disease likely to cause dementia. The AD cases with concomitant vascular dementia had, in addition to histopathological evidence of multiple infarcts/ischaemic lesions and moderate to severe atheroma and/or arteriosclerosis, neurofibrillary tangle and neuritic and Aβ plaque pathology of sufficient severity to indicate a high likelihood that AD neuropathological change would itself have been a sufficient explanation for the dementia. The normal controls had no clinical history of dementia, few or no neuritic plaques, and no other neuropathological abnormalities.

Acknowledgements: We would like to thank the South West Dementia Brain Bank (SWDBB) for providing DNA for this study. The SWDBB is part of the Brains for Dementia Research programme, jointly funded by Alzheimer's Research UK and Alzheimer's Society and is supported by BRACE (Bristol Research into Alzheimer's and Care of the Elderly) and the Medical Research Council.

COHORT: MAS

PI: Prof. Carlo Masullo; Department of Neuroscience, Section of Neurology, Catholic University of the Sacred Heart, Roma, Italy.

Resource: **UCSC** Cohort

Descrition: UCSC cohort was gathered by enrolling subjects as they entered the outpatient neurogeriatrics unit at the 'Fondazione Policlinico Universitario A. Gemelli IRCCS', Catholic University of the Sacred Heart, Roma, Italy. Subjects have been referred for cognitive assessment. Each subject underwent a complete neurological examination and a standardized

neuropsychological battery (Caltagirone et Al, 1979) including MMSE, ADL and IADL scores. We selected 110 patients who had been diagnosed with VCI in accordance with standardized VCI diagnostic clinical criteria (NINDS-AIREN). All subjects underwent a brain-MRI imaging study and a complete blood screening test. All subjects were evaluated by two board certified neurologists with expertise in dementia.[21]

Clinical Diagnostic Criteria: NINDS-AIREN

Acknowledgements: The study has been partially funded by the Italian Ministry of University and Research (MIUR) to Carlo Masullo.

COHORT: MON

PI: Prof. Roberto Monastero, MD, PhD; Department of Biomedicine, Neuroscience and Advanced Diagnostics (BIND), University of Palermo, Palermo, Italy; Dementia and Parkinson's disease Center, University Hospital "P. Giaccone", Palermo, Italy

Resource: Population based cohort study - Zabùt Aging Project **(ZAP)**

Description: ZAP is a prospective population-based cohort study regarding normal and pathological aging, conducted in an Italian cohort of a rural village in southern Italy, Sambuca di Sicilia. The study included a baseline assessment and a 10-year follow-up examination. All subjects underwent a multidimensional protocol including physical, neurological, functional, cognitive-behavioural examination, laboratory testing, DNA sampling with APOE genotyping and - whenever available - neuroimaging with computed tomography or magnetic resonance. The ZAP study was performed in accordance with the principles outlined in the Helsinki declaration and all participants or their caregiver provided written informed consent. The ZAP study design was approved by the local ethical committee ASP–1 ("Azienda Sanitaria Provinciale", i.e., provincial health authority) of Agrigento, Italy, and general authorization for the genetic data treatment was provided by the Italian data Protection Authority.

Clinical diagnostic criteria: The diagnosis of dementia was made according to the DSM-IV-TR criteria and probable AD was diagnosed according to the criteria established by the National Institute on Aging and the Alzheimer's Association (McKhann GM et al, Alzheimer's Dement 2011). Vascular dementia was diagnosed according to the NINDS-AIREN International Workshop Diagnostic Criteria (Román GC et al, Neurology 1993). The diagnosis of Mild Vascular Cognitive

Disorder was assessed using the Diagnostic Criteria for Vascular Cognitive Disorder: VASCOG statement (Sachdev P, Alzheimer Dis Assoc Disord 2014). Mild Cognitive Impairment was diagnosed according to Petersen's criteria (J Intern Med 2004), while Subjective Cognitive Decline was diagnosed according to the criteria of Jessen et al. (Alzheimer's Dement 2014).

Publication reference: Marino Gammazza A, Restivo V, Baschi R, Caruso Bavisotto C, Cefalù AB, Accardi G, Conway de Macario E, Macario AJL, Cappello F, Monastero R. Circulating Molecular Chaperones in Subjects with Amnestic Mild Cognitive Impairment and Alzheimer's Disease: Data from the Zabùt Aging Project. J Alzheimers Dis. 2022;87(1):161-172. doi: 10.3233/JAD-180825.

Oral Health Status in Subjects with Amnestic Mild Cognitive Impairment and Alzheimer's Disease: Data from the Zabút Aging Project. J Alzheimers Dis. 2022;87(1):173-183. doi: 10.3233/JAD-200385.

Spina R, Noto D, Barbagallo CM, Monastero R, Ingrassia V, Valenti V, Baschi R, Pipitone A, Giammanco A, La Spada MP, Misiano G, Scrimali C, Cefalù AB, Averna MR. Genetic epidemiology of autosomal recessive hypercholesterolemia in Sicily: Identification by next-generation sequencing of a new kindred. J Clin Lipidol. 2018 Jan-Feb;12(1):145-151. doi: 10.1016/j.jacl.2017.10.014.

Acknowledgements: The ZAP data collection was supported by a Grant project for young researcher 2007 (GR–2007–686973) from the Italian Ministry of Health to Roberto Monastero, who is the Principal Investigator of the ZAP. The authors thank all participants and all persons working in the Zabùt Aging Project for data collection and management.

COHORT: **QUI**

PI: Asst. Prof. Shawn Westaway; Layton Aging and Alzheimer's Disease Center, Oregon Health & Science University, USA

Resource: Clinical cohort study - National Institute on Aging (NIA)− Layton Oregon Aging and Alzheimer's Disease Center **(OADC)**.

Description: A selection of 133 participants of the OADC longitudinal cohort studies was made for this study as follows: the Oregon Brain Aging Study (OBAS) (n = 48), the Intelligent Systems for Assessment of Aging Changes (ISAAC) Study (n = 11), the Klamath Exceptional Aging Project (KEAP) (n = 24), the African American Dementia and Aging Project (AADAPt) (n = 1),

the Oregon Community Brain Donor Program (CBDP) (n = 24), the Oregon Living Laboratory (OLL) (n = 3), and the OADC patient registry(n=22)). All studies were approved by the Oregon Health & Science University's institutional review board, and all participants provided written informed consent. Participants underwent cognitive test batteries annually. Comprehensive longitudinal datasets including demographic background, known APOE status, (determined via restriction digest, sequencing a PCR product, or by SNP genotyping) and cognitive decline were obtained.

Clinical diagnostic criteria: Participants were evaluated by board certified neurologists with expertise in dementia. A clinical diagnosis is defined in a consensus conference of neurologists, neuropsychologists, psychiatrist, and nursing staff, according to established clinical criteria (McKhann 1984; Erkinjuntti 1994; Albert 2011).

Post-mortem diagnostic criteria: For those participants who received brain autopsy, the brain tissue was examined according to the National Alzheimer's Coordinating Centre (NACC) protocol and diagnosis rendered by a neuropathologist with expertise in dementia.

Publication reference: https://doi.org/10.1186/s13293-019-0228-8; doi: 10.1212/wnl.54.1.105. https://www.alz.washington.edu/WEB/forms_np.html

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COHORT: SADEM

PI: Dra. Teresa Juárez-Cedillo; Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social (IMSS), Ciudad de México, Mexico.

Resource: The Study on Aging and Dementia in Mexico **(SADEM)**, National Council of Science and Technology (CONACYT) and Found for the Promotion of Health Research, Instituto Mexicano del Seguro Social (FIS/IMSS)

Study description: The Study on Aging and Dementia in Mexico (SADEM), is a cohort with a random sample represented of individuals over 60 years of age, drawn from the senior citizen registry of IMSS in 24 of the 32 delegations across Mexico City. The research protocol was reviewed and approved by The National Commission of Scientific Research and the IMSS Ethics Commission (registration number 2015-785-012). Subjects are assessed for up to 10 years.

Clinical diagnostic criteria: The diagnosis of dementia was done in two stages. Phase 1: Screening The Mini-Mental State Exam (MMSE) was used as a screening tool, and a formal diagnosis was only made in phase 2. Diagnostic confirmation with screening test were evaluated in consultation by a specialist used the Clinical Dementia Rating (CDR) and each diagnosis was based on the criteria for dementia in DSM-5, the subjects were grouped according NINCDS-ADRDA and/or the NINDS-AIREN. For clinical assessment we used: MMSE, phonological fluency, Alzheimer disease assessment scale-cognitive (ADAS-cog) and the Frontal Assessment. The level of abnormalities was evaluated by the magnetic resonance images. The diagnoses fell into three categories: a) Probable Alzheimer's disease (AD), b) vascular dementia (VaD), and c) mixed dementia (MD) without established criteria for MD.

Publication reference: doi: 10.3233/JAD-220012, doi: 10.3233/JAD-200574, doi: 10.1159/000345251, doi: 10.1002/gps.4030, doi: 10.1002/gps.4030, doi: 10.1007/s00277-014-2155-4, doi: 10.1002/gps.4216, doi: 10.1016/j.imlet.2016.07.011, doi: 10.1007/s40618-017-0654-6, doi: 10.1002/mgg3.918, doi: 10.1007/s12035-020-02162-3, doi: 10.1007/s11011-021-00740-5, doi: 10.1007/s12035-020-02162-3, doi.org/10.3389/fnagi.2022.952173.

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COHORT: **SER**

PI: Davide Seripa; Department of Hematology and Stem Cell Transplant, Vito Fazzi Hospital, Lecce, Italy.

Resource: Geriatric Unit

Description: Cohort of elderly attending a geriatric ward

Clinical diagnostic criteria: NINCDS-ADRDA; Petersen; NINDS-AIREN

We thank our EADB collaborators (see EADB acknowledgements) who contributed genotype data:

- **EADB-GSA** (please refer to the EADB acknowledgements)
- **Copenhagen City Heart Study (CCHS)** - Ruth Frikke-Schmidt; Department of Clinical Biochemistry, Copenhagen University Hospital – Rigshospitalet and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. The Copenhagen City Heart Study (CCHS) is a prospective study of the Danish general population initiated in 1976-78 with follow-up examinations in 1981-83, 1991-94, 2001-03, and 2011-13. 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. Genotypes were available on 8,118 individuals from the 1991-94 examination following genotyping on the Illumina Metabochip. ICD10 code F01 was used for the diagnosis. The Copenhagen City Heart Study (CCHS) was funded by The Danish Heart Foundation and the Velux Foundation.
- **DemGene** - Ole A. Andreassen, NORMENT Centre, University of Oslo, Oslo, Norway. DemGene Network is a Norwegian network of clinical sites collecting cases from Memory Clinics based on standardised examination of cognitive, functional and behavioural measures and data on the progression of most patients. The Norwegian DemGene Network includes 2,224 cases and 1,855 healthy controls. The cases were diagnosed according to the recommendations from the National Institute on Aging–Alzheimer's Association (NIA/AA), the NINCDS-ADRDA criteria or the ICD-10 research criteria. The controls were screened with a standardised interview and cognitive tests. Individuals from the

DemGene Study were genotyped using the Human Omni Express-24 v.1.1 (Illumina Inc., San Diego, CA, USA) at deCODE Genetics (Reykjavik, Iceland). The project has received funding from The Research Council of Norway (RCN) Grant Nos. 213837, 223273, 225989, and 324252 and EU JPND Program RCN Grant Nos. 237250, 311993, the South-East Norway Health Authority Grant No. 2013-123, the Norwegian Health Association, and KG Jebsen Stiftelsen. The RCN FRIPRO Mobility grant scheme (FRICON) is co-funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under Marie Curie grant agreement No 608695. European Community's grant PIAPP-GA-2011-286213 PsychDPC.

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- **Sydney Memory and Ageing Study (SMAS)** - Prof. Perminder Sachdev; Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales Sydney, New South Wales, Australia. Participants aged 70-90 years of age were recruited randomly from the community in Sydney, Australia (N=1037) into a longitudinal study to investigate mild cognitive impairment and related syndromes and to determine the rate of cognitive change. A face-to-face interview was undertaken, and questionnaire data collected, including demographics, cognitive performance, a medical exam and medical history. Most participants provided a blood sample for genetic and biochemistry analyses. Neuroimaging was performed on a subset of participants. The majority of participants had an informant, who was able to answer questions about the participant's cognitive performance and daily

functions. The University of New South Wales and the South Eastern Sydney Illawarra Area Health Service Human Research Ethics Committees gave ethics approval for the study. Written informed consent was provided by all participants. All participants whose neuropsychological or functional profiles indicated the possibility of dementia were given consensus diagnoses. Consensus diagnoses were made by an expert panel of clinicians including old age psychiatrists, neuropsychiatrists, clinical neuropsychologists and clinical psychologists using all available clinical data and MRI where available. Participants were classified as VCI if they had MCI (Winblad et al., 2004, J Int Med, 256, 240-246) and any one of the following a) self-reported stroke; b) self-reported TIA; c) presence of 2 or more lacunae; d) any infarcts; e) self-report atrial fibrillation and/or f) were in the upper quartile of white matter hyperintensity (WMH) burden (>17,140 mm3). The diagnosis of dementia was based on DSM-IV criteria (APA 2000); the presence of multiple cognitive deficits that represent a decline from a previous level of functioning and include memory impairment and at least one other cognitive disturbance. The cognitive deficits are sufficiently severe to cause impairment in functioning. doi: 10.1017/S1041610210001067. We gratefully acknowledge and thank the Sydney MAS participants, their supporters and the Sydney MAS Research Team (current and former staff and students). Funding was awarded from the Australian National Health and Medical Research Council (NHMRC) Program Grants (350833, 568969, 109308).

Genotyping, quality control and imputation.

Genotyping

Individuals from the EADB dataset were genotyped on the Illumina GSA array in three independent centers (Centre National de Recherche en Génomique Humaine, Evry, France; Life&Brain, Bonn, Germany; Erasmus Medical University, Rotterdam, The Netherlands).

Individuals from the SMAS dataset were genotyped on Illumina GSA array at the Centre National de Recherche en Génomique Humaine (CNRGH, Evry, France).

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).

Individuals from the CCHS dataset were genotyped on the Illumina Metabochip and/or the Illumina HumanExome.

Individuals from the FinnGen were genotyped on a FinnGen ThermoFisher Axiom custom array at the Thermo Fisher genotyping service facility in San Diego.

Quality control and imputation

Standard quality control was performed on variants and samples on all datasets individually, as described elsewhere.[22] The samples from EADB, SMAS and CCHS datasets were then imputed with the Trans-Omics for Precision Medicine (TOPMed) reference panel.[1,23] For DemGene dataset, we used the provided cleaned and imputed data (imputation was performed with the Haplotype Reference Consortium (HRC) panel).[24]

FinnGen quality control and imputation can be found on the FinnGen website (https://finngen.gitbook.io/documentation/methods/phewas). Imputation was performed using SiSu reference panel consisting of Finnish individuals.

Association testing

Association tests were conducted separately in each dataset using logistic regression assuming an additive genetic model as implemented in SNPTEST[25], except in FinnGen. Analyses were performed on the genotype probabilities in SNPTEST (newml method) and were adjusted for principal components and genotyping centers when necessary. Detailed description of the FinnGen analysis pipeline can be found on the FinnGen website (https://finngen.gitbook.io/documentation/methods/phewas): Briefly, genome statistics were analyzed using Scalable and Accurate Implementation of Generalized mixed model (SAIGE), which uses saddle point approximation (SPA) to calibrate unbalanced case-control ratios[26] and the first ten genetic PCs, sex, age, and genotyping batch were used as covariates

We filtered out duplicated variants and variants with (i) missing effect size, standard error or P value, (ii) absolute value of effect size above 5, (iii) imputation quality less than 0.3. For datasets not imputed with the TOPMed reference panel, we also excluded (i) variants for which conversion of position or alleles from the GRCh37 assembly to the GRCh38 assembly was not possible or problematic, or (ii) variants with very large difference of frequency between the TOPMed reference panel and the reference panels used to perform imputation.

Results were then combined across studies with a fixed-effect meta-analysis using the inverse variance weighted approach as implemented in the METAL software.[27] We excluded (i) variants with heterogeneity P value below 5x10-8, (ii) variants with a minor allele frequency below 0.01, and (iii) variants with frequency amplitude above 0.4 (defined as the difference between the maximum and minimum frequency across studies). We further excluded variants not analyzed in the EADB-TOPMed dataset.

1 – 6. The Framingham Heart Study (FHS)

The FHS is a three-generation, single-site, community-based, ongoing cohort study that was initiated in 1948. It now comprises three generations of participants including the Original cohort followed since 1948 (n=5,209)[28], their Offspring and spouses of the offspring (n=5,216) followed since 1971[29]; and children from the largest Offspring families enrolled in 2000 (Gen 3)[30].

Participants in the Original and Offspring cohorts are used in these analyses, but Gen 3 participants were not included since they are young (mean age 40±9 years in 2000) and none had developed Alzheimer's disease. The Original cohort enrolled 5,209 men and women who comprised two-thirds of the adult population then residing in Framingham, Massachusetts. Survivors continue to receive biennial examinations. The Offspring cohort comprises 5,124 persons (including 3,514 biological offspring) who have been examined approximately once every 4 years. Almost all the FHS Original and Offspring participants are NHW. FHS participants had DNA extracted and provided consent for genotyping in the 1990s. All available eligible participants were genotyped at Affymetrix (Santa Clara, CA) through an NHLBI funded SNP-Health Association Resource (SHARe) project using the Affymetrix GeneChip® Human Mapping 500K Array Set and 50K Human Gene Focused Panel®. In 272 persons, small amounts of DNA were extracted from stored whole blood and required whole genome amplification prior to genotyping. Cell lines were available for most of the remaining participants. Genotyping was attempted in 5,293 Original and Offspring cohort participants, and 4,425 persons met QC criteria. Failures (call rate<97%, extreme heterozygosity or high Mendelian error rate) were largely restricted to persons with whole-genome amplified DNA and DNA extracted from stored serum samples. In addition, since the persons with whole genome amplified DNA represent a group of survivors who may differ from the others we included whole genome amplified status as a

covariate in FHS analyses. For the prevalent analyses, we also excluded 2,268 participants who were less than 65 years old at the time of the DNA draw and 14 persons with dementia other than Alzheimer's disease; the remaining 2,143 subjects constitute the FHS sample for the prevalent study. A total of 806 well-genotyped persons from the Original cohort (which has been under ongoing surveillance for incident dementia since 1975) were included in the incident Alzheimer's disease analyses. The FHS component of this study was approved by the Institutional Review Board of the Boston Medical Center.

The Original cohort of the FHS has been evaluated biennially since 1948, was screened for prevalent dementia and Alzheimer's disease in 1974-76 and has been under surveillance for incident dementia and Alzheimer's disease since then[31-33]. The Offspring have been examined once every 4 years and have been screened for prevalent dementia with a neuropsychological battery and brain MRI[34,35]. In order to be consistent with the sampling frame for the AGES and CHS samples, we excluded FHS subjects with a baseline age <65 yrs at the time of DNA draw which was in the 1990s. To minimize survival biases, Original cohort and Offspring participants who developed dementia prior to the date of DNA draw were treated as prevalent cases, and subsequent events in the Original cohort occurring prior to December 2006 were included in the incident analyses.

All-cause and vascular dementia ascertainment.

At each clinic exam, participants receive questionnaires, physical examinations and laboratory testing; between examinations they remain under surveillance (regardless of whether or not they live in the vicinity) via physician referrals, record linkage and annual telephone health history updates. Methods used for dementia screening and follow-up have been previously described[31,36]. Briefly, surviving cohort members who attended biennial examination cycles 14 and 15 (May 1975-November 1979) were administered a standardized neuropsychological test battery to establish a dementia-free cohort.

Beginning at examination cycle 17 (1982), the MMSE was administered biennially to the cohort. A MMSE score below the education-specific cutoff score, a decline of three or more points on subsequent administrations, a decline of more than five points compared with any previous examination, or a physician or family referral prompted further in-depth testing. The Offspring cohort that was enrolled in 1971 has undergone eight re-examinations, one approximately every

four years. Starting at the second Offspring examination, participants were questioned regarding any subjective memory complaints and since the fifth Offspring examination participants have been administered the MMSE at each visit. In addition, concurrent with the seventh and eighth Offspring examinations (between 1999 and 2004 and then again between 2005 and 2009) surviving Original cohort and all eligible and consenting Offspring participants have undergone volumetric brain MRI and neuropsychological testing[34,35]. The neuropsychological test battery included the Reading subtest of the Wide Range Achievement Test (WRAT-3), the Logical Memory and the Paired Associates Learning tests from the Wechsler Memory Scale, the Visual Reproduction and Hooper Visual Organization Tests, Trails A and B, the Similarities subtest from the Wechsler Adult Intelligence test, the 30-iterm version of the Boston Naming Test and at the second assessment only, the Digit Span, Controlled Word Association and Clock Drawing Tests. Offspring participants suspected to have cognitive impairment based on their MMSE scores, participant, family or physician referral, hospital records or performance in the neuro-psychological test battery described above were referred for more detailed neuropsychological and neurological evaluation.

Each participant thus identified underwent baseline neurologic and neuropsychological examinations. Neurologists (trained in geriatric behavioral assessment) supplemented their clinical assessment with a few structured cognitive tests and administered the Clinical Dementia Rating (CDR). Persons were reassessed systematically for the onset of at least mild dementia. A panel consisting of at least 1 neurologist (S.A., P.A.W., or S.S.) and 1 neuropsychologist (R.A.) reviewed all available medical records to arrive at a final determination regarding the presence or absence of dementia, the date of onset of dementia, and the type of dementia. For this determination, we used data from the neurologist's examination, neuropsychological test performance, Framingham Study records, hospital records, information from primary care physicians, structured family interviews, computed tomography and magnetic resonance imaging records, and autopsy confirmation when available. All individuals identified as having dementia satisfied the DSM-IV criteria, had dementia severity equivalent to a CDR of 1 or greater, and had symptoms of dementia for at least 6 months. All individuals identified as having Alzheimer-related dementia met the NINCDS-ADRDA criteria for definite, probable, or possible Alzheimer's disease. Vascular Dementia was diagnosed using the ADDTC criteria, but the presence of vascular dementia did not disqualify a participant from obtaining a concomitant diagnosis of Alzheimer's disease if

indicated. The recruitment of Original cohort participants at FHS had occurred long before the DNA collection with the result that the majority of dementia events in the FHS (although ascertained prospectively) were prevalent at the time of DNA collection or these persons had died prior to DNA draw and were thus excluded from analyses of incident disease. Due to the limited number of incident dementia and Alzheimer's disease events in the Framingham Offspring only the Original cohort were included in our analyses of incident events. For this study, FHS contributed data on 330 Alzheimer's disease cases and 3,910 healthy controls with Alzheimer's disease-free status confirmed as of most recent follow-up.

Genotyping, quality control and imputation and association testing

In the 1990s and early 2000s, DNA samples were collected in the three FHS generations for genetic research. All individuals provided consent for genotyping. In 2007, the FHS began genotyping for the NHLBI funded Single Nucleotide Polymorphism (SNP)-Health Association Resource (SHARe) project using approximately 550 000 SNPs (Affymetrix 250K Nsp and 250K Sty mapping arrays plus Affymetrix 50K gene-centered supplemental array) in 9,274 participants from the three generations (including over 1,500 families). Individuals who did not pass QC criteria (call rate < 97%, extreme heterozygosity or high Mendelian error rate) were excluded. Imputation was performed on the Michigan Imputation Server using miniMACH3 and the Haplotype Reference Consortium (HRC) reference panel release 1.1 April 2016 17 using SNPs passing the following criteria: call-rate ≥ 97%, Hardy-Weinberg P ≥ 10-6, < 1000 Mendelian errors, and minor allele frequency (MAF) ≥ 1%. Prior to imputation, phasing was performed using the duoHMM algorithm incorporated into SHAPEIT2 to account for parental genotypes.

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AG058589, AG061872 and U01-AG049505) and the National Institute of Neurological Disorders and Stroke (R01-NS017950, UH2 NS100605). Dr. DeCarli is supported by the Alzheimer's Disease Center (P30 AG 010129). We thank the study participants, as well as the study team (especially the investigators and staff of the neurology team) for their contributions and dedication to the study. The authors are pleased to acknowledge that the computational work reported on in this paper was performed on the Shared Computing Cluster that is administered by Boston University Research Computing Services. URL: www.bu.edu/tech/support/research/.

1 – 7. INGI-Friuli Venezia Giulia (INGI-FVG)

The INGI-Friuli Venezia Giulia (INGI-FVG) cohort is a collection of samples coming from six small villages (Clauzetto, Erto, Illegio, Resia, San Martino del Carso, and Sauris) located in North-Eastern Italy, in the Friuli Venezia Giulia region. The FVG Genetic Park is part of the INGI project, a collaboration between research institutions in Italy aimed at reconstructing the molecular bases of complex traits and pathologies by investigating genetically isolated Italian populations.[37] Studies were conducted referring to a common operational protocol. Genotyping and phenotypic data for 1590 samples are available. A written informed consent for participation was obtained from all subjects. The project was approved by the Ethical committee of the IRCCS Burlo-Garofolo.

All-cause and vascular dementia ascertainment.

Eight hundred seventy-seven genotyped individuals carried out a neurological visit. Based on ICD-codes we defined cases of prevalent all-cause dementia.

Genotyping, quality control and imputation.

All samples have been genotyped with Illumina 370K/700K high-density SNP array (Illumina Inc., San Diego, CA, USA). Genotypes were called with Illumina GenomeStudio. Each batch was processed according to standard quality control procedures with the following criteria for inclusion: sample call-rate ≥ 0.95, gender check, SNP call rate ≥ 0.95, Hardy-Weinberg Equilibrium (HWE) p-value > 1 × 10−6, and minor allele frequency (MAF) ≥ 0.01. Genotype

imputation was conducted using IMPUTE2 considering as reference a custom panel generated merging the 1000 Genomes phase 3 and whole-genome sequences of INGI samples.[37-39]

Association testing.

The analyses were performed with linear mixed models (LMM) using the GEMMA (Genome-wide Efficient Mixed Model Association) software which uses a generalized mixed model to account for sample relatedness and cryptic population structure.[40] Sex and age were included in the analysis as covariates.

Funding.

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1 – 8. The Genome Research at ACE Alzheimer Center Barcelona (GR@ACE)

The Genome Research at Ace Alzheimer Center Barcelona (GR@ACE) and Dementia Genetics Spanish Consortium (DEGESCO) is a dementia and population-based cohort study of risk factors for Alzheimer's disease conducted across different centers in Spain (DEGESCO Consortium). The population included in this study was 12,599 participants with European descent (7,516 ACD and 1,953 VaD)) and all participants provided written informed consent. This research protocol was approved by the ethics and scientific committees (Acta 25/2016, Ethics Committee H., Clinic I Provincial, Barcelona, Spain).

All-cause and vascular dementia ascertainment.

Study participants completed neurological, neuropsychological and social evaluations at Ace Alzheimer Center Barcelona. For each individual, a consensus-based diagnosis about the cognitive status was reached at the time of the study recruitment by a multidisciplinary team of professionals that included neurologists, neuropsychologists and social workers[41]. Cognitive assessment consisted of the Spanish version of the Mini-Mental State Examination (MMSE)[42,43] the memory part of the Spanish version of the 7 Minutes test[44] the Spanish version of the Neuropsychiatric Inventory Questionnaire (NPI-Q)[45] the GDS[46] the Clinical Dementia Rating Score (CDR)[47] the Blessed Dementia Scale[48], and a comprehensive neuropsychological battery of Fundació ACE

(NBACE)[49] Alzheimer's disease dementia and Vascular dementia were defined according to the NIA-AA[50] and NINDS-AIREN International Workshop Criteria[51] respectively. Mild cognitive impairment (MCI) was defined using Petersen's[52] and the Cardiovascular health and cognition study criteria[53] The control group included healthy controls and individuals with subjective cognitive decline (SCD). SCD refers to the perception of memory or other cognitive problems without impairment on standardized cognitive tests[54] All individuals in the control group had a CDR of 0, a preserved performance (score ≥ 27) on the MMSE and a strictly normal performance in the NBACE.

Genotyping, quality control, imputation, and association testing.

DNA was extracted from peripheral blood according to standard procedures using the Chemagic system (Perkin Elmer). Samples reaching DNA concentrations (>10 ng/µl) and presenting high integrity were included for genotyping. Cases and controls were randomized across sample plates to avoid batch effects. For genotyping, we used the Axiom 815K Spanish biobank array (Thermo Fisher) at the Spanish National Centre for Genotyping (CeGEN, Santiago de Compostela, Spain). Details on genotyping and quality-control procedures are provided in previous publications.[55] Briefly, individuals with low-quality samples, excess of heterozygosity, sex discrepancies, and familial relations between samples (PI-HAT > 0.1875) were excluded from the analysis. A principal component analysis (PCA) was performed and population outliers were removed. Variants with call rate below 95% or deviation from the Hardy–Weinberg equilibrium ($p \leq 1\times10^{-06}$) were also removed from the analysis. To maximize genetic coverage, we performed single-nucleotide polymorphism (SNP) imputation on genome build GRCh38 using the Trans-Omics for Precision Medicine (TOPMed) imputation server.[23,56] Rare variants (MAF <1%) and low imputation quality variants ($R^2 < 0.30$) were excluded.

We conducted an association analysis adjusting for age, sex, and population structure (4PCs) to test the association of each variant with VaD and ACD using plink (v2.00a).

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1 – 9. The Salus in Apulia Study (SAS)

The "Salus in Apulia Study" is an ongoing population-based prospective cohort comprising 2,472 individuals aged ≥ 65 years and residents in Castellana Grotte, a town located near Bari, Puglia, in the Southeast of Italy. It focused on the sequence of lifestyle including diet, frailty, and other age-related impairments and age-related disease outcomes. In detail, Salus is a public health initiative funded by the Apulia Regional Government and carried on at IRCCS "S. De Bellis" that combines data from two previous populations: the baseline data (MICOL3, M3) were recorded from 2003 to 2005 and the follow-up data from 2013 to 2015 (GreatAGE Study - MICOL4, M4). The GreatAGE study has been described elsewhere.[57] The invitation included also subjects of the MICOL studies that were in the respective age range above 64 years. In the GreatAge-M4 examination, in addition to the assessment of clinical and lifestyle aspects, neuropsychological features and genetic components have been also evaluated. The study adhered to the "Standards for Reporting Diagnostic Accuracy Studies" (STARD) guidelines (http://www.stard-statement.org/), the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines (https://www.strobe-statement.org/).

The study was approved in the 2014 by the Institutional Review Board of the National Institute of Gastroenterology "S. De Bellis".

All-cause and vascular dementia ascertainment.

Diagnoses of dementia are mainly made obtaining data from hospital registries on ICD-9 and ICD-10 codes from all inpatient and outpatient contacts from 1987 through 2018 for all genotyped participants in the Salus in Apulia study. A subset of these diagnoses has been validated against the ICD-10 criteria for Alzheimer's disease by two neurologists. Based on ICD-codes we defined cases of prevalent all-cause dementia, vascular dementia and Alzheimer disease. We defined participants as controls if they had never received any of the diagnoses listed under all-cause dementia until 2021.

Genotyping, quality control and imputation.

A total of 1801 individuals were successfully genotyped with the Illumina Infinium Global Screening Array (GSA) v1 at IRCCS S. De Bellis, Castellana Grotte, Bari, Italy. Genotype calling was performed using Illumina GenomeStudio. Pre-imputation QC included removing SNP call rate < 0.97; Hardy-Weinberg p-value < $1x10^{-6}$; MAF < 0.01, sample call rate < 0.97, gender check. Imputation was performed using the Michigan University Imputation server and reference panel HRC (Build 37). EAGLE v2.4 was using for phasing and MINIMAC v4 for imputation process

Association testing.

The analyses were performed with linear mixed models (LMM) using the GEMMA (Genome-wide Efficient Mixed Model Association) software which uses a generalized mixed model to account for sample relatedness and cryptic population structure.[40] Sex and age were included in the analysis as covariates.

Funding.

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1 – 10. The Hong Kong Osteoporosis Study (HKOS)

The Hong Kong Osteoporosis Study (HKOS) has been established since 1995, and the cohort was described elsewhere.[58] In brief, 9,449 Southern Chinese community-dwelling participants were recruited from public road shows and health fairs in Hong Kong from 1995 to 2010. Self-reported questionnaires, anthropometric data, clinical measurements, biochemical measurements, and bone mineral density measurements were collected from the study participants at baseline and follow-up visits. The HKOS participants were also followed in silico using the representative electronic medical database in Hong Kong, namely Clinical Data Analysis and Reporting System (CDARS), which is managed by the Hong Kong Hospital Authority.

All-cause and vascular dementia ascertainment.

The demographic data and diagnosis records (in the form of ICD-9) of all the genotyped HKOS participants were retrieved from CDARS from 1 January 1995 up to 31 December 2019 (study end date). Prevalent all-cause and vascular dementia cases were defined as study participants who had the ICD-9 diagnosis codes in Table SI-2, up to 31 December 2019. Incident cases were study participants who did not have relevant ICD-9 diagnosis codes of all-cause and vascular dementia prior to baseline visit, but were diagnosed during the follow-up period up to the study end date. Controls were defined as study participants who had never been diagnosed with all-cause and vascular dementia up to the study end date.

Genotyping, quality control and imputation.

The study participants were either genotyped using Illumina HumanHap 610 Quad chip or Illumina Global Screening Array. Genetic variants which did not pass the quality control criteria (call rate <95%, minor allele frequency [MAF]<1%, or/and violating Hardy-Weinberg equilibrium ($p<1x10^{-6}$ among the controls) were excluded. Upon pre-phasing by duoHMM of SHAPEIT, the data of each genotyping platform was separately imputed with reference to the Haplotype Reference Consortium (HRC) reference panel by Michigan Imputation Server. For imputed genetic variants, only those with info score ≥0.4 were included in further analysis. Quality control was applied again to the imputed data. Genetic variants not passing the quality control criteria (call

rate <95%, MAF<1% or/and Hardy-Weinberg equilibrium ($p<1x10^{-6}$ in controls) were excluded. Samples with >5% genotyping missing rate were removed from further analysis.

Association testing.

Since the trait is binary, only individuals distantly related were kept, with a cutoff of estimated genetic relationship >0.05 using GCTA. For prevalent all-cause and vascular dementia, GWAS was performed using logistic regression model implemented by PLINK1.9, with the adjustment for gender and age as covariates. For incident all-cause and vascular dementia, Cox proportional hazards regression analysis was performed with age as x-axis and adjustment for gender using the GenABEL package in R.

Funding.

Nil

1 – 11. The Nord-Trøndelag Health Study (HUNT)

The HUNT consists of three different population-based health surveys conducted in the county of Nord-Trøndelag, Norway over approximately 20 years (HUNT1 [1984-1986], HUNT2 [1995-1997] and HUNT3 [2006-2008]).[1] In each survey, the entire adult population (≥ 20 years) was invited to participate by completing questionnaires, attending clinical examinations and interviews. Participation rates in HUNT1, HUNT2 and HUNT3 were 89.4% (n=77,212), 69.5% (n=65 237) and 54.1% (n=50 807), respectively.[1] Taken together, the study included more than 120,000 different individuals from Nord-Trøndelag County. Biological samples including DNA have been collected for approximately 80,000 participants. The HUNT Study has been described in more detail elsewhere.[1] For the present study, we included participants from HUNT2 and HUNT3. The current study is approved by the Regional Committee for Medical and Health Research Ethics (ref. 2017/1031).

All-cause and vascular dementia ascertainment.

The health care system in Norway is publicly funded. Levanger hospital and Namsos hospital, which are the two only hospitals in Nord-Trøndelag, have catchment area responsibilities for the

whole county. Diagnoses of dementia are mainly made at geriatric, neurological, and old age psychiatric wards and outpatient clinics. We obtained data from hospital registries on ICD-9 and ICD-10 codes from all inpatient and outpatient contacts from 1987 through 2018 for all genotyped participants in the HUNT study. A subset of these diagnoses has been validated against the ICD-10 criteria for Alzheimer's disease by four specialists in geriatrics and old age psychiatry as part of the Health and Memory Study.2

Based on ICD-codes we defined cases of prevalent all-cause dementia, vascular dementia and Alzheimer disease, by at least one local hospital contact due to the diagnoses given in the table below. Incident cases were defined as those who at participation in HUNT had never received any of the diagnoses listed under all-cause dementia in the table below, but fulfilled criteria for either of the dementia types during follow-up (till 2018). We defined participants as controls if they had never received any of the diagnoses listed under all-cause dementia in the table below during follow-up (until 2018).

Genotyping, quality control and imputation.

In total, DNA from 71,860 HUNT samples was genotyped using one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1 and UM HUNT Biobank v1.0). Samples that failed to reach a 99% call rate, had contamination > 2.5% as estimated with BAF Regress,3 large chromosomal copy number variants, lower call rate of a technical duplicate pair and twins, gonosomal constellations other than XX and XY, or whose inferred sex contradicted the reported gender, were excluded. Samples that passed quality control were analysed in a second round of genotype calling following the Genome Studio quality control protocol described elsewhere.4 Genomic position, strand orientation and the reference allele of genotyped variants were determined by aligning their probe sequences against the human genome (Genome Reference Consortium Human genome build 37 and revised Cambridge Reference Sequence of the human mitochondrial DNA; http://genome.ucsc.edu) using BLAT.5 Variants were excluded if their probe sequences could not be perfectly mapped, cluster separation was < 0.3, Gentrain score < 0.15, showed deviations from Hardy Weinberg equilibrium in unrelated samples of European ancestry with p-value < 0.0001), had a call rate < 99%, or another assay with higher call rate genotyped the same variant. Ancestry of all samples was inferred by projecting all genotyped samples into the space of the principal components of the Human Genome Diversity

Project (HGDP) reference panel (938 unrelated individuals; downloaded from http://csg.sph.umich.edu/chaolong/LASER/),6,7 using PLINK. Recent European ancestry was defined as samples that fell into an ellipsoid spanning exclusively European population of the HGDP panel. The different arrays were harmonized by reducing to a set of overlapping variants and excluding variants that showed frequency differences > 15% between data sets, or that were monomorphic in one and had MAF > 1% in another data set. The resulting genotype data were phased using Eagle2 v2.3 47.8

Imputation

Imputation was performed on the 69,715 samples of recent European ancestry using Minimac3 (v2.0.1, http://genome.sph.umich.edu/wiki/Minimac3)9 with default settings (2.5 Mb reference based chunking with 500kb windows) and a customized Haplotype Reference consortium release 1.1 (HRC v1.1) for autosomal variants and HRC v1.1 for chromosome X variants.10 The customized reference panel represented the merged panel of two reciprocally imputed reference panels: (1) 2,201 low-coverage whole-genome sequences samples from the HUNT study and (2) HRC v1.1 with 1,023 HUNT WGS samples removed before merging. We excluded imputed variants with Rsq < 0.3 or minor allele count <3.

Association testing.

We used the Scalable and Accurate Implementation of GEneralized mixed model (SAIGE),11 which uses a generalized mixed model to account for sample relatedness and cryptic population structure. We ran a mixed logistic regression model, including sex, birth year, genotyping batch, and the first 4 principal components as covariates. The principal components were calculated by projecting all samples into the space of the principal components of unrelated HUNT samples, using directly genotyped variants in PLINK v1.9012.

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the Norwegian Institute of Public Health. The genotyping was financed by the National Institute of health (NIH), University of Michigan, The Norwegian Research council, and Central Norway Regional Health Authority and the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). The genotype quality control and imputation has been conducted by the K.G. Jebsen center for genetic epidemiology, Department of public health and nursing, Faculty of medicine and health sciences, Norwegian University of Science and Technology (NTNU).

1 – 12. The MEMENTO cohort

Memento is a French multicenter cohort that aims to improve current knowledge of the natural history of Alzheimer's disease and related disorders (ADRD) and identify new patient phenotypes associated with the risk of developing dementia. The Memento cohort includes patients from the 26 participating memory clinics across France between 2011 and 2014. Participants were followed at least annually for a median of 5 years.[59,60] Individuals were eligible for inclusion if they (1) were 18 years or older; presented with at least one cognitive deficit defined as performing worse than 1 SD to the mean in one or more cognitive domains (considered as MCI), or (2) presented with an isolated cognitive complaint and were 60 years of age or older. They also had to score on the clinical dementia rating (CDR) scale ≤0.5 (i.e., not demented); have sufficient visual and auditory abilities to partake in neuropsychological testing; and have health insurance, as required by the French government (France has universal access to health care for all legal residents, independent of age, professional standing, or revenue).[61] All participants signed an informed consent form.

All-cause and vascular dementia ascertainment.

All incident cases of dementia were reviewed by a panel of expert neurologists/geriatricians, blinded to genetic and biological biomarkers using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV criteria).

The etiologic diagnosis of dementia was made according to NINCDS-ADRDA for Alzheimer Disease, DLB consortium for dementia with Lewy bodies, Rascovsky criteria for frontotemporal lobar degeneration and NINDS-AIREN for Vascular dementia.

Genotyping, quality control, imputation, and association testing.

All samples were genotyped using the Illumina Global Screening Array (GSA). Pre-imputation QC included removing SNPs with MAF<0.01, call-rate<0.98 and HWE<0.001; removing samples with call-rate<0.05, heterozygosity beyond 3SD, failed sex-check using genotype data of X-chromosome, related sample based on IBD (pi_hat>0.1875). PCA analysis was performed using Plink v1.90. PCA outliers were defined beyond 6SD of PC1 and PC2. Imputation was performed using the Michigan Imputation Server panel with HRC.r1.1.2016 (predominantly European Ancestry), and phasing was performed using Eagle. GWAS was conducted using Plink v1.90 using logistic regression adjusting for age, sex, center, and PCs 1-4.

Funding.

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1 – 13. The Monongahela-Youghiogheny Healthy Aging Team (MYHAT)

MYHAT is an age-stratified random sample drawn from the publicly available voter registration list for a group of small towns in southwestern, Pennsylvania, USA. This population-based cohort was recruited between 2006 and 2008 and is being followed annually for the development of mild

cognitive impairment (MCI) and dementia. Inclusion criteria at study entry included 1) being 65 years and older, 2) living in one of the designated towns, 3) not residing in a long-term-care facility, 4) having vision and hearing sufficient to permit neuropsychological testing, and 5) not being decisionally impaired. Eligible participants who consented were briefly assessed using the Mini-Mental State Exam (MMSE). (Folstein *et al.*, 1975) Only participants without substantial cognitive impairment at recruitment (age-education adjusted MMSE score (Mungas *et al.*, 1996) ≥21) were invited to complete the full assessment and thus eligible for annual follow-up. The University of Pittsburgh Institutional Review Board approved all study procedures, and all participants provided written informed consent. (Ganguli *et al.*, 2009)

All-cause and vascular dementia ascertainment.

Dementia was ascertained by means of the Clinical Dementia Rating (CDR ®) Staging Instrument (https://knightadrc.wustl.edu/professionals-clinicians/cdr-dementia-staging-instrument/) which is based on individuals' cognitively-driven everyday functioning. Participants were assessed by interviewers trained and certified in the CDR.[62] We classified participants with CDR=0 as normal, CDR=0.5 as MCI, and CDR ≥1 as dementia.

Genotyping, quality control and imputation.

A total of 907 MYHAT samples were genotyped with two different Illumina Omni chips, including HumanOmni1S-8-v1 chip, and HumanOmni2-5-8-v1 chip. No sample had a genotyping rate of less than 95% in either chip. The genotype probs with missing call rate > 5% or only present on one chip were removed. The rest of the common genotype probs were phased with the Eagle and then imputed on the Michigan Imputation Server with 1000 Genome Phase 1 Version 3 reference panel. In post-imputation QC, SNPs with low quality score (R^2< 0.3), MAF<0.01 and Hardy-Weinberg equilibrium test p-value <1E-5 were removed. A sliding window approach with a window size of 2000 bp shifted every 200 variants was implemented to estimate correlation (r^2). The principal component analysis (PCA) was implemented with Plink 2.0 after filtering out SNPs with MAF<0.05 and having highly correlation SNPs (r^2 > 0.5).

Association testing.

The association analysis was also performed on Plink with sex, age, years of education, and the first four PCs.

Funding.

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1 – 14. The Religious Orders Study and Memory and Aging Project (ROSMAP)

ROSMAP are two community-based cohort studies. The ROS has been ongoing since 1993, with a rolling admission. Through July of 2010, 1,139 older nuns, priests, and brothers from across the United States initially free of dementia who agreed to annual clinical evaluation and brain donation at the time of death completed their baseline evaluation. The MAP has been on-going since 1997, also with a rolling admission. Through July of 2010, 1,356 older persons from across northeastern Illinois initially free of dementia who agreed to annual clinical evaluation and organ donation at the time of death completed their baseline evaluation. Details of the clinical and neuropathologic evaluations have been previously reported[63-65].

All-cause and vascular dementia ascertainment.

A clinical diagnosis of cognitive status is rendered at every assessment based on a three-stage process including computer scoring of cognitive tests, clinical judgment by a neuropsychologist, and diagnostic classification by a clinician.

All participants undergo a uniform, structured, clinical evaluation including a battery of 19 cognitive tests. These tests were scored by computer using a decision tree designed to mimic clinical judgment and a rating of severity of impairment was given for 5 cognitive domains. A neuropsychologist, blinded to participant demographics, reviews the impairment ratings and other clinical information and renders a clinical judgment regarding the presence of impairment and dementia. A clinician (neurologist, geriatrician, or geriatric nurse practitioner) then reviews all available data and examines the participant and renders a final diagnostic classification.

Clinical diagnosis of dementia and clinical Alzheimer's dementia are based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). The diagnosis of Alzheimer's dementia requires evidence of a meaningful decline in cognitive function relative to a previous level of performance with impairment in memory and at least one other area of cognition.

Diagnosis of mild cognitive impairment (MCI) is rendered for persons who are judged to have cognitive impairment by the neuropsychologist but are judged to not meet criteria for dementia by the clinician.

Persons diagnosed with MCI or Alzheimer's dementia may also be diagnosed with another condition that contributes to their cognitive impairment (CI).

Persons without dementia or mild cognitive impairment (MCI) are categorized as having no cognitive impairment (NCI).

Genotyping, quality control and imputation.

Genotyping was done on Affy 6.0 and Illimina Omni Express. Imputation was performed using the Michigan Imputation Server panel with HRC.r1 (predominantly European Ancestry). Pre-imputation QC included removing SNPs with MAF<0.01, call-rate<0.95 and HWE<10^{-6}. Post-imputation QC included removing monomorphic variants, variants with info<0.3, variants with MAC<5.

Association testing.

GWAS for prevalent all-cause dementia was performed using Plink v1.9, with covariates including baseline age, sex, and PCs 1-4. GWAS for incident all-cause dementia was performed using R, with covariates including age at baseline, sex, education, and PCs 1-4.

Funding.

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1 – 15. The Rotterdam Study (RS1, RS2, RS3)

The Rotterdam Study is a population-based cohort study among inhabitants of a district of Rotterdam (Ommoord), the Netherlands, that aims to examine the determinants of disease and health in the elderly with a focus on neurogeriatric, cardiovascular, bone, and eye disease.[8] In 1990-1993, 7,983 persons aged ≥ 55 years participated and were re-examined every 3 to 4 years (**RS1**). In 2000-2001, the cohort was expanded by 3,011 persons who were of the same age but

had not yet been part of the Rotterdam Study (**RS2**) and recently moved into the area. In 2006-2008 a second expansion (**RS3**) of 3,932 persons aged 45 and over was realized. All participants had DNA extracted at their first visit. Genotyping was attempted in participants with high-quality extracted DNA in 2007-2008. In total, 6,291 samples from the Rotterdam Study I, 2,157 samples from Rotterdam Study II and 3,048 samples from Rotterdam Study III were available with good quality genotyping data. Genotyping was done at the Human Genotyping Facility, Genetic Laboratory Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands. All participants had blood collected during their first center visit, which was followed by DNA extraction.

All-cause and vascular dementia ascertainment.

Participants were screened for dementia at baseline and subsequent centre visits with the Mini-Mental State Examination and the Geriatric Mental Schedule organic level.[66]Those with a Mini-Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly. At each centre visit, all participants also underwent routine cognitive assessment, including a verbal fluency test (animal categories), 15-word learning test, letter-digit substitution task, Stroop test, and Purdue pegboard task. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care. Available information on clinical neuroimaging was used when required for diagnosis of dementia subtype. A consensus panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (DSM-III-R) and Alzheimer's disease (NINCDS–ADRDA). Follow-up until 1st January 2016 was virtually complete (96.3% of potential person-years). Within this period, participants were censored at date of dementia diagnosis, death, loss to follow-up, or 1st January 2016, whichever came first.

Genotyping, quality control, imputation, and association testing.

Genotyping was done in participants with high-quality extracted DNA in 2007-2008 and was performed at the Human Genotyping Facility, Genetic Laboratory Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. Imputation of SNPs was established using

the Michigan Imputation server and the HRC reference panel. More specifically, the SHAPEIT2 software was used (v2.r790) to phase the data and Minimac 3 was employed for imputation to the HRC reference panel (v1.0). QC included deletion of participants with a genotype completion rate (<90%), a low genotype call rate (<95%), sex-mismatches, duplicate pairs (just one participant), uncalled variants in over 5% of the individuals and significant violations of the expected Hardy–Weinberg Equilibrium proportions (P<10−6). The GWAS software used was rvtest. Covariates in the association analyses were age, sex, and PCs (1-5).

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1 – 16. The San Antonio Longitudinal Study of Aging (SALSA)

The San Antonio Longitudinal Study of Aging (SALSA) is a community-based study of the disablement process in older Mexican Americans (MAs) and European Americans (EAs). Detailed descriptions of the sampling design and response rates have been published previously.[67,68] Briefly,

participants were randomly sampled from three types of neighborhoods purposively selected based on census indicators to represent distinct levels of SES and assimilation to the broader society among Mexican Americans: (1) low-income, almost exclusively MA neighborhoods, where a highly traditional MA cultural orientation predominated (barrio); (2) middle income, ethnically balanced neighborhoods, where upwardly mobile MA families had gradually moved in and EA families had moved out (transitional); and (3) high income, predominantly EA neighborhoods, where MAs had largely adopted the cultural orientation of the broader society (suburbs). The SALSA baseline examination was carried out from April 1992 to June 1996 and consisted of a comprehensive home-based assessment, conducted in the participant's home, and a performance-based assessment, conducted at a clinical research center. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and all subjects gave informed consent

1 – 17. HARMONIZATION

Harmonization study is ongoing memory-clinic study, which recruits participants from National University Hospital, Singapore. Four diagnostic categories at baseline were eligible for inclusion in this study:[69] No cognitive impairment (NCI): individuals who had no objective cognitive impairment on neuropsychological tests, or functional loss, Cognitive impairment no dementia (CIND) was diagnosed in patients who were impaired in at least one cognitive domain on a neuropsychological test battery without loss of daily functions. Vascular CIND was defined as a history of ischemic stroke within the past 6–24 months and neuroimaging evidence of cerebral infarction, with objective evidence of neuropsychological deficits.[70] Dementia was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria.

All-cause and vascular dementia ascertainment.

The etiological diagnoses of dementia were based on internationally accepted criteria: Alzheimer's Disease (AD) was diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[50]; Vascular dementia (VaD) was defined using the National Institute of Neurological

Disorders and Stroke and Association Internationale pour la Recherché et l' Enseignement en Neurosciences (NINDS-AIREN) criteria.[51]

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1 – 18. Three-City (3C)

The 3C is a cohort study conducted in three French cities (Bordeaux, Dijon, and Montpellier), comprising 9,294 participants, designed to estimate the risk of dementia and cognitive impairment attributable to vascular factors. Eligibility criteria included living in the city and being registered on the electoral rolls in 1999, 65 years or older, and not institutionalized. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and each participant signed an informed consent.

All-cause and vascular dementia ascertainment.

Diagnosis of dementia was based on a classical three-step procedure. At baseline and each follow-up examination), trained psychologists administered a battery of neuropsychological tests.[1] Second, a neurologist examined all the participants in Bordeaux and Montpellier. In Dijon, due to the large number of participants, only those who screened positive for dementia using the mini-mental state examination (MMSE) and the Isaacs' Set Test (IST), with education-level dependent cutoff points,[71] underwent further clinical examination. The IST is a measure of verbal fluency, and response rapidity, which consists of generating words belonging to given semantic categories (e.g. animal names) in 15 seconds.[72] This test has been reported to show the earliest decline in the decade preceding dementia diagnosis.[73,74] Cut-off scores were defined according to education level as previously described; For participants suspected of having dementia, further data on cognitive functioning and daily activities, severity of cognitive disorders (Clinical Dementia Rating Scale), functional assessment which included assessment of disabilities using the Katz (activities of daily living),[75] Lawton (instrumental activities of daily living)[76] and Rosow and Breslau scales,[72,77] and where possible, hospitalization records, CT scans (which was most often used at the beginning of

the follow-up period),and magnetic resonance images, were collected using a standardized protocol. Then the study neurologist or geriatrician established a provisional diagnosis. At follow-up, all participants with suspected incident dementia (on the basis on their neuropsychological performances or decline relative to a previous examination) were examined by a neurologist in the three study centers. Third, an independent committee of neurologists and geriatricians reviewed all potential prevalent and incident cases of dementia to reach consensus on the diagnosis and etiology, in accordance with the DSM-IV criteria.[72,78] The final diagnosis of dementia was made based on all available information.

Dementia subtyping was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for AD, and on the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) for vascular dementia.[9,10]In our study, probable and possible VaD cases were combined with mixed dementia (AD with vascular contributions) to define the "all VaD" phenotype, whereas 'pure' VaD only considered the probable cases.

Genotyping, quality control and imputation.

Genotyping was conducted at the Centre National de Genotypage (www.cng.fr), Evry, France, using the on Illumina Human610-Quad BeadChips. Genotyping was performed on 4,263 participants, of which 186 were excluded for the following reasons: non-Caucasian ethnicity (N=20), first-degree relatives (N=128), call rate < 0.95, gender inconsistencies and population stratification outliers (with principal component values using EIGENSOFT® > 6 standard deviations from the mean of the corresponding component, N=38). After applying quality control measures (call rates of <98%, MAF <1%, Hardy-Weinberg equilibrium p $<10^{-6}$) 537,029 autosomal genotyped SNPs were available for imputation. Imputation to the HRC r1.1 2016 panel was performed on the Michigan imputation server.

Association testing.

The GWAS was performed under the additive model of genetic inheritance using the Plink v1.90 software. The association tests were performed using logistic regression adjusting for covariates age, sex, city, and PCs 1-4.

Funding.

3C Study is conducted under a partnership agreement among the Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Bordeaux, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education Nationale (MGEN), Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques." Christophe Tzourio and Stéphanie Debette have received investigator-initiated research funding from the French National Research Agency (ANR) and from the Fondation Leducq. We thank Dr. Anne Boland (CNG) for her technical help in preparing the DNA samples for analyses. This work was supported by the National Foundation for Alzheimer's disease and related disorders, the Institut Pasteur de Lille, the labex DISTALZ and the Centre National de Génotypage. S.D. is supported by a grant overseen by the French National Research Agency (ANR) as part of the "Investment for the Future Programme" ANR-18-RHUS-0002, by European Union's Horizon 2020 research and innovation programme under grant agreement No 640643 and 754517.

1 – 19. The UK Biobank (UKBB)

UK Biobank is a large cohort study of more than 500,000 people recruited from across England, Scotland, and Wales. Strengths of UK Biobank include its size, detailed baseline assessment and measurements including biological samples, follow-up assessments for certain issues, and the availability of long-term linkage to outcome data. This has allowed investigators to explore various aspects of multimorbidity including demographic patterns [4], prevalence of disease clusters [8], association with related states such as frailty or sarcopenia [9,10], the impact of lifestyle factors in the context of multimorbidity [11], and associations between multimorbidity and adverse health outcomes [4,12–15]. This study has been conducted using the UK Biobank Resource under Application Number 58341

All-cause and vascular dementia ascertainment.

Although VaD in UKB was defined based on ICD-10 codes (see Table below), we used the family history of dementia GWAS ("imputed dementia") recently published by Marioni et al for ACD.[79] Imputed dementia was defined as individuals >= 65 years reporting a history of dementia in one or both parents. As explained in Ghosh et al. [80] the effect sizes and standard errors of the imputed dementia GWAS were doubled 2 to analytically correct for the use of proxy phenotypes.

Genotyping, quality control and imputation.

Samples were genotyped at the Affymetrix Research Services Laboratory in Santa Clara, California, USA. Upon receipt of a 96-well plate containing 94 UK Biobank samples, Affymetrix added two control individuals (from 1000 Genomes) to the same well positions on each plate: HG00097 to well A12 and HG00264 to well E12. See Affymetrix laboratory process documentation for further details.

Axiom Array plates were processed on the Affymetrix GeneTitan® Multi-Channel (MC) Instrument. Genotypes were then called from the resulting intensities in batches of ~4,700 samples (~4,800 including the controls) using the Affymetrix Power Tools software and the Affymetrix Best Practices Workflow. Supplementary Table S1 shows the number of samples and plates per batch in the interim release (which includes the 11 UK BiLEVE batches and 22 UK Biobank batches, i.e. 11 batches genotyped on the UK BiLEVE Axiom array and 22 batches genotyped on the UK Biobank Axiom array).

Association testing.

The UKB association analyses were performed with linear mixed models (LMM) using the BOLT-LMM [ref] software. BOLT-LMM has the advantage over other methods in that it accounts for cryptic relatedness and population structure and thus, allows the inclusion of related individuals in the models which increase the overall sample size

1 – 20. Accessed GWAS summary statistics

We used the following data representing GWAS summary statistics of Alzheimer's disease performed within the ADGC consortium. These data were selected because the participants included did not overlap with other cohorts.

Traits	**Article**	**PMID**	**GWAS access**
ACD – European – ADGC	Naj et al. 2011	PMID: 21460841	NIAGADS application
ACD – European - UKBB	Marionni et al. 2018	PMID: 29777097	Nature Supplementary Information
ACD – African	Reitz et al 2013	PMID: 23571587	NIAGADS application

Table SI-1: Accessed GWAS summary statistics used in this project

2 - ICD9-10 codes used by cohorts in this project

ICD version	*ICD code*	*ICD description*
All-cause dementia		
ICD-9	290	Dementia
ICD-9	294.1	Dementia with conditions classified elsewhere
ICD-9	294.9	Unspecified dementia with conditions classified elsewhere
ICD-9	331.0	Alzheimer disease
ICD-9	331.1	Pick's disease
ICD-9	331.2	Senile degeneration of brain
ICD-9	331.7	Cerebral degeneration in diseases classified elsewhere
ICD-9	331.8	Other cerebral degeneration
ICD-9	331.9	Cerebral degeneration unspecified
ICD-10	F00	Dementia in Alzheimer disease
ICD-10	F01	Vascular dementia
ICD-10	F02	Dementia with diseases classified elsewhere

ICD-10	F03	Unspecified dementia
ICD-10	F05.1	Delirium in relation to dementia
ICD-10	F06.7	Mild cognitive disorder
ICD-10	G30	Alzheimer disease
ICD-10	G31.0	Localized brain atrophy
ICD-10	G31.1	Senile degeneration of brain, not elsewhere classified
Alzheimer disease (AD)		
ICD-9	331.0	Alzheimer disease
ICD-10	G30	Alzheimer disease
ICD-10	F00	Dementia in Alzheimer disease
Vascular dementia		
ICD-9	290.4	Vascular dementia
ICD-10	F01	Vascular dementia

Table SI-2: ICD9 and ICD10 codes used in this study

3 - Software availability

Gene expression weights for TWAS: http://gusevlab.org/projects/fusion/

HESS/□-HESS: https://huwenboshi.github.io/hess/local_hsqg/

LDSR: https://github.com/bulik/ldsc

GWAS-PW: https://github.com/joepickrell/gwas-pw

Radial-MR: https://github.com/WSpiller/RadialMR

GREP: https://github.com/saorisakaue/GREP

EPIGWAS: https://immunogenomics.hms.harvard.edu/code

Magma.Celltyping: https://github.com/NathanSkene/MAGMA_Celltyping

MR-MEGA: https://www.geenivaramu.ee/en/tools/mr-mega;

4 – Additional Information for EADB

4 – 1. Supplementary list of authors EADB

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