



## ORIGINAL ARTICLE



WILEY

# Genetic comorbidity between major depression and cardio-metabolic traits, stratified by age at onset of major depression

Saskia P. Hagenaars<sup>1,2</sup> | Jonathan R. I. Coleman<sup>1,2</sup> | Shing Wan Choi<sup>1</sup> |  
 H el ena Gaspar<sup>1,2</sup> | Mark J. Adams<sup>3</sup> | David M. Howard<sup>1,3</sup> | Karen Hodgson<sup>1,2</sup> |  
 Matthew Traylor<sup>4</sup> | Tracy M. Air<sup>5</sup> | Till F. M. Andlauer<sup>6,7</sup> | Volker Arolt<sup>8</sup> |  
 Bernhard T. Baune<sup>8,9,10</sup> | Elisabeth B. Binder<sup>6,11</sup> | Douglas H. R. Blackwood<sup>12</sup> |  
 Dorret I. Boomsma<sup>13</sup> | Archie Campbell<sup>12</sup> | Micah Cearns<sup>9</sup> | Darina Czamara<sup>6</sup> |  
 Udo Dannlowski<sup>8</sup> | Katharina Domschke<sup>15,16</sup> | Eco J. C. de Geus<sup>13</sup> |  
 Steven P. Hamilton<sup>17</sup> | Caroline Hayward<sup>12,18</sup> | Ian B. Hickie<sup>19</sup> |  
 Jouke Jan Hottenga<sup>13</sup> | Marcus Ising<sup>14</sup> | Ian Jones<sup>20</sup> | Lisa Jones<sup>21</sup> |  
 Zoltan Kutalik<sup>22,23</sup> | Susanne Lucae<sup>14</sup> | Nicholas G. Martin<sup>24</sup> |  
 Yuri Milaneschi<sup>25</sup> | Bertram Mueller-Myhsok<sup>6,26,27</sup> | Michael J. Owen<sup>20</sup> |  
 Sandosh Padmanabhan<sup>12,28</sup> | Brenda W. J. H. Penninx<sup>25</sup> | Giorgio Pistis<sup>29</sup> |  
 David J. Porteous<sup>12</sup> | Martin Preisig<sup>29</sup> | Stephan Ripke<sup>30,31,32</sup> | Stanley I. Shyn<sup>33</sup> |  
 Patrick F. Sullivan<sup>34,35,36</sup> | John B. Whitfield<sup>24</sup> | Naomi R. Wray<sup>37,38</sup> |  
 Andrew M. McIntosh<sup>3,12,39</sup> | Ian J. Deary<sup>39,40</sup> | Gerome Breen<sup>1,2</sup> |  
 Cathryn M. Lewis<sup>1,2</sup>

<sup>1</sup>Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

<sup>2</sup>NIHR Biomedical Research Centre, South London and Maudsley NHS Trust, London, UK

<sup>3</sup>Division of Psychiatry, University of Edinburgh, Edinburgh, UK

<sup>4</sup>Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London, UK

<sup>5</sup>Discipline of Medicine, University of Adelaide, Adelaide, Australia

<sup>6</sup>Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

<sup>7</sup>Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

<sup>8</sup>Department of Psychiatry, University of M unster, M unster, Germany

<sup>9</sup>Department of Psychiatry, Melbourne Medical School, University of Melbourne, Melbourne, Australia

<sup>10</sup>Florey Institute for Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia

<sup>11</sup>Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

<sup>12</sup>Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

<sup>13</sup>Netherlands Twin Register, Biological Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit, Amsterdam, The Netherlands

<sup>14</sup>Max Planck Institute of Psychiatry, Munich, Germany

<sup>15</sup>Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

<sup>16</sup>Center for NeuroModulation, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Members of Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium and MEGASTROKE consortium are given in Appendix.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

  2020 The Authors. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* published by Wiley Periodicals LLC.

- <sup>17</sup>Department of Psychiatry, Kaiser Permanente Northern California, San Francisco, California
- <sup>18</sup>MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
- <sup>19</sup>Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia
- <sup>20</sup>MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK
- <sup>21</sup>Department of Psychological Medicine, University of Worcester, Worcester, UK
- <sup>22</sup>Center for Primary Care and Public Health, University of Lausanne, Lausanne, Switzerland
- <sup>23</sup>Swiss Institute of Bioinformatics, Lausanne, Switzerland
- <sup>24</sup>Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
- <sup>25</sup>Department of Psychiatry, Amsterdam Public Health and Amsterdam Neuroscience Research Institutes, Amsterdam UMC/Vrije Universiteit, Amsterdam, The Netherlands
- <sup>26</sup>Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
- <sup>27</sup>Department of Health Data Science, Institute of Population Health, University of Liverpool, Liverpool, UK
- <sup>28</sup>Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
- <sup>29</sup>Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
- <sup>30</sup>Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts
- <sup>31</sup>Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, Maryland
- <sup>32</sup>Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts
- <sup>33</sup>Behavioral Health Services, Kaiser Permanente Washington, Seattle, Washington
- <sup>34</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
- <sup>35</sup>Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
- <sup>36</sup>Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
- <sup>37</sup>Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia
- <sup>38</sup>Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
- <sup>39</sup>Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
- <sup>40</sup>Department of Psychology, University of Edinburgh, Edinburgh, UK

#### Correspondence

Cathryn M. Lewis, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, UK.  
Email: cathryn.lewis@kcl.ac.uk

#### Funding information

National Institute for Health Research, Grant/Award Number: Maudsley Biomedical Research Centre; National Institute of Mental Health, Grant/Award Numbers: U01 MH109528, U01 MH1095320; Medical Research Council, Grant/Award Numbers: MR/S0151132, MR/N015746/1; European Union

#### Abstract

It is imperative to understand the specific and shared etiologies of major depression and cardio-metabolic disease, as both traits are frequently comorbid and each represents a major burden to society. This study examined whether there is a genetic association between major depression and cardio-metabolic traits and if this association is stratified by age at onset for major depression. Polygenic risk scores analysis and linkage disequilibrium score regression was performed to examine whether differences in shared genetic etiology exist between depression case control status ( $N$  cases = 40,940,  $N$  controls = 67,532), earlier ( $N$  = 15,844), and later onset depression ( $N$  = 15,800) with body mass index, coronary artery disease, stroke, and type 2 diabetes in 11 data sets from the Psychiatric Genomics Consortium, Generation Scotland, and UK Biobank. All cardio-metabolic polygenic risk scores were associated with depression status. Significant genetic correlations were found between depression and body mass index, coronary artery disease, and type 2 diabetes. Higher polygenic risk for body mass index, coronary artery disease, and type 2 diabetes was associated with both early and later onset depression, while higher polygenic risk for stroke was associated with later onset depression only. Significant genetic correlations were found between body mass index and later onset depression, and between coronary artery disease and both early and late onset depression. The phenotypic associations between major depression and cardio-metabolic traits may partly reflect their overlapping genetic etiology irrespective of the age depression first presents.

## KEYWORDS

age at onset, cardio-metabolic disease, depression, genetics, polygenic risk scores

## 1 | INTRODUCTION

Major depressive disorder (MDD) and cardio-metabolic traits are both major causes of morbidity and mortality in high-income countries. Epidemiological studies have shown a well-established association between them (B. W. J. H. Penninx, 2017): MDD increases the risk of cardio-metabolic disease onset and mortality, but cardio-metabolic disease itself can also increase risk of developing MDD. Specifically, a meta-analysis of 124,509 individuals across 21 studies showed that depression is associated with an 80% increased risk for developing coronary artery disease (Nicholson, Kuper, & Hemingway, 2006). Mezuk et al (Mezuk, Eaton, Albrecht, & Golden, 2008) showed that MDD predicted a 60% increased risk of type 2 diabetes, while type 2 diabetes predicted a 15% increased risk in MDD. MDD is associated with an increased risk of developing stroke (HR 1.45) (Pan, Sun, Okereke, Rexrode, & Hu, 2011), but meta-analyses have also shown that ~30% of stroke survivors suffered from MDD (Ayerbe, Ayis, Wolfe, & Rudd, 2013; Hackett & Pickles, 2014). Risk factors for cardio-metabolic disease, such as obesity, are also linked to depression. Milaneschi et al. (Milaneschi, Simmons, van Rossum, & Penninx, 2018) showed a bidirectional association between depression and obesity, where obesity increases risk for depression and depression increases risk for subsequent obesity. A more detailed review of the comorbidity between depression and cardio-metabolic traits is given in B. W. Penninx, Milaneschi, Lamers, and Vogelzangs (2013).

Multiple mechanisms have been proposed to explain the association between MDD and cardio-metabolic diseases, for example biological dysregulation, or an unhealthy lifestyle (B. W. J. H. Penninx, 2017). However, it remains unclear to what extent these mechanisms influence the association, as most studies examining the mechanisms were based on epidemiological observational study designs. The association between MDD and cardio-metabolic disease could also be due to shared genetic factors. Twin studies have shown that genetic factors contribute ~40% of the variation in liability to both MDD (Sullivan, Neale, & Kendler, 2000) and coronary artery disease (Polderman et al., 2015; Schunkert et al., 2011), 72% to type 2 diabetes (Willemsen et al., 2015), and 40–70% to BMI (Locke et al., 2015). No twin heritability estimates are available for stroke, as such studies have very limited numbers of twins. The most recent published GWAS for major depression, including 246,363 cases and 561,190 controls, identified 102 loci that were significantly associated with major depression, highlighting the highly polygenic nature of major depression (Howard et al., 2019). The heritability for major depression based on single nucleotide polymorphisms ( $h^2_{\text{SNP}}$ ) was estimated to be 8.9% on the liability scale, based on a lifetime risk of 0.15. Similarly, recent efforts to identify common variants associated with cardio-metabolic disease have shown these traits to be highly polygenic (Malik et al., 2018; Nikpay et al., 2015; Scott et al., 2017; Yengo et al., 2018).

Several studies have shown genetic overlap between MDD and cardio-metabolic traits, in particular with coronary artery disease (Wray et al., 2018). Findings for other cardio-metabolic traits have been inconsistent. Previous studies have identified genetic overlap between MDD and BMI using polygenic risk scores (PRS) (Milaneschi et al., 2017), but not based on genetic correlations (Wong et al., 2018). However, more recent GWAS studies now have the power to detect a genetic correlation between MDD and BMI (Wray et al., 2018). Studies using twin data also showed that the phenotypic association between MDD and type 2 diabetes was partly due to genetic effects (Kan et al., 2016). This finding has been replicated using a polygenic risk score approach (Wong et al., 2019), but not using genetic correlations (Clarke et al., 2016; Wong et al., 2019). The Brainstorm Consortium did not find a significant genetic correlation between MDD and stroke (Anttila et al., 2018), while Wassentheil-Smoller et al (Wassentheil-Smoller et al., 2018) showed that higher polygenic risk for MDD was associated with increased risk for stroke, in particular small vessel disease.

The inconsistency in results is likely due to differences in methodological approaches or in summary statistics, but could also be due to the heterogeneity of MDD. MDD onset can occur at any stage of life, but the factors associated with MDD are often age specific or age restricted (Power et al., 2017). Increased genetic risk for major depression is associated with earlier age at onset (AAO) compared with later AAO (Wray et al., 2018). Earlier AAO MDD has a higher heritability and is associated with increased risk for MDD in relatives. On the other hand, vascular disease and its risk factors are linked to a later AAO for MDD (G. S. Alexopoulos et al., 1997; Naismith, Norrie, Mowszowski, & Hickie, 2012; Taylor, Aizenstein, & Alexopoulos, 2013). A large study of Swedish twins showed that a later AAO for MDD in one twin was associated with a higher risk for vascular disease in the other twin (Kendler, Fiske, Gardner, & Gatz, 2009). To date, no molecular genetic studies have examined the association between late onset MDD and cardio-metabolic traits and in the current study we have more power to replicate and further investigate this association leveraging both summary statistics and common genetic variant information.

The main aim of the present study is to examine the genetic association between MDD and cardio-metabolic traits using PRS and genetic correlations. Secondly, we will examine the association stratified by AAO for MDD to test whether a higher genetic predisposition for cardio-metabolic traits is associated with a later AAO for MDD.

## 2 | METHODS AND MATERIALS

### 2.1 | Samples

This study was performed using data from the Psychiatric Genomics Consortium (PGC) MDD working group (PGC-MDD), Generation

Scotland: The Scottish Family Health Study (GS:SFHS), and UK Biobank.

### 2.1.1 | PGC

Full details of the studies that form the PGC-MDD have previously been published (Wray et al., 2018). In summary, a subset of 11 studies from the full PGC-MDD analysis were included in the current study, based on the availability of AAO for MDD. All cases were required to have a lifetime diagnosis of MDD based on international consensus criteria (DSM-IV, ICD-9, or ICD-10) (American Psychiatric Association, 1994; World Health Organization, 1978, 1992). This was ascertained using structured diagnostic instruments from direct interview by trained interviewers or clinician administered checklists. In most studies (10/11), controls were randomly selected from the general population and were screened for absence of lifetime MDD. This led to a total of 9,518 cases and 11,557 controls with genotype data and AAO information.

### 2.1.2 | GS:SFHS

GS:SFHS is a family-based study consisting of 23,690 participants recruited from the population via general medical practices across Scotland. Sample characteristics and recruitment protocols have been described elsewhere (B. H. Smith et al., 2013; Smith et al., 2006). In summary, MDD diagnosis was based on the structured clinical interview for DSM-IV disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1997). Participants who answered positively to two mental health screening questions were invited to complete the full SCID to ascertain MDD diagnosis. Cases were further refined through NHS linkage. Controls were defined as participants who answered negatively to the two screening questions or participants who did not complete the SCID but did not meet criteria for MDD. This resulted in 1947 cases and 4,858 controls, based on unrelated individuals.

### 2.1.3 | UK Biobank

UK Biobank is a large resource for identifying determinants of diseases in middle aged and older healthy individuals ([www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk)) (Sudlow et al., 2015). A total 502,655 community-dwelling participants aged between 37 and 73 years were recruited between 2006 and 2010 in the United Kingdom, and underwent extensive testing including mental health assessments. MDD status in UK Biobank was derived from the online mental health questionnaire as previously described (Coleman et al., 2020; Davis et al., 2018). Briefly, MDD cases were defined as individuals meeting lifetime criteria for MDD based on questions from the Composite International Diagnostic Interview. Individuals reporting previous self-reported diagnosis of schizophrenia (or other psychosis) or bipolar disorder were excluded as MDD cases. Controls were defined as individuals who did not have any self-reported diagnosis of mental illness, did not take any anti-

depressant medications, had not previously been hospitalized with a mood disorder, and did not meet previously defined criteria for a mood disorder (D. J. Smith et al., 2013). For the current study, this led to 29,475 cases and 51,243 controls.

## 2.2 | AAO

AAO was defined as follows, based on previous work by Power et al (Power et al., 2017) developed to account for the substantial by-study heterogeneity in the measure. Heterogeneity in AAO within the PGC MDD cohorts has been extensively investigated. Responses depend on the specific setting in which AAO is asked, and may reflect age at first symptoms, first visit to general practitioner or first diagnosis) (Power et al., 2017). Using cut offs for AAO (e.g., onset under 30) does not capture the variance in this measure, and we therefore followed Power et al. (Power et al., 2017) to use the within study distribution to define early and later onset depression. This approach assumes that all cases were recruited from the same age at onset distribution with differences due to study-specific parameters. Cases reporting AAO older than the recorded age at interview were excluded from each study. Within each study, cases were ordered by AAO and divided into equal octiles (O1–O8). The first three octiles (O1–O3) were combined into the early AAO group, the last three octiles (O6–O8) into the late AAO group. Splitting into equal octiles can result in individuals with the same AAO being arbitrarily placed in different octiles. To address this, cases in O4 with the same AAO as the maximum AAO in O3 were assigned to the early AAO group. Similarly, cases in O5 with the same AAO as the minimum AAO in O6 were assigned to the late AAO group. This led to a total of 15,844 MDD cases with early AAO and 15,800 MDD cases with late AAO, and 67,532 controls.

## 2.3 | Genotyping and quality control

Genotyping procedures have been described in the original analysis for each study (Bycroft et al., 2018; Nagy et al., 2017; Wray et al., 2018). All analysis were based on individuals from European ancestry only.

PGC cohorts were genotyped following their local protocols. Individual genotype data for all PGC cohorts was processed using the PGC "RicoPili" pipeline for standardized quality control, imputation and analysis (<https://github.com/Nealelab/ricopili>) (Lam et al., 2019). Further details on the default parameters used for the current study can be found in the Supplementary material.

For GS:SFHS, genotyping and imputation procedures have previously been published by Nagy et al (Nagy et al., 2017), a brief summary can be found in the Supplementary Material. Monogenic variants and variants with low imputation quality (INFO <0.4) were removed.

Two highly-overlapping custom genotyping arrays (UK BiLEVE Axiom array and UK Biobank Axiom array, ~800,000 markers) were used to genotype all UK Biobank participants ( $N = 487,410$ ) (Bycroft et al., 2018). Detailed QC procedures are described in the Supplementary Material.

## 2.4 | Statistical analysis

### 2.4.1 | PRS

Six PRS were calculated based on GWAS summary statistics for body mass index (BMI), coronary artery disease (CAD) (Nikpay et al., 2015), stroke and two stroke subtypes (Malik et al., 2018), and type 2 diabetes (T2D) (Scott et al., 2017) based on external GWAS  $p$ -value  $<0.5$ . In order to lower the multiple testing burden a  $p$ -value threshold of 0.5 was chosen, as often representative of the predictive ability, since  $R^2$  values often plateau across the range of  $p$ -values = .05–1. Table 1 provides further detail on the GWAS summary statistics.

PRS were calculated in all genotyped participants in each study using PRSice v2 (<https://github.com/choishingwan/PRSice>) (Euesden, Lewis, & O'Reilly, 2015). Prior to creating the scores, clumping was used to obtain SNPs in linkage disequilibrium with an  $r^2 < 0.25$  within a 250 kb window. Due to the large number of overlapping samples between published BMI GWAS (Locke et al., 2015) and the PGC studies, a new GWAS was performed in the UK Biobank. The analysis used BGENIE v1.2 (Bycroft et al., 2018) on 291,684 individuals in UK Biobank that did not complete the Mental Health Questionnaire and were therefore independent of prediction samples, as MDD case control status was defined from the Mental Health Questionnaire. The Manhattan and QQ plot of the BMI GWAS can be found in the Supplementary Figure 2.

Logistic regression was used to test the associations between the six PRS and four different MDD case–control sets (all MDD cases vs. control subjects, early AAO cases vs. control subjects, late AAO cases vs. control subjects, and late AAO cases vs. early AAO cases). These analyses test our two hypotheses; (a) testing the association of genetic risk for cardiometabolic traits with MDD, and whether this association differs by AAO by comparing controls and MDD cases (all MDD cases vs. control subjects, early AAO cases vs. control subjects, late AAO cases vs. control subjects), and (b) testing the association of genetic risk for cardiometabolic traits with MDD AAO itself, by comparing late AAO cases vs. early AAO cases only. Analyses were performed separately for each study, adjusting for relevant covariates in each study (PGC & GS:SFHS: 5 genetic principal components for population stratification; UK Biobank: 6 genetic principal components for population stratification, assessment center, and genotyping batch). All PRS were standardized with each study across samples. Meta-

analyses of the results across studies for each PRS–MDD subtype combination were then conducted to synthesize the findings for maximum statistical power and to check for heterogeneity. Fixed-effects models were used in which the standardized regression coefficients were weighted by the inverse of their squared SE. We tested for the presence of between-study heterogeneity using Cochran's Q. We corrected for multiple testing across all 24 meta-analysis models (4 phenotypes  $\times$  6 PRS) using the Benjamini Hochberg false discovery rate method (Benjamini & Hochberg, 1995), using a critical  $p$ -value of .0026, which means that all  $p$ -values equal to or below the critical  $p$ -value are considered significant.

### 2.4.2 | GWAS meta-analysis and genetic correlations

Genome wide association analyses for three AAO-stratified MDD case–control subsets were performed within each study, with adjustments for population stratification. Study-specific covariates—for example, site or familial relationships—were also fitted as required (see Supplementary Material). The GWAS for GS:SFHS included all individuals (compared with unrelated individuals in the PRS analysis) to maximize power. Quality control of the study-level summary statistics was performed using the EasyQC software (Winkler et al., 2014), which implemented the exclusion of SNPs with imputation quality  $<0.8$  and minor allele count  $<25$ .  $p$ -value based meta-analyses, with genomic control, were then performed for each of the three outcome measures, using the METAL package (Willer, Li, & Abecasis, 2010). SNPs with a combined sample size of less than 1,000 participants were excluded.

Genetic correlations between the cardio-metabolic traits and the four MDD summary statistics were calculated using Linkage Disequilibrium score regression (LDSC) (B. K. Bulik-Sullivan et al., 2015) using the default HapMap LD reference. To maximize power (and given genetic correlation analyses in LDSC are robust to sample overlap), the largest available summary statistics were used. These included the previously described summary statistics for coronary artery disease (Nikpay et al., 2015), stroke (Malik et al., 2018), and type 2 diabetes (Scott et al., 2017), as well as summary statistics for major depression from the PGC-MDD and 23andMe GWAS, including UK Biobank (Wray et al., 2018), and the most recent BMI GWAS, including both UK

**TABLE 1** Information about GWAS summary statistics, based on European individuals only, to create polygenic risk scores in PGC-MDD, GS:SFHS, and UK Biobank

Trait	Origin	N cases/N controls	SNPs with $p$ -value $<5 \times 10^{-8}$
Body mass index	UK Biobank	291,683 individuals	27,164
Coronary artery disease	CARDIoGRAM (Nikpay et al., 2015)	60,801 cases–123,504 controls	2,213
Stroke: All	MEGASTROKE (Malik et al., 2018)	40,585 cases–406,111 controls	371
Stroke: Ischaemic	MEGASTROKE (Malik et al., 2018)	34,217 cases–406,111 controls	307
Stroke: Small vessel disease	MEGASTROKE (Malik et al., 2018)	5,386 cases–406,111 controls	0
Type 2 diabetes	DIAGRAM (Scott et al., 2017)	26,676 cases–132,532 controls	1,788



Biobank and the GIANT consortium (Yengo et al., 2018). All results were corrected for multiple testing using the Benjamini Hochberg false discovery rate method (critical  $p$ -value = .0064). Differences between genetic correlations were assessed using block-jackknife (Supplementary Material) (B. Bulik-Sullivan et al., 2015; Quenouille, 1956; Tukey, 1958).

### 3 | RESULTS

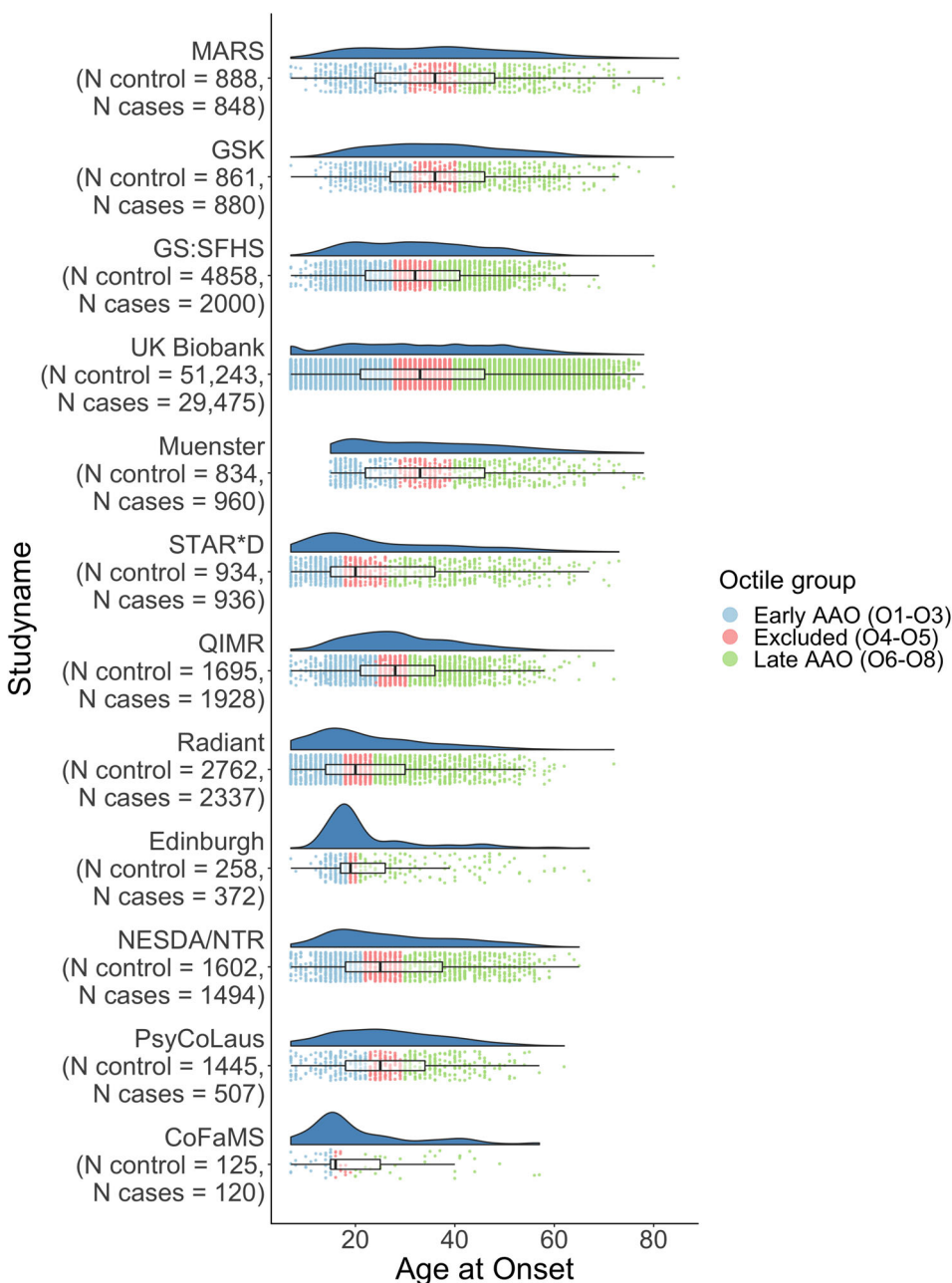
#### 3.1 | Summary of AAO

The total sample consisted of 40,940 cases, including 15,844 cases classified as early AAO, 15,800 cases as late AAO, 6296 general cases not included in AAO-specific analysis, and 67,532 controls. The mean

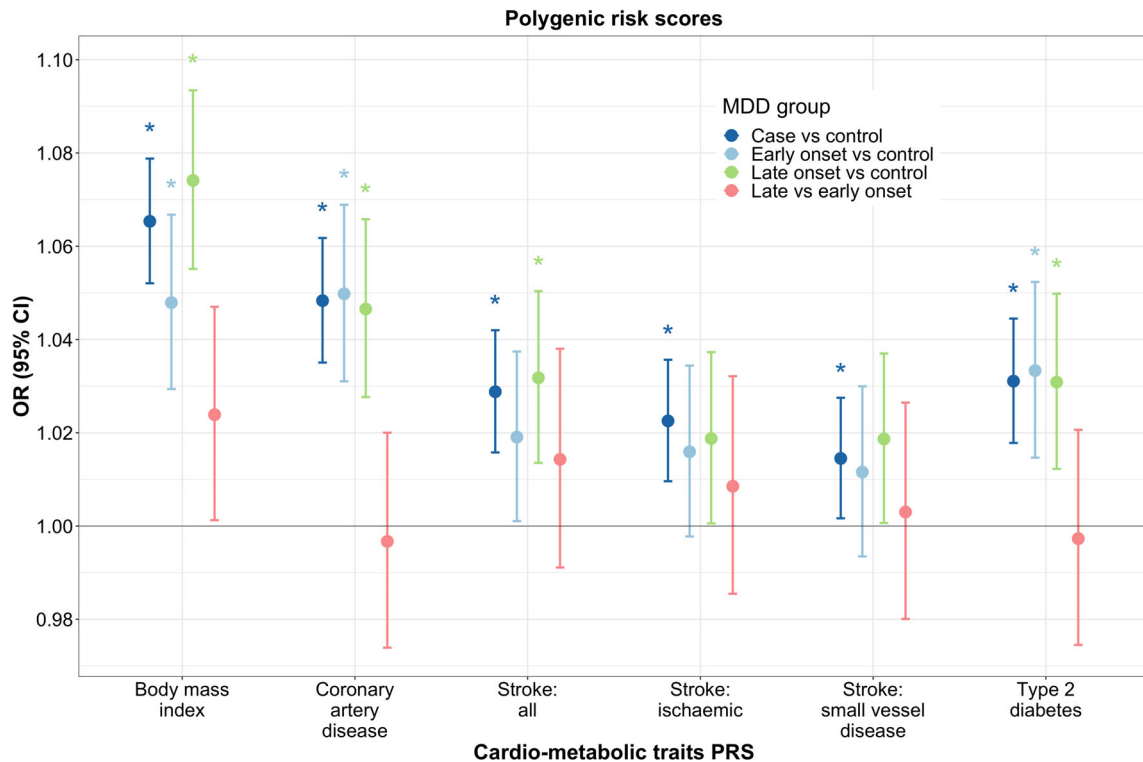
AAO (SD) across samples was 32.36 (15.22) years. The mean AAO per study ranged from 21.22 to 37.23 years, with the German PGC-MDD samples, GS:SFHS and UK Biobank having a higher mean AAO (Table S1). Figure 1 shows the distribution of AAO and the stratification in the early and late AAO groups in each of the studies. Figure S1 shows the cumulative distribution of AAO in each study.

#### 3.2 | Polygenic risk analysis of cardio-metabolic disease

The meta-analyses across studies showed that PRS for BMI, coronary artery disease, all stroke, ischaemic stroke, small vessel disease, and type 2 diabetes were significantly associated with MDD case control



**FIGURE 1** Distribution of Age at onset for MDD per sample. Scatterplot represents the stratification of the early and late AAO groups within each sample [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 2** Meta-analysis of associations between cardio-metabolic PRS and stratified MDD outcomes. OR, Odds Ratio; 95% CI, 95% confidence interval; PRS, polygenic risk score, \* $p$ -value  $< .0264$  [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

status (Figure 2, Table S2). Study specific results can be found in Table S3.

When stratifying by AAO and comparing with controls, higher PRS for BMI was more strongly associated with late AAO (OR = 1.07, 95% CI = 1.06–1.09,  $p = 4.10 \times 10^{-15}$ ) than early AAO (OR = 1.05, 95% CI = 1.03–1.07,  $p = 2.60 \times 10^{-7}$ ), however, the difference between them was not significant (Figure 2). No significant difference was found between BMI PRS and late versus early AAO within MDD cases (OR = 1.02, 95% CI = 1.00–1.05,  $p = .04$ ). Higher PRS for CAD was associated with both late (OR = 1.05, 95% CI = 1.03–1.07,  $p = 8.66 \times 10^{-7}$ ) and early AAO (OR = 1.05, 95% CI = 1.03–1.07,  $p = 1.50 \times 10^{-7}$ ) compared with controls, while no significant difference was found between late and early AAO in MDD cases only (OR = 1.00, 95% CI = 0.97–1.02,  $p = .776$ ). Higher PRS for all stroke was only associated with late AAO compared with controls (OR = 1.03, 95% CI = 1.01–1.05,  $p = .0006$ ). Higher PRS for type 2 diabetes was associated with both late (OR = 1.03, 95% CI = 1.01–1.05,  $p = .001$ ) and early (OR = 1.03, 95% CI = 1.01–1.05,  $p = .0004$ ) AAO compared with controls, the association between late and early AAO in MDD cases only was nonsignificant (OR = 1.00, 95% CI = 0.97–1.02,  $p = .82$ ).

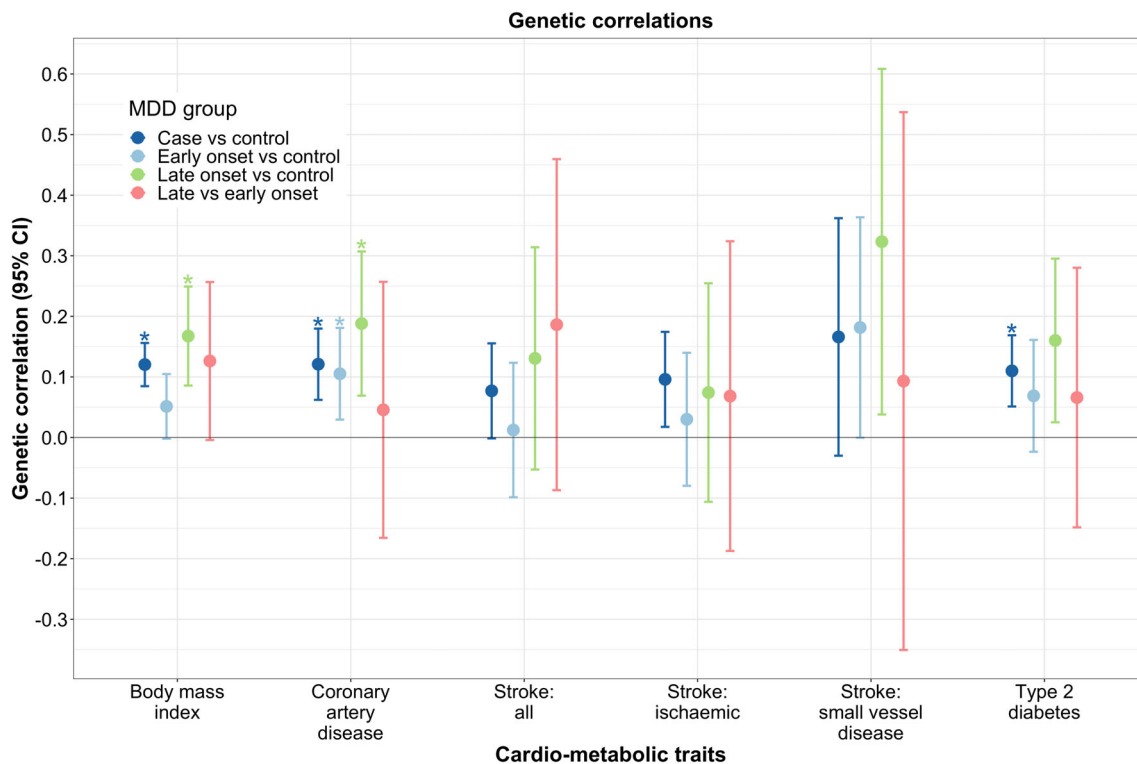
### 3.3 | Genetic correlations with cardio-metabolic traits

Genetic correlations were calculated between MDD and cardio-metabolic traits based on the largest available GWAS (Figure 3,

Table S4). Significant genetic correlations were identified between MDD and BMI ( $r_g = 0.13$ ,  $SE = 0.02$ ,  $p = 3.43 \times 10^{-11}$ ), coronary artery disease ( $r_g = 0.12$ ,  $SE = 0.03$ ,  $p = 8.47 \times 10^{-6}$ ), and type 2 diabetes ( $r_g = 0.11$ ,  $SE = 0.03$ ,  $p = .0001$ ). The genetic correlation between ischaemic stroke and MDD was 0.10 ( $SE = 0.04$ ,  $p = .026$ ), however this correlation did not survive the correction for multiple testing ( $p < .0064$ ). No significant genetic correlations were identified for all stroke and small vessel disease.

In order to calculate genetic correlations between the AAO stratified MDD traits and cardio-metabolic traits, we ran GWAS on the AAO stratified traits. Figure S3–S5 shows the Manhattan and QQ plots for these traits. Table S4 provides further detail on the heritability estimates of the stratified MDD traits. One genome-wide significant variant was identified in the GWAS for early AAO versus controls (rs2789313 on chromosome 10, Z-score = 5.56,  $p = 2.74 \times 10^{-8}$ ). This variant is located in the *MALRD1* gene, which is involved in hepatic bile acid metabolism and lipid homeostasis (Vergnes, Lee, Chin, Auwerx, & Reue, 2013). This gene has not previously been associated with depression. Figure S3 shows a locus zoom plot of the region on chromosome 10 including rs2789313. Tables S5–S7 provide summary statistics on all suggestive ( $p < 1 \times 10^{-5}$ ) variants for the stratified GWAS.

The results for the stratified AAO traits showed a significant genetic correlation between BMI and late AAO versus controls ( $r_g = 0.19$ ,  $SE = 0.04$ ,  $p = 2.42 \times 10^{-5}$ ), no significant genetic correlations were identified for either early AAO versus controls ( $r_g = 0.05$ ,  $SE = 0.03$ ,  $p = .059$ ) or late versus early AAO ( $r_g = 0.11$ ,  $SE = 0.05$ ,



**FIGURE 3** Genetic correlations (SE), derived using LD score regression, between cardio-metabolic traits and stratified MDD outcomes. \* $p$ -value  $< .0064$  [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

$p = .037$ ). A stronger genetic correlation was found between late AAO and CAD ( $r_g = 0.19$ ,  $SE = 0.06$ ,  $p = .002$ ) compared with early AAO and CAD ( $r_g = 0.11$ ,  $SE = 0.04$ ,  $p = .006$ ), however, the difference between the two genetic correlations was nonsignificant (block jackknife test for comparison of  $r_g$ ,  $p = .227$ ). No significant genetic correlations were found between any of the AAO stratified MDD outcomes and all stroke, ischaemic stroke, small vessel disease, or type 2 diabetes (Figure 3, Table S4).

## 4 | DISCUSSION

This study explored whether the association between MDD and cardio-metabolic traits is partly due to genetic factors. Using data from publicly available GWAS and from the PGC, UK Biobank, and Generation Scotland, we showed significant genetic overlap between MDD and BMI, coronary artery disease, and type 2 diabetes from PRS and genetic correlations.

Coronary artery disease and type 2 diabetes showed similar patterns of association. Both were associated with MDD in general and with late and early AAO, however, the association with late versus early AAO was null. This indicates that both traits are associated with MDD irrespective of the AAO, and not associated with AAO itself. The current study is based on an extension of the strategies applied by Power et al. (Power et al., 2017), who showed significant associations between polygenic risk for coronary artery disease and MDD, as well as with early and late onset MDD compared with controls. The results in the

current study are based on a larger sample and more recent effect estimates for coronary artery disease, and have therefore greater power to detect an effect. A recent study by Khandaker et al. (2019) did not find a significant association between depression and coronary artery disease polygenic risk in UK Biobank. The effect sizes were similar to our study, but the depression phenotype was based on the definition as described by D. J. Smith, Nicholl, et al. (2013), and has lower heritability than the Mental Health Questionnaire phenotype used here (Cai et al., 2020; D. J. Smith, Nicholl, et al., 2013). This difference in results is likely due to power: based on the heritability, sample size, and disease prevalence, our study has 60% power to detect an association between depression and coronary artery disease, compared with 18% in Khandaker et al. (2019) (Dudbridge, 2013).

This is the first study to show genetic overlap between MDD and type 2 diabetes using both PRS and genetic correlations. Twin studies have previously shown genetic overlap between MDD and type 2 diabetes, but evidence from genetic studies has been weaker. The current study, however, does show evidence for a shared genetic etiology between MDD and type 2 diabetes based on both PRS and genetic correlations (Clarke et al., 2016; Kan et al., 2016; Wong et al., 2019).

The polygenic risk score analysis showed that individuals with a stronger genetic liability for stroke (and its subtypes) were more likely to suffer from MDD. Clinical and neuroimaging studies have shown that stroke could predispose the development of MDD by disrupting frontostriatal circuits in the brain involved in mood regulation (George S. Alexopoulos, 2017; Herrmann, Le Masurier, & Ebmeier, 2008; van Sloten et al., 2015), specifically in older individuals with MDD or those



with a later AAO for MDD. We did not find a significant association between genetic risk for stroke and AAO. This could be due to a lack of power, as the stroke outcomes had low heritability estimates (observed  $h^2 \sim 1\%$ , Table S4B) and the sample size of the stratified MDD outcomes is smaller than the overall MDD case-control comparison.

When stratifying by AAO, higher polygenic risk for BMI was more strongly associated with late AAO than early AAO compared with controls, while a significant genetic correlation was only found between late AAO versus control and BMI. A causal association using Mendelian randomization has previously been identified between BMI and depression, showing a 1.12 fold increase in depression for each SD increase in BMI (Wray et al., 2018). Similarly, Vogelzangs et al (Vogelzangs et al., 2010) have shown that over a 5 year period both overall and abdominal obesity were associated with an increased risk for MDD onset in men. Although the differences observed in this study are not significant following multiple testing correction, in the context of previous findings, they tentatively suggest that the etiological processes underlying later onset MDD are linked to vascular pathology and its risk factors such as obesity.

LD score regression produced fewer significant associations than the polygenic risk score analysis. Genetic correlations using LD score regression are based on summary statistics only and could therefore be less powerful than a polygenic risk score approach based on raw genotype data. However, the direction of effect was the same across both analysis approaches and significant genetic correlations were corroborated by significant polygenic risk score associations.

The current study has a number of limitations. The measures for AAO for MDD rely on self-report and are assessed differently across cohorts. We addressed this by stratifying AAO into octiles relative to the mean in each study, therefore assuming that each study recruited AAO from the same distribution with differences between studies due to differences in ascertainment measure. It should be noted that the mean AAO for late onset cases was 47.85 years, which is below what is generally considered to be late onset or geriatric depression (onset >60 years). More pronounced overlap might exist between late onset MDD and cardio-metabolic traits when focusing on cases with a later AAO, however this study only had a small number of these included. However, this study does show that the effect of genetic risk for somatic conditions on depression is not limited to late onset or geriatric depression. By standardizing the PRS in all models we have possibly introduced bias into our results. When the sample prevalence of a trait is not equal to the population prevalence, the mean of the PRS will not represent the mean of the PRS in the population, and thus introducing bias which could lead to inflated effect estimates.

Future studies could focus on the effects of medication or disease status for the cardio-metabolic traits, as the current study was unable to adjust for this due to lack of information on these variables. Pathway analysis might provide further insight into the biology underlying the association between cardio-metabolic traits and MDD. In order to further dissect the comorbidity between MDD and cardio-metabolic disease, it is imperative to have cleaner phenotypes, in particular with

regard to AAO. Biobanks with electronic health records might aid in providing improved phenotyping, but this still does not provide the same information as one gets from clinical research studies.

In summary, this study showed genetic overlap between MDD and cardio-metabolic traits based on PRS and genetic correlations. These associations were largely irrespective of AAO for MDD, in particular for coronary artery disease and type 2 diabetes. The association with BMI showed some evidence for a stronger link with later onset MDD, however this finding needs to be replicated. Cardio-metabolic traits and its risk factors are to open to preventative strategies, therefore further understanding of the shared genetic etiology between cardio-metabolic traits and MDD could play an important role in the prevention or management of MDD.

#### AUTHOR CONTRIBUTIONS

Saskia P. Hagenaars, Cathryn M. Lewis designed the study, analyzed data, and interpreted the results. Jonathan R. I. Coleman, Shing Wan Choi, H el ena Gaspar, Mark J. Adams, David Howard, Karen Hodgson, Matthew Traylor contributed to data quality control and analysis pipelines. All other authors contributed study materials. All authors critically revised the manuscript and approved the final version.

#### ACKNOWLEDGMENTS

S. P. H. is funded by the Medical Research Council (MR/S0151132). CML is funding by the Medical Research Council (N015746/1). This study presents independent research supported by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. We thank participants and scientists involved in making the UK Biobank resource available (<http://www.ukbiobank.ac.uk/>). UK Biobank data used in this study were obtained under approved application 16577. We are deeply indebted to the investigators who comprise the PGC, and to the hundreds of thousands of subjects who have shared their life experiences with PGC investigators. The PGC has received major funding from the US National Institute of Mental Health and the US National Institute of Drug Abuse (U01 MH109528 and U01 MH1095320). Statistical analyses were carried out on the NL Genetic Cluster Computer (<http://www.geneticcluster.org/>) hosted by SURFsara, and the King's Health Partners High Performance Compute Cluster funded with capital equipment grants from the GSTT Charity (TR130505) and Maudsley Charity (980). We would like to thank the research participants and employees of 23andMe for making this work possible. Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates [CZD/16/6] and the Scottish Funding Council [HR03006]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "Stratifying Resilience and Depression Longitudinally" [STRADL] Reference 104036/Z/14/Z). Ethics approval for the Generation Scotland

was given by the NHS Tayside committee on research ethics (reference 15/ES/0040), and all participants provided written informed consent for the use of their data. The MEGASTROKE project received funding from sources specified at <http://www.megastroke.org/acknowledgments.html>. CM Lewis is a member of Myriad Neuroscience SAB. PF Sullivan is on the scientific advisory board for Pfizer, Inc., and the advisory committee for Lundbeck. All other authors reported no biomedical financial interest or potential conflicts of

interest. The table below lists the funding that supported the primary studies analyzed in this article. In addition, PGC investigators received personal funding from the following sources. NR Wray award 1078901, 1087889, and 1113400, NHMRC, Australia. DI Boomsma award PAH/6635, KNAW Academy Professor Award, Netherlands. PF Sullivan award D0886501, Vetenskapsrådet, Sweden. AM McIntosh award 602450, European Union, UK; award BADiPS, NC3Rs, UK. C Hayward, Core funding, Medical Research Council, UK.

Study	Lead investigator	Award number	Funder	Country
PGC	PF Sullivan	U01 MH109528	NIMH	USA
PGC	A Agrawal	U01 MH109532	NIDA	USA
PGC	D Posthuma	480-05-003	Netherlands scientific organization	Netherlands
PGC	D Posthuma	-	Dutch Brain Foundation and the VU University Amsterdam	Netherlands
CoFaMS - Adelaide	BT Baune	APP1060524	NHMRC	Australia
Generation Scotland	AM McIntosh	104036/Z/14/Z	Wellcome Trust	UK
Münster MDD cohort	BT Baune	N Health-F2-2008-222963	European Union	Germany
Münster MDD cohort	TG Schulze	01ZX1314K	BMBF Integument	Germany
Münster MDD cohort	TG Schulze		Dr. Lisa Oehler foundation	Germany
Münster MDD cohort	TG Schulze	SCHU 1603/5-1	German Research Foundation (DFG)	Germany
Münster MDD cohort	U Dannowski	FOR2107 DA1151/5-1; SFB- TRR58, Project C09	German Research Foundation (DFG)	Germany
Münster MDD cohort	U Dannowski	Dan3/012/17	Interdisciplinary Center for Clinical Research, Medical Faculty of University of Münster	Germany
Münster MDD cohort	V Arolt	N Health-F2-2008-222,963	European Union	Germany
NESDA	BWJH Penninx	ZonMW Geestkracht grant	N.W.O.	Netherlands
NESDA	BJWH Penninx	1RC2 MH089951; 1RC2 MH089995	NIH	USA
NTR	DI Boomsma	1RC2 MH089951; 1RC2 MH089995	NIH	Netherlands
PsyColaus	M Preisig	3200B0-105993, 3200B0-118308, 33CS0-122661, 33CS30-139468, 33CS30-148401	Swiss National Science Foundation	Switzerland
QIMR	NG Martin	941177, 971232, 3399450 and 443011	National Health and Medical Research Council	Australia
QIMR	AC Heath	AA07535, AA07728, and AA10249	NIAAA	USA
RADIANT	C Lewis, G Breen	G0701420	MRC	UK
RADIANT	G Breen	G0901245	MRC	UK
RADIANT	G Breen	U01 MH109528	NIMH	UK
STAR*D	SP Hamilton	R01 MH-072802	NIMH	USA
UK Biobank	G Breen		NIHR	UK

## ORCID

Saskia P. Hagenaars <https://orcid.org/0000-0001-9697-8596>  
 Jonathan R. I. Coleman <https://orcid.org/0000-0002-6759-0944>  
 Till F. M. Andlauer <https://orcid.org/0000-0002-2917-5889>  
 Darina Czamara <https://orcid.org/0000-0001-7381-904X>  
 Nicholas G. Martin <https://orcid.org/0000-0003-4069-8020>  
 Naomi R. Wray <https://orcid.org/0000-0001-7421-3357>

## REFERENCES

- Alexopoulos, G. S. (2017). Depression and cerebrovascular disease: What is to be done? *The American Journal of Geriatric Psychiatry*, 25(2), 129–130. <https://doi.org/10.1016/j.jagp.2016.11.013>
- Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). Vascular depression hypothesis. *Archives of General Psychiatry*, 54(10), 915–922.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders*. Washington DC: American Psychiatric Association.
- Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., ... Neale, B. M. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, 360(6395), eaap8757. <https://doi.org/10.1126/science.aap8757>
- Ayerbe, L., Ayis, S., Wolfe, C. D. A., & Rudd, A. G. (2013). Natural history, predictors and outcomes of depression after stroke: Systematic review and meta-analysis. *British Journal of Psychiatry*, 202(1), 14–21. <https://doi.org/10.1192/bjp.bp.111.107664>
- Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B: Methodological*, 57(1), 289–300.
- Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., Loh, P.-R., ... Neale, B. M. (2015). An atlas of genetic correlations across human diseases and traits. *Nature Genetics*, 47, 1236–1241. <https://doi.org/10.1038/ng.3406>, <https://www.nature.com/articles/ng.3406#supplementary-information>
- Bulik-Sullivan, B. K., Loh, P.-R., Finucane, H. K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics, C., ... Neale, B. M. (2015). LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*, 47, 291–295. <https://doi.org/10.1038/ng.3211>, <https://www.nature.com/articles/ng.3211#supplementary-information>
- Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L. T., Sharp, K., ... Marchini, J. (2018). The UKBiobank resource with deep phenotyping and genomic data. *Nature*, 562(7726), 203–209. <https://doi.org/10.1038/s41586-018-0579-z>
- Cai, N., Revez, J. A., Adams, M. J., Andlauer, T. F. M., Breen, G., Byrne, E. M., ... Flint, J. (2020). Minimal phenotyping yields genome-wide association signals of low specificity for major depression. *Nature Genetics*, 52(4), 437–447. <http://dx.doi.org/10.1038/s41588-020-0594-5>
- Clarke, T.-K., Obsteter, J., Hall, L. S., Hayward, C., Thomson, P. A., Smith, B. H., ... McIntosh, A. M. (2016). Investigating shared aetiology between type 2 diabetes and major depressive disorder in a population based cohort. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 174(3), 227–234. <https://doi.org/10.1002/ajmg.b.32478>
- Coleman, J. R. I., Purves, K. L., Davis, K. A. S., Rayner, C., Choi, S. W., Hübel, C., ... Breen, G. (2020). Genome-wide gene-environment analyses of depression and reported lifetime traumatic experiences in UK Biobank. *Molecular Psychiatry*, 25, 1430–1446. <https://doi.org/10.1038/s41380-019-0546-6>
- Davis, K. A. S., Coleman, J. R. I., Adams, M., Allen, N., Breen, G., Cullen, B., ... Hotopf, M. (2018). Mental health in UKBiobank: Development, implementation and results from an online questionnaire completed by 157 366 participants. *The British Journal of Psychiatry*, 4(3), 83–90. <https://doi.org/10.1192/bjo.2018.12>
- Dudbridge, F. (2013). Power and predictive accuracy of polygenic risk scores. *PLoS Genetics*, 9(3), e1003348. <https://doi.org/10.1371/journal.pgen.1003348>
- Euesden, J., Lewis, C. M., & O'Reilly, P. F. (2015). PRSice: Polygenic risk score software. *Bioinformatics*, 31(9), 1466–1468. <https://doi.org/10.1093/bioinformatics/btu848>
- First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1997). *Structured clinical interview for DSM-IV Axis I disorders, clinician version (SCID-CV)*. Washington, DC, USA: American Psychiatric Publishing, Inc.
- Hackett, M. L., & Pickles, K. (2014). Part I: Frequency of depression after stroke: An updated systematic review and meta-analysis of observational studies. *International Journal of Stroke*, 9(8), 1017–1025. <https://doi.org/10.1111/ijs.12357>
- Herrmann, L. L., Le Masurier, M., & Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: A systematic review. *Journal of Neurology, Neurosurgery & Psychiatry*, 79(6), 619–624. <https://doi.org/10.1136/jnnp.2007.124651>
- Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shihali, M., ... Major Depressive Disorder Working Group of the Psychiatric Genomics, C. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, 22(3), 343–352. <https://doi.org/10.1038/s41593-018-0326-7>
- Kan, C., Pedersen, N. L., Christensen, K., Bornstein, S. R., Licinio, J., MacCabe, J. H., ... Rijsdijk, F. (2016). Genetic overlap between type 2 diabetes and depression in Swedish and Danish twin registries. *Molecular Psychiatry*, 21, 903–909. <https://doi.org/10.1038/mp.2016.28>, <https://www.nature.com/articles/mp201628#supplementary-information>
- Kendler, K. S., Fiske, A., Gardner, C. O., & Gatz, M. (2009). Delineation of two genetic pathways to major depression. *Biological Psychiatry*, 65(9), 808–811. <https://doi.org/10.1016/j.biopsych.2008.11.015>
- Khandaker, G. M., Zuber, V., Rees, J. M. B., Carvalho, L., Mason, A. M., Foley, C. N., ... Burgess, S. (2019). Shared mechanisms between coronary heart disease and depression: Findings from a large UK general population-based cohort. *Molecular Psychiatry*, 25(7), 1477–1486. <https://doi.org/10.1038/s41380-019-0395-3>
- Lam, M., Awasthi, S., Watson, H. J., Goldstein, J., Panagiotaropoulou, G., Trubetskoy, V., ... Ripke, S. (2019). RICOPILI: Rapid imputation for consortias pipeline. *Bioinformatics*, 36(3), 930–933. <https://doi.org/10.1093/bioinformatics/bt633>
- Locke, A. E., Kahali, B., Berndt, S. I., Justice, A. E., Pers, T. H., Day, F. R., ... Speliotes, E. K. (2015). Genetic studies of body mass index yield new insights for obesity biology. *Nature*, 518, 197–206. <https://doi.org/10.1038/nature14177>, <https://www.nature.com/articles/nature14177#supplementary-information>
- Malik, R., Chauhan, G., Traylor, M., Sargurupremraj, M., Okada, Y., Mishra, A., ... Dichgans, M. (2018). Multiethnic genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nature Genetics*, 50(4), 524–537. <https://doi.org/10.1038/s41588-018-0058-3>
- Mezuk, B., Eaton, W. W., Albrecht, S., & Golden, S. H. (2008). Depression and type 2 diabetes over the lifespan. A meta-analysis. *Diabetes Care*, 31(12), 2383–2390. <https://doi.org/10.2337/dc08-0985>
- Milaneschi, Y., Lamers, F., Peyrot, W. J., Baune, B. T., Breen, G., Dehghan, A., ... CHARGE Inflammation Working Group and the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. (2017). Genetic association of major depression with atypical features and obesity-related immunometabolic dysregulations. *JAMA Psychiatry*, 74(12), 1214–1225. <https://doi.org/10.1001/jamapsychiatry.2017.3016>
- Milaneschi, Y., Simmons, W. K., van Rossum, E. F. C., & Penninx, B. W. J. H. (2018). Depression and obesity: Evidence of shared biological mechanisms. *Molecular Psychiatry*, 24, 18–33. <https://doi.org/10.1038/s41380-018-0017-5>

- Nagy, R., Boutin, T. S., Marten, J., Huffman, J. E., Kerr, S. M., Campbell, A., ... Hayward, C. (2017). Exploration of haplotype research consortium imputation for genome-wide association studies in 20,032 generation Scotland participants. *Genome Medicine*, 9(1), 23. <https://doi.org/10.1186/s13073-017-0414-4>
- Naismith, S. L., Norrie, L. M., Mowszowski, L., & Hickie, I. B. (2012). The neurobiology of depression in later-life: Clinical, neuropsychological, neuroimaging and pathophysiological features. *Progress in Neurobiology*, 98(1), 99–143. <https://doi.org/10.1016/j.pneurobio.2012.05.009>
- Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiological and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal*, 27(23), 2763–2774. <https://doi.org/10.1093/eurheartj/ehl338>
- Nikpay, M., Goel, A., Won, H. H., Hall, L. M., Willenborg, C., Kanoni, S., ... Farrall, M. (2015). A comprehensive 1,000 genomes-based genome-wide association meta-analysis of coronary artery disease. *Nature Genetics*, 47(10), 1121–1130. <https://doi.org/10.1038/ng.3396>
- Pan, A., Sun, Q., Okereke, O. I., Rexrode, K. M., & Hu, F. B. (2011). Depression and risk of stroke morbidity and mortality: A meta-analysis and systematic review. *JAMA*, 306(11), 1241–1249. <https://doi.org/10.1001/jama.2011.1282>
- Penninx, B. W., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. *BMC Medicine*, 11(1), 129. <https://doi.org/10.1186/1741-7015-11-129>
- Penninx, B. W. J. H. (2017). Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neuroscience & Biobehavioral Reviews*, 74, 277–286. <https://doi.org/10.1016/j.neubiorev.2016.07.003>
- Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics*, 47, 702–709. <https://doi.org/10.1038/ng.3285>, <https://www.nature.com/articles/ng.3285#supplementary-information>
- Power, R. A., Tansey, K. E., Buttenschön, H. N., Cohen-Woods, S., Bigdeli, T., Hall, L. S., ... Lewis, C. M. (2017). Genome-wide Association for Major Depression through age at onset stratification: Major depressive disorder working Group of the Psychiatric Genomics Consortium. *Biological Psychiatry*, 81(4), 325–335. <https://doi.org/10.1016/j.biopsych.2016.05.010>
- Quenouille, M. H. (1956). Notes on bias in estimation. *Biometrika*, 43(3/4), 353–360. <https://doi.org/10.2307/2332914>
- Schunkert, H., König, I. R., Kathiresan, S., Reilly, M. P., Assimes, T. L., Holm, H., ... Samani, N. J. (2011). Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nature Genetics*, 43, 333. <https://doi.org/10.1038/ng.784>, <https://www.nature.com/articles/ng.784#supplementary-information>
- Scott, R. A., Scott, L. J., Mägi, R., Marullo, L., Gaulton, K. J., Kaakinen, M., ... Prokopenko, I. (2017). An expanded genome-wide association study of type 2 diabetes in Europeans. *Diabetes*, 66(11), 2888–2902. <https://doi.org/10.2337/db16-1253>
- Smith, B. H., Campbell, A., Linksted, P., Fitzpatrick, B., Jackson, C., Kerr, S. M., ... Morris, A. D. (2013). Cohort profile: Generation Scotland: Scottish family health study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. *International Journal of Epidemiology*, 42(3), 689–700. <https://doi.org/10.1093/ije/dys084>
- Smith, B. H., Campbell, H., Blackwood, D., Connell, J., Connor, M., Deary, I. J., ... Morris, A. D. (2006). Generation Scotland: The Scottish family health study; a new resource for researching genes and heritability. *BMC Medical Genetics*, 7(1), 74. <https://doi.org/10.1186/1471-2350-7-74>
- Smith, D. J., Nicholl, B. I., Cullen, B., Martin, D., Ul-Haq, Z., Evans, J., ... Pell, J. P. (2013). Prevalence and characteristics of probable major depression and bipolar disorder within UKBiobank: Cross-sectional study of 172,751 participants. *PLoS ONE*, 8(11), e75362. <https://doi.org/10.1371/journal.pone.0075362>
- Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., ... Collins, R. (2015). UKBiobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Medicine*, 12(3), e1001779. <https://doi.org/10.1371/journal.pmed.1001779>
- Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *The American Journal of Psychiatry*, 157(10), 1552–1562. <https://doi.org/10.1176/appi.ajp.157.10.1552>
- Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Molecular Psychiatry*, 18, 963–974. <https://doi.org/10.1038/mp.2013.20>
- Tukey, J. (1958). Bias and confidence in not quite large samples. *The Annals of Mathematical Statistics*, 29, 614.
- van Sloten, T. T., Sigurdsson, S., van Buchem, M. A., Phillips, C. L., Jonsson, P. V., Ding, J., ... Launer, L. J. (2015). Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: The AGES-Reykjavik study. *American Journal of Psychiatry*, 172(6), 570–578. <https://doi.org/10.1176/appi.ajp.2014.14050578>
- Vergnes, L., Lee, J. M., Chin, R. G., Auwerx, J., & Reue, K. (2013). Diet1 functions in the FGF15/19 Enterohepatic signaling Axis to modulate bile acid and lipid levels. *Cell Metabolism*, 17(6), 916–928. <https://doi.org/10.1016/j.cmet.2013.04.007>
- Vogelzangs, N., Kritchevsky, S. B., Beekman, A. T. F., Brenes, G. A., Newman, A. B., Satterfield, S., ... Penninx, B. W. J. H. (2010). Obesity and onset of significant depressive symptoms: Results from a community-based cohort of older men and women. *The Journal of Clinical Psychiatry*, 71(4), 391–399. <https://doi.org/10.4088/JCP.08m04743blu>
- Wassertheil-Smoller, S., Qi, Q., Dave, T., Mitchell, B. D., Jackson, R. D., Liu, S., ... Smoller, J. W. (2018). Polygenic risk for depression increases risk of ischemic stroke: From the stroke genetics network study. *Stroke*, 49(3), 543–548. <https://doi.org/10.1161/strokeaha.117.018857>
- Willemsen, G., Ward, K. J., Bell, C. G., Christensen, K., Bowden, J., Dalgård, C., ... Spector, T. (2015). The concordance and heritability of type 2 diabetes in 34,166 twin pairs from international twin registers: The discordant twin (DISCOTWIN) consortium. *Twin Research and Human Genetics*, 18(6), 762–771. <https://doi.org/10.1017/thg.2015.83>
- Willer, C. J., Li, Y., & Abecasis, G. R. (2010). METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*, 26(17), 2190–2191. <https://doi.org/10.1093/bioinformatics/btq340>
- Winkler, T. W., Day, F. R., Croteau-Chonka, D. C., Wood, A. R., Locke, A. E., Mägi, R., ... The Genetic Investigation of Anthropometric Traits, C. (2014). Quality control and conduct of genome-wide association meta-analyses. *Nature Protocols*, 9, 1192–1212. <https://doi.org/10.1038/nprot.2014.071>, <https://www.nature.com/articles/nprot.2014.071#supplementary-information>
- Wong, B. C.-F., Chau, C. K.-L., Ao, F.-K., Mo, C.-H., Wong, S.-Y., Wong, Y.-H., & So, H.-C. (2019). Differential associations of various depression-related phenotypes with cardiometabolic risks: Identification of shared genetic factors and implications for drug repositioning. *Depress Anxiety*, 36(4), 330–344. <https://doi.org/10.1002/da.22861>
- Wong, B. C.-F., Chau, C. K.-L., Ao, F.-K., Mo, C.-H., Wong, S.-Y., Wong, Y.-H., & So, H.-C. (2018). Differential associations of depression-related phenotypes with cardiometabolic risks: Polygenic analyses and



- exploring shared genetic variants and pathways. *Depression and Anxiety*, 36, 330–344. <https://doi.org/10.1002/da.22861>
- World Health Organization. (1978). The international classification of diseases: Ninth revision (ICD-9). *Annals of Internal Medicine*, 88(3), 424–426. <https://doi.org/10.7326/0003-4819-88-3-424>
- World Health Organization. (1992). *International classification of diseases*. Geneva: World Health Organization.
- Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., ... Sullivan, P. F. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, 50(5), 668–681. <https://doi.org/10.1038/s41588-018-0090-3>
- Yengo, L., Sidorenko, J., Kempner, K. E., Zheng, Z., Wood, A. R., Weedon, M. N., ... Visscher, P. M. (2018). Meta-analysis of genome-wide association studies for height and body mass index in ~700,000 individuals of European ancestry. *Human Molecular Genetics*, 27(20), 3641–3649. <https://doi.org/10.1093/hmg/ddy271>

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Hagenars SP, Coleman JRI, Choi SW, et al. Genetic comorbidity between major depression and cardio-metabolic traits, stratified by age at onset of major depression. *Am J Med Genet Part B*. 2020;183B:309–330. <https://doi.org/10.1002/ajmg.b.32807>

## APPENDIX

### Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium

Naomi R Wray\* 1, 2 Stephan Ripke\* 3, 4, 5 Manuel Mattheisen\* 6, 7, 8 Maciej Trzaskowski 1 Enda M Byrne 1 Abdel Abdellaoui 9 Mark J Adams 10 Esben Agerbo 11, 12, 13 Tracy M Air 14 Till F M Andlauer 15, 16 Silviu-Alin Bacanu 17 Marie Bækvad-Hansen 13, 18 Aartjan T F Beekman 19 Tim B Bigdeli 17, 20 Elisabeth B Binder 15, 21 Julien Bryois 22 Henriette N Buttenschøn 13, 23, 24 Jonas Bybjerg-Grauholm 13, 18 Na Cai 25, 26 Enrique Castelao 27 Jane Hvarregaard Christensen 8, 13, 24 Toni-Kim Clarke 10 Jonathan R I Coleman 28 Lucia Colodro-Conde 29 Baptiste Couvy-Duchesne 2, 30 Nick Craddock 31 Gregory E Crawford 32, 33 Gail Davies 34 Ian J Deary 34 Franziska Degenhardt 35 Eske M Derks 29 Nese Direk 36, 37 Conor V Dolan 9 Erin C Dunn 38, 39, 40 Thalia C Eley 28 Valentina Escott-Price 41 Farnush Farhadi Hassan Kiadeh 42 Hilary K Finucane 43, 44 Jerome C Foo 45 Andreas J Forstner 35, 46, 47, 48 Josef Frank 45 Hélène A Gaspar 28 Michael Gill 49 Fernando S Goes 50 Scott D Gordon 29 Jakob Grove 8, 13, 24, 51 Lynsey S Hall 10, 52 Christine Søholm Hansen 13, 18 Thomas F Hansen 53, 54, 55 Stefan Herms 35, 47 Ian B Hickie 56 Per Hoffmann 35, 47 Georg Homuth 57 Carsten Horn 58 Jouke-Jan Hottenga 9 David M Hougaard 13, 18 David M Howard 10, 28 Marcus Ising 59 Rick Jansen

19 Ian Jones 60 Lisa A Jones 61 Eric Jorgenson 62 James A Knowles 63 Isaac S Kohane 64, 65, 66 Julia Kraft 4 Warren W. Kretzschmar 67 Zoltán Kutalik 68, 69 Yihan Li 67 Penelope A Lind 29 Donald J MacIntyre 70, 71 Dean F MacKinnon 50 Robert M Maier 2 Wolfgang Maier 72 Jonathan Marchini 73 Hamdi Mbarek 9 Patrick McGrath 74 Peter McGuffin 28 Sarah E Medland 29 Divya Mehta 2, 75 Christel M Middeldorp 9, 76, 77 Evelin Mihailov 78 Yuri Milaneshi 19 Lili Milani 78 Francis M Mondimore 50 Grant W Montgomery 1 Sara Mostafavi 79, 80 Niamh Mullins 28 Matthias Nauck 81, 82 Bernard Ng 80 Michel G Nivard 9 Dale R Nyholt 83 Paul F O'Reilly 28 Hogni Oskarsson 84 Michael J Owen 60 Jodie N Painter 29 Carsten Bøcker Pedersen 11, 12, 13 Marianne Giørtz Pedersen 11, 12, 13 Roseann E Peterson 17, 85 Wouter J Peyrot 19 Giorgio Pistis 27 Danielle Posthuma 86, 87 Jorge A Quiroz 88 Per Qvist 8, 13, 24 John P Rice 89 Brien P. Riley 17 Margarita Rivera 28, 90 Saira Saeed Mirza 36 Robert Schoevers 91 Eva C Schulte 92, 93 Ling Shen 62 Jianxin Shi 94 Stanley I Shyn 95 Engilbert Sigurdsson 96 Grant C B Sinnamoni 97 Johannes H Smit 19 Daniel J Smith 98 Hreinn Stefansson 99 Stacy Steinberg 99 Fabian Streit 45 Jana Strohmaier 45 Katherine E Tansey 100 Henning Teismann 101 Alexander Teumer 102 Wesley Thompson 13, 54, 103, 104 Pippa A Thomson 105 Thorgerir E Thorgerirsson 99 Matthew Traylor 106 Jens Treutlein 45 Vassily Trubetskoy 4 André G Uitterlinden 107 Daniel Umbricht 108 Sandra Van der Auwera 109 Albert M van Hemert 110 Alexander Viktorin 22 Peter M Visscher 1, 2 Yunpeng Wang 13, 54, 104 Bradley T. Webb 111 Shantel Marie Weinsheimer 13, 54 Jürgen Wellmann 101 Gonneke Willemsen 9 Stephanie H Witt 45 Yang Wu 1 Hualin S Xi 112 Jian Yang 2, 113 Futao Zhang 1 Volker Arolt 114 Bernhard T Baune 114, 115, 116 Klaus Berger 101 Dorret I Boomsma 9 Sven Cichon 35, 47, 117, 118 Udo Dannlowski 114 EJC de Geus 9, 119 J Raymond DePaulo 50 Enrico Domenici 120 Katharina Domschke 121, 122 Tõnu Esko 5, 78 Hans J Grabe 109 Steven P Hamilton 123 Caroline Hayward 124 Andrew C Heath 89 Kenneth S Kendler 17 Stefan Kloiber 59, 125, 126 Glyn Lewis 127 Qingqin S Li 128 Susanne Lucae 59 Pamela AF Madden 89 Patrik K Magnusson 22 Nicholas G Martin 29 Andrew M McIntosh 10, 34 Andres Metspalu 78, 129 Ole Mors 13, 130 Preben Bo Mortensen 11, 12, 13, 24 Bertram Müller-Myhsok 15, 131, 132 Merete Nordentoft 13, 133 Markus M Nöthen 35 Michael C O'Donovan 60 Sara A Paciga 134 Nancy L Pedersen 22 Brenda WJH Penninx 19 Roy H Perlis 38, 135 David J Porteous 105 James B Potash 136 Martin Preisig 27 Marcella Rietschel 45 Catherine Schaefer 62 Thomas G Schulze 45, 93, 137, 138, 139 Jordan W Smoller 38, 39, 40 Kari Stefansson 99, 140 Henning Tiemeier 36, 141, 142 Rudolf Uher 143 Henry Völzke 102 Myrna M Weissman 74, 144 Thomas Werge 13, 54, 145 Cathryn M Lewis\* 28, 146 Douglas F Levinson\* 147 Gerome Breen\* 28, 148 Anders D Børglum\* 8, 13, 24 Patrick F Sullivan\* 22, 149, 150.

1, Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU.

2, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU.

3, Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US.



- 4, Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE.
- 5, Medical and Population Genetics, Broad Institute, Cambridge, MA, US.
- 6, Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, DE.
- 7, Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, SE.
- 8, Department of Biomedicine, Aarhus University, Aarhus, DK.
- 9, Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL.
- 10, Division of Psychiatry, University of Edinburgh, Edinburgh, GB.
- 11, Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK.
- 12, National Centre for Register-Based Research, Aarhus University, Aarhus, DK.
- 13, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK.
- 14, Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU.
- 15, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE.
- 16, Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Munich, DE.
- 17, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US.
- 18, Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK.
- 19, Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL.
- 20, Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, US.
- 21, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, US.
- 22, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE.
- 23, Department of Clinical Medicine, Translational Neuropsychiatry Unit, Aarhus University, Aarhus, DK.
- 24, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK.
- 25, Human Genetics, Wellcome Trust Sanger Institute, Cambridge, GB.
- 26, Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, GB.
- 27, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, CH.
- 28, Social, Genetic and Developmental Psychiatry Centre, King's College London, London, GB.
- 29, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU.
- 30, Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, AU.
- 31, Psychological Medicine, Cardiff University, Cardiff, GB.
- 32, Center for Genomic and Computational Biology, Duke University, Durham, NC, US.
- 33, Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, US.
- 34, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB.
- 35, Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, DE.
- 36, Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL.
- 37, Psychiatry, Dokuz Eylül University School Of Medicine, Izmir, TR.
- 38, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US.
- 39, Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US.
- 40, Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US.
- 41, Neuroscience and Mental Health, Cardiff University, Cardiff, GB.
- 42, Bioinformatics, University of British Columbia, Vancouver, BC, CA.
- 43, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, US.
- 44, Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, US.
- 45, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE.
- 46, Department of Psychiatry (UPK), University of Basel, Basel, CH.
- 47, Department of Biomedicine, University of Basel, Basel, CH.
- 48, Centre for Human Genetics, University of Marburg, Marburg, DE.
- 49, Department of Psychiatry, Trinity College Dublin, Dublin, IE.
- 50, Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US.
- 51, Bioinformatics Research Centre, Aarhus University, Aarhus, DK.
- 52, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, GB.
- 53, Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, DK.
- 54, Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK.
- 55, iPSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, DK.
- 56, Brain and Mind Centre, University of Sydney, Sydney, NSW, AU.
- 57, Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE.

- 58, Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH.
- 59, Max Planck Institute of Psychiatry, Munich, DE.
- 60, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, GB.
- 61, Department of Psychological Medicine, University of Worcester, Worcester, GB.
- 62, Division of Research, Kaiser Permanente Northern California, Oakland, CA, US.
- 63, Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, US.
- 64, Department of Biomedical Informatics, Harvard Medical School, Boston, MA, US.
- 65, Department of Medicine, Brigham and Women's Hospital, Boston, MA, US.
- 66, Informatics Program, Boston Children's Hospital, Boston, MA, US.
- 67, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, GB.
- 68, Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital and University of Lausanne, Lausanne, VD, CH.
- 69, Swiss Institute of Bioinformatics, Lausanne, VD, CH.
- 70, Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB.
- 71, Mental Health, NHS 24, Glasgow, GB.
- 72, Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE.
- 73, Statistics, University of Oxford, Oxford, GB.
- 74, Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US.
- 75, School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, AU.
- 76, Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, AU.
- 77, Child Health Research Centre, University of Queensland, Brisbane, QLD, AU.
- 78, Estonian Genome Center, University of Tartu, Tartu, EE.
- 79, Medical Genetics, University of British Columbia, Vancouver, BC, CA.
- 80, Statistics, University of British Columbia, Vancouver, BC, CA.
- 81, DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE.
- 82, Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE.
- 83, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, AU.
- 84, Humus, Reykjavik, IS.
- 85, Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US.
- 86, Clinical Genetics, Vrije Universiteit Medical Center, Amsterdam, NL.
- 87, Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, NL.
- 88, Solid Biosciences, Boston, MA, US.
- 89, Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, US.
- 90, Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Biomedical Research Center (CIBM), University of Granada, Granada, ES.
- 91, Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, NL.
- 92, Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilian University Munich, Munich, DE.
- 93, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, Ludwig Maximilian University Munich, Munich, DE.
- 94, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, US.
- 95, Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, US.
- 96, Faculty of Medicine, Department of Psychiatry, University of Iceland, Reykjavik, IS.
- 97, School of Medicine and Dentistry, James Cook University, Townsville, QLD, AU.
- 98, Institute of Health and Wellbeing, University of Glasgow, Glasgow, GB.
- 99, deCODE Genetics/Amgen, Reykjavik, IS.
- 100, College of Biomedical and Life Sciences, Cardiff University, Cardiff, GB.
- 101, Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE.
- 102, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE.
- 103, Department of Psychiatry, University of California, San Diego, San Diego, CA, US.
- 104, KG Jepsen Centre for Psychosis Research, Norway Division of Mental Health and Addiction, Oslo University Hospital, Oslo, NO.
- 105, Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, GB.
- 106, Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London, GB.
- 107, Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, NL.
- 108, Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH.
- 109, Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE.
- 110, Department of Psychiatry, Leiden University Medical Center, Leiden, NL.
- 111, Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US.

- 112, Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, US.
- 113, Institute for Molecular Bioscience; Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU.
- 114, Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, DE.
- 115, Department of Psychiatry, Melbourne Medical School, University of Melbourne, Melbourne, AU.
- 116, Florey Institute for Neuroscience and Mental Health, University of Melbourne, Melbourne, AU.
- 117, Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, CH.
- 118, Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, DE.
- 119, Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, NL.
- 120, Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, IT.
- 121, Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, DE.
- 122, Center for NeuroModulation, Faculty of Medicine, University of Freiburg, Freiburg, DE.
- 123, Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, US.
- 124, Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, GB.
- 125, Department of Psychiatry, University of Toronto, Toronto, ON, CA.
- 126, Centre for Addiction and Mental Health, Toronto, ON, CA.
- 127, Division of Psychiatry, University College London, London, GB.
- 128, Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, US.
- 129, Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE.
- 130, Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, DK.
- 131, Munich Cluster for Systems Neurology (SyNergy), Munich, DE.
- 132, University of Liverpool, Liverpool, GB.
- 133, Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, DK.
- 134, Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, US.
- 135, Psychiatry, Harvard Medical School, Boston, MA, US.
- 136, Psychiatry, University of Iowa, Iowa City, IA, US.
- 137, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US.
- 138, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Niedersachsen, DE.
- 139, Human Genetics Branch, NIMH Division of Intramural Research Programs, Bethesda, MD, US.

- 140, Faculty of Medicine, University of Iceland, Reykjavik, IS.
- 141, Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL.
- 142, Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL.
- 143, Psychiatry, Dalhousie University, Halifax, NS, CA.
- 144, Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY, US.
- 145, Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK.
- 146, Department of Medical & Molecular Genetics, King's College London, London, GB.
- 147, Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, US.
- 148, NIHR Maudsley Biomedical Research Centre, King's College London, London, GB.
- 149, Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US.
- 150, Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US.

#### MEGASTROKE CONSORTIUM

- Rainer Malik 1, Ganesh Chauhan 2, Matthew Traylor 3, Muralidharan Sargurupremraj 4,5, Yukinori Okada 6,7,8, Aniket Mishra 4,5, Loes Rutten-Jacobs 3, Anne-Katrin Giese 9, Sander W van der Laan 10, Solveig Gretarsdottir 11, Christopher D Anderson 12,13,14,14, Michael Chong 15, Hieab HH Adams 16,17, Tetsuro Ago 18, Peter Almgren 19, Philippe Amouyel 20,21, Hakan Ay 22,13, Traci M Bartz 23, Oscar R Benavente 24, Steve Bevan 25, Giorgio B Boncoraglio 26, Robert D Brown, Jr. 27, Adam S Butterworth 28,29, Caty Carrera 30,31, Cara L Carty 32,33, Daniel I Chasman 34,35, Wei-Min Chen 36, John W Cole 37, Adolfo Correa 38, Ioana Cotlarciuc 39, Carlos Cruchaga 40,41, John Danesh 28,42,43,44, Paul IW de Bakker 45,46, Anita L DeStefano 47,48, Marcel den Hoed 49, Qing Duan 50, Stefan T Engelter 51,52, Guido J Falcone 53,54, Rebecca F Gottesman 55, Raji P Grewal 56, Vilmundur Gudnason 57,58, Stefan Gustafsson 59, Jeffrey Haessler 60, Tamara B Harris 61, Ahamad Hassan 62, Aki S Havulinna 63,64, Susan R Heckbert 65, Elizabeth G Holliday 66,67, George Howard 68, Fang-Chi Hsu 69, Hyacinth I Hyacinth 70, M Arfan Ikram 16, Erik Ingelsson 71,72, Marguerite R Irvin 73, Xueqiu Jian 74, Jordi Jiménez-Conde 75, Julie A Johnson 76,77, J Wouter Jukema 78, Masahiro Kanai 6,7,79, Keith L Keene 80,81, Brett M Kissela 82, Dawn O Kleindorfer 82, Charles Kooperberg 60, Michiaki Kubo 83, Leslie A Lange 84, Carl D Langefeld 85, Claudia Langenberg 86, Lenore J Launer 87, Jin-Moo Lee 88, Robin Lemmens 89,90, Didier Leys 91, Cathryn M Lewis 92,93, Wei-Yu Lin 28,94, Arne G Lindgren 95,96, Erik Lorentzen 97, Patrik K Magnusson 98, Jane Maguire 99, Ani Manichaikul 36, Patrick F McArdle 100, James F Meschia 101, Braxton D Mitchell 100,102, Thomas H Mosley 103,104, Michael A Nalls 105,106, Toshiharu Ninomiya 107, Martin J O'Donnell 15,108, Bruce M Psaty 109,110,111,112, Sara L Pulit 113,45, Kristiina Rannikmäe 114,115, Alexander P Reiner 65,116, Kathryn M Rexrode 117, Kenneth Rice 118, Stephen S Rich 36, Paul

M Ridker 34,35, Natalia S Rost 9,13, Peter M Rothwell 119, Jerome I Rotter 120,121, Tatjana Rundek 122, Ralph L Sacco 122, Saori Sakaue 7,123, Michele M Sale 124, Veikko Salomaa 63, Bishwa R Sapkota 125, Reinhold Schmidt 126, Carsten O Schmidt 127, Ulf Schminke 128, Pankaj Sharma 39, Agnieszka Slowik 129, Cathie LM Sudlow 114,115, Christian Tanislav 130, Turgut Tatlisumak 131,132, Kent D Taylor 120,121, Vincent NS Thijs 133,134, Gudmar Thorleifsson 11, Unnur Thorsteinsdottir 11, Steffen Tiedt 1, Stella Trompet 135, Christophe Tzourio 5,136,137, Cornelia M van Duijn 138,139, Matthew Walters 140, Nicholas J Wareham 86, Sylvia Wassertheil-Smoller 141, James G Wilson 142, Kerri L Wiggins 109, Qiong Yang 47, Salim Yusuf 15, Najaf Amin 16, Hugo S Aparicio 185,48, Donna K Arnett 186, John Attia 187, Alexa S Beiser 47,48, Claudine Berr 188, Julie E Buring 34,35, Mariana Bustamante 189, Valeria Caso 190, Yu-Ching Cheng 191, Seung Hoan Choi 192,48, Ayesha Chowhan 185,48, Natalia Cullell 31, Jean-François Dartigues 193,194, Hossein Delavaran 95,96, Pilar Delgado 195, Marcus Dörr 196,197, Gunnar Engström 19, Ian Ford 198, Wander S Gurpreet 199, Anders Hamsten 200,201, Laura Heitsch 202, Atsushi Hozawa 203, Laura Ibanez 204, Andreea Ilinca 95,96, Martin Ingelsson 205, Motoki Iwasaki 206, Rebecca D Jackson 207, Katarina Jood 208, Pekka Jousilahti 63, Sara Kaffashian 4,5, Lalit Kalra 209, Masahiro Kamouchi 210, Takanari Kitazono 211, Olafur Kjartansson 212, Manja Kloss 213, Peter J Koudstaal 214, Jerzy Krupinski 215, Daniel L Labovitz 216, Cathy C Laurie 118, Christopher R Levi 217, Linxin Li 218, Lars Lind 219, Cecilia M Lindgren 220,221, Vasileios Lioutas 222,48, Yong Mei Liu 223, Oscar L Lopez 224, Hirata Makoto 225, Nicolas Martinez-Majander 172, Koichi Matsuda 225, Naoko Minegishi 203, Joan Montaner 226, Andrew P Morris 227,228, Elena Muiño 31, Martina Müller-Nurasyid 229,230,231, Bo Norrving 95,96, Soichi Ogishima 203, Eugenio A Parati 232, Leema Reddy Peddareddygar 56, Nancy L Pedersen 98,233, Joanna Pera 129, Markus Perola 63,234, Alessandro Pezzini 235, Silvana Pileggi 236, Raquel Rabionet 237, Iolanda Riba-Llena 30, Marta Ribasés 238, Jose R Romero 185,48, Jaume Roquer 239,240, Anthony G Rudd 241,242, Antti-Pekka Sarin 243,244, Ralhan Sarju 199, Chloe Sarnowski 47,48, Makoto Sasaki 245, Claudia L Satizabal 185,48, Mamoru Satoh 245, Naveed Sattar 246, Norie Sawada 206, Gerli Sibolt 172, Ásgeir Sigurdsson 247, Albert Smith 248, Kenji Sobue 245, Carolina Soriano-Tárraga 240, Tara Stanne 249, O Colin Stine 250, David J Stott 251, Konstantin Strauch 229,252, Takako Takai 203, Hideo Tanaka 253,254, Kozo Tanno 245, Alexander Teumer 255, Liisa Tomppo 172, Nuria P Torres-Aguila 31, Emmanuel Touze 256,257, Shoichiro Tsugane 206, Andre G Uitterlinden 258, Einar M Valdimarsson 259, Sven J van der Lee 16, Henry Völzke 255, Kenji Wakai 253, David Weir 260, Stephen R Williams 261, Charles DA Wolfe 241,242, Quenna Wong 118, Huichun Xu 191, Taiki Yamaji 206, Dharambir K Sanghera 125,169,170, Olle Melander 19, Christina Jern 171, Daniel Strbian 172,173, Israel Fernandez-Cadenas 31,30, W T Longstreth, Jr 174,65, Arndt Rolfs 175, Jun Hata 107, Daniel Woo 82, Jonathan Rosand 12,13,14, Guillaume Pare 15, Jemma C Hopewell 176, Danish Saleheen 177, Kari Stefansson 11,178, Bradford B Worrall 179, Steven J Kittner 37, Sudha Seshadri 180,48, Myriam Fornage 74,181, Hugh S

Markus 3, Joanna MM Howson 28, Yoichiro Kamatani 6,182, Stephanie DeBette 4,5, Martin Dichgans 1,183,184.

1 Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany.

2 Centre for Brain Research, Indian Institute of Science, Bangalore, India.

3 Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London, UK.

4 INSERM U1219 Bordeaux Population Health Research Center, Bordeaux, France.

5 University of Bordeaux, Bordeaux, France.

6 Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan.

7 Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan.

8 Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan.

9 Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

10 Laboratory of Experimental Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, University of Utrecht, Utrecht, Netherlands.

11 deCODE genetics/AMGEN inc, Reykjavik, Iceland.

12 Center for Genomic Medicine, Massachusetts General Hospital (MGH), Boston, MA, USA.

13 J. Philip Kistler Stroke Research Center, Department of Neurology, MGH, Boston, MA, USA.

14 Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA.

15 Population Health Research Institute, McMaster University, Hamilton, Canada.

16 Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands.

17 Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, Netherlands.

18 Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

19 Department of Clinical Sciences, Lund University, Malmö, Sweden.

20 Univ. Lille, Inserm, Institut Pasteur de Lille, LabEx DISTALZ-UMR1167, Risk factors and molecular determinants of aging-related diseases, F-59000 Lille, France.

21 Centre Hosp. Univ Lille, Epidemiology and Public Health Department, F-59000 Lille, France.

22 AA Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

23 Cardiovascular Health Research Unit, Departments of Biostatistics and Medicine, University of Washington, Seattle, WA, USA.

24 Division of Neurology, Faculty of Medicine, Brain Research Center, University of British Columbia, Vancouver, Canada.

25 School of Life Science, University of Lincoln, Lincoln, UK.

- 26 Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy.
- 27 Department of Neurology, Mayo Clinic Rochester, Rochester, MN, USA.
- 28 MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
- 29 The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, UK.
- 30 Neurovascular Research Laboratory, Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona, Vall d'Hebrón Hospital, Barcelona, Spain.
- 31 Stroke Pharmacogenomics and Genetics, Fundació Docència i Recerca MutuaTerrassa, Terrassa, Spain.
- 32 Children's Research Institute, Children's National Medical Center, Washington, DC, USA.
- 33 Center for Translational Science, George Washington University, Washington, DC, USA.
- 34 Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA.
- 35 Harvard Medical School, Boston, MA, USA.
- 36 Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA.
- 37 Department of Neurology, University of Maryland School of Medicine and Baltimore VAMC, Baltimore, MD, USA.
- 38 Departments of Medicine, Pediatrics and Population Health Science, University of Mississippi Medical Center, Jackson, MS, USA.
- 39 Institute of Cardiovascular Research, Royal Holloway University of London, UK & Ashford and St Peters Hospital, Surrey UK.
- 40 Department of Psychiatry, The Hope Center Program on Protein Aggregation and Neurodegeneration (HPAN), Washington University, School of Medicine, St. Louis, MO, USA.
- 41 Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO, USA.
- 42 NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.
- 43 Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK.
- 44 British Heart Foundation, Cambridge Centre of Excellence, Department of Medicine, University of Cambridge, Cambridge, UK.
- 45 Department of Medical Genetics, University Medical Center Utrecht, Utrecht, Netherlands.
- 46 Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.
- 47 Boston University School of Public Health, Boston, MA, USA.
- 48 Framingham Heart Study, Framingham, MA, USA.
- 49 Department of Immunology, Genetics and Pathology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.
- 50 Department of Genetics, University of North Carolina, Chapel Hill, NC, USA.
- 51 Department of Neurology and Stroke Center, Basel University Hospital, Switzerland.
- 52 Neurorehabilitation Unit, University and University Center for Medicine of Aging and Rehabilitation Basel, Felix Platter Hospital, Basel, Switzerland.
- 53 Department of Neurology, Yale University School of Medicine, New Haven, CT, USA.
- 54 Program in Medical and Population Genetics, The Broad Institute of Harvard and MIT, Cambridge, MA, USA.
- 55 Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
- 56 Neuroscience Institute, SF Medical Center, Trenton, NJ, USA.
- 57 Icelandic Heart Association Research Institute, Kopavogur, Iceland.
- 58 University of Iceland, Faculty of Medicine, Reykjavik, Iceland.
- 59 Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.
- 60 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.
- 61 Laboratory of Epidemiology and Population Science, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.
- 62 Department of Neurology, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, UK.
- 63 National Institute for Health and Welfare, Helsinki, Finland.
- 64 FIMM - Institute for Molecular Medicine Finland, Helsinki, Finland.
- 65 Department of Epidemiology, University of Washington, Seattle, WA, USA.
- 66 Public Health Stream, Hunter Medical Research Institute, New Lambton, Australia.
- 67 Faculty of Health and Medicine, University of Newcastle, Newcastle, Australia.
- 68 School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA.
- 69 Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA.
- 70 Aflac Cancer and Blood Disorder Center, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA.
- 71 Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, CA, USA.
- 72 Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.
- 73 Epidemiology, School of Public Health, University of Alabama at Birmingham, USA.
- 74 Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA.
- 75 Neurovascular Research Group (NEUVAS), Neurology Department, Institut Hospital del Mar d'Investigació Mèdica, Universitat Autònoma de Barcelona, Barcelona, Spain.
- 76 Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, College of Pharmacy, Gainesville, FL, USA.



77 Division of Cardiovascular Medicine, College of Medicine, University of Florida, Gainesville, FL, USA.

78 Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.

79 Program in Bioinformatics and Integrative Genomics, Harvard Medical School, Boston, MA, USA.

80 Department of Biology, East Carolina University, Greenville, NC, USA.

81 Center for Health Disparities, East Carolina University, Greenville, NC, USA.

82 University of Cincinnati College of Medicine, Cincinnati, OH, USA.

83 RIKEN Center for Integrative Medical Sciences, Yokohama, Japan.

84 Department of Medicine, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA.

85 Center for Public Health Genomics and Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA.

86 MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK.

87 Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.

88 Department of Neurology, Radiology, and Biomedical Engineering, Washington University School of Medicine, St. Louis, MO, USA.

89 KU Leuven - University of Leuven, Department of Neurosciences, Experimental Neurology, Leuven, Belgium.

90 VIB Center for Brain & Disease Research, University Hospitals Leuven, Department of Neurology, Leuven, Belgium.

91 Univ.-Lille, INSERM U 1171. CHU Lille. Lille, France.

92 Department of Medical and Molecular Genetics, King's College London, London, UK.

93 SGDP Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.

94 Northern Institute for Cancer Research, Paul O'Gorman Building, Newcastle University, Newcastle, UK.

95 Department of Clinical Sciences Lund, Neurology, Lund University, Lund, Sweden.

96 Department of Neurology and Rehabilitation Medicine, Skåne University Hospital, Lund, Sweden.

97 Bioinformatics Core Facility, University of Gothenburg, Gothenburg, Sweden.

98 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

99 University of Technology Sydney, Faculty of Health, Ultimo, Australia.

100 Department of Medicine, University of Maryland School of Medicine, MD, USA.

101 Department of Neurology, Mayo Clinic, Jacksonville, FL, USA.

102 Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, MD, USA.

103 Division of Geriatrics, School of Medicine, University of Mississippi Medical Center, Jackson, MS, USA.

104 Memory Impairment and Neurodegenerative Dementia Center, University of Mississippi Medical Center, Jackson, MS, USA.

105 Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.

106 Data Tecnica International, Glen Echo MD, USA.

107 Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

108 Clinical Research Facility, Department of Medicine, NUI Galway, Galway, Ireland.

109 Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA.

110 Department of Epidemiology, University of Washington, Seattle, WA.

111 Department of Health Services, University of Washington, Seattle, WA, USA.

112 Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA.

113 Brain Center Rudolf Magnus, Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands.

114 Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK.

115 Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.

116 Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA.

117 Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA.

118 Department of Biostatistics, University of Washington, Seattle, WA, USA.

119 Nuffield Department of Clinical Neurosciences, University of Oxford, UK.

120 Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA.

121 Division of Genomic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA.

122 Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA.

123 Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan.

124 Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA.

125 Department of Pediatrics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

126 Department of Neurology, Medical University of Graz, Graz, Austria.

127 University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany.

- 128 University Medicine Greifswald, Department of Neurology, Greifswald, Germany.
- 129 Department of Neurology, Jagiellonian University, Krakow, Poland.
- 130 Department of Neurology, Justus Liebig University, Giessen, Germany.
- 131 Department of Clinical Neurosciences/Neurology, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.
- 132 Sahlgrenska University Hospital, Gothenburg, Sweden.
- 133 Stroke Division, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, Australia.
- 134 Austin Health, Department of Neurology, Heidelberg, Australia.
- 135 Department of Internal Medicine, Section Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands.
- 136 INSERM U1219, Bordeaux, France.
- 137 Department of Public Health, Bordeaux University Hospital, Bordeaux, France.
- 138 Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center Rotterdam, Netherlands.
- 139 Center for Medical Systems Biology, Leiden, Netherlands.
- 140 School of Medicine, Dentistry and Nursing at the University of Glasgow, Glasgow, UK.
- 141 Department of Epidemiology and Population Health, Albert Einstein College of Medicine, NY, USA.
- 142 Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA.
- 143 A full list of members and affiliations appears in the Supplementary Note.
- 144 Department of Human Genetics, McGill University, Montreal, Canada.
- 145 Department of Pathophysiology, Institute of Biomedicine and Translation Medicine, University of Tartu, Tartu, Estonia.
- 146 Department of Cardiac Surgery, Tartu University Hospital, Tartu, Estonia.
- 147 Clinical Gene Networks AB, Stockholm, Sweden.
- 148 Department of Genetics and Genomic Sciences, The Icahn Institute for Genomics and Multiscale Biology Icahn School of Medicine at Mount Sinai, New York, NY, USA.
- 149 Department of Pathophysiology, Institute of Biomedicine and Translation Medicine, University of Tartu, Biomeedikum, Tartu, Estonia.
- 150 Integrated Cardio Metabolic Centre, Department of Medicine, Karolinska Institutet, Karolinska Universitetssjukhuset, Huddinge, Sweden.
- 151 Clinical Gene Networks AB, Stockholm, Sweden.
- 152 Sorbonne Universités, UPMC Univ. Paris 06, INSERM, UMR\_S 1166, Team Genomics & Pathophysiology of Cardiovascular Diseases, Paris, France.
- 153 ICAN Institute for Cardiometabolism and Nutrition, Paris, France.
- 154 Department of Biomedical Engineering, University of Virginia, Charlottesville, VA, USA.
- 155 Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA.
- 156 Seattle Epidemiologic Research and Information Center, VA Office of Research and Development, Seattle, WA, USA.
- 157 Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA.
- 158 Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Gjøttum, Norway.
- 159 Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore.
- 160 National Heart and Lung Institute, Imperial College London, London, UK.
- 161 Department of Gene Diagnostics and Therapeutics, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan.
- 162 Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA.
- 163 Department of Cardiology, University Medical Center Groningen, University of Groningen, Netherlands.
- 164 MRC-PHE Centre for Environment and Health, School of Public Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK.
- 165 Department of Epidemiology and Biostatistics, Imperial College London, London, UK.
- 166 Department of Cardiology, Ealing Hospital NHS Trust, Southall, UK.
- 167 National Heart, Lung and Blood Research Institute, Division of Intramural Research, Population Sciences Branch, Framingham, MA, USA.
- 168 A full list of members and affiliations appears at the end of the manuscript.
- 169 Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.
- 170 Oklahoma Center for Neuroscience, Oklahoma City, OK, USA.
- 171 Department of Pathology and Genetics, Institute of Biomedicine, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.
- 172 Department of Neurology, Helsinki University Hospital, Helsinki, Finland.
- 173 Clinical Neurosciences, Neurology, University of Helsinki, Helsinki, Finland.
- 174 Department of Neurology, University of Washington, Seattle, WA, USA.
- 175 Albrecht Kossel Institute, University Clinic of Rostock, Rostock, Germany.
- 176 Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK.

- 177 Department of Genetics, Perelman School of Medicine, University of Pennsylvania, PA, USA.
- 178 Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
- 179 Departments of Neurology and Public Health Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA.
- 180 Department of Neurology, Boston University School of Medicine, Boston, MA, USA.
- 181 Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA.
- 182 Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.
- 183 Munich Cluster for Systems Neurology (SyNergy), Munich, Germany.
- 184 German Center for Neurodegenerative Diseases (DZNE), Munich, Germany.
- 185 Boston University School of Medicine, Boston, MA, USA.
- 186 University of Kentucky College of Public Health, Lexington, KY, USA.
- 187 University of Newcastle and Hunter Medical Research Institute, New Lambton, Australia.
- 188 Univ. Montpellier, Inserm, U1061, Montpellier, France.
- 189 Centre for Research in Environmental Epidemiology, Barcelona, Spain.
- 190 Department of Neurology, Università degli Studi di Perugia, Umbria, Italy.
- 191 Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA.
- 192 Broad Institute, Cambridge, MA, USA.
- 193 Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, UMR 1219, Bordeaux, France.
- 194 Bordeaux University Hospital, Department of Neurology, Memory Clinic, Bordeaux, France.
- 195 Neurovascular Research Laboratory. Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona. Vall d'Hebrón Hospital, Barcelona, Spain.
- 196 University Medicine Greifswald, Department of Internal Medicine B, Greifswald, Germany.
- 197 DZHK, Greifswald, Germany.
- 198 Robertson Center for Biostatistics, University of Glasgow, Glasgow, UK.
- 199 Hero DMC Heart Institute, Dayanand Medical College & Hospital, Ludhiana, India.
- 200 Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden.
- 201 Karolinska Institutet, Stockholm, Sweden.
- 202 Division of Emergency Medicine, and Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA.
- 203 Tohoku Medical Megabank Organization, Sendai, Japan.
- 204 Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA.
- 205 Department of Public Health and Caring Sciences / Geriatrics, Uppsala University, Uppsala, Sweden.
- 206 Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan.
- 207 Department of Internal Medicine and the Center for Clinical and Translational Science, The Ohio State University, Columbus, OH, USA.
- 208 Institute of Neuroscience and Physiology, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden.
- 209 Department of Basic and Clinical Neurosciences, King's College London, London, UK.
- 210 Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Japan.
- 211 Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Japan.
- 212 Landspítali National University Hospital, Departments of Neurology & Radiology, Reykjavik, Iceland.
- 213 Department of Neurology, Heidelberg University Hospital, Germany.
- 214 Department of Neurology, Erasmus University Medical Center.
- 215 Hospital Universitari Mutua Terrassa, Terrassa (Barcelona), Spain.
- 216 Albert Einstein College of Medicine, Montefiore Medical Center, New York, NY, USA.
- 217 John Hunter Hospital, Hunter Medical Research Institute and University of Newcastle, Newcastle, NSW, Australia.
- 218 Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, UK.
- 219 Department of Medical Sciences, Uppsala University, Uppsala, Sweden.
- 220 Genetic and Genomic Epidemiology Unit, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
- 221 The Wellcome Trust Centre for Human Genetics, Oxford, UK.
- 222 Beth Israel Deaconess Medical Center, Boston, MA, USA.
- 223 Wake Forest School of Medicine, Wake Forest, NC, USA.
- 224 Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA.
- 225 BioBank Japan, Laboratory of Clinical Sequencing, Department of Computational biology and medical Sciences, Graduate school of Frontier Sciences, The University of Tokyo, Tokyo, Japan.
- 226 Neurovascular Research Laboratory, Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona. Vall d'Hebrón Hospital, Barcelona, Spain.
- 227 Department of Biostatistics, University of Liverpool, Liverpool, UK.
- 228 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
- 229 Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
- 230 Department of Medicine I, Ludwig-Maximilians-Universität, Munich, Germany.

- 231 DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany.
- 232 Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy.
- 233 Karolinska Institutet, MEB, Stockholm, Sweden.
- 234 University of Tartu, Estonian Genome Center, Tartu, Estonia, Tartu, Estonia.
- 235 Department of Clinical and Experimental Sciences, Neurology Clinic, University of Brescia, Italy.
- 236 Translational Genomics Unit, Department of Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy.
- 237 Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain.
- 238 Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain.
- 239 Department of Neurology, IMIM-Hospital del Mar, and Universitat Autònoma de Barcelona, Spain.
- 240 IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.
- 241 National Institute for Health Research Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust and King's College London, London, UK.
- 242 Division of Health and Social Care Research, King's College London, London, UK.
- 243 FIMM-Institute for Molecular Medicine Finland, Helsinki, Finland.
- 244 THL-National Institute for Health and Welfare, Helsinki, Finland.
- 245 Iwate Tohoku Medical Megabank Organization, Iwate Medical University, Iwate, Japan.
- 246 BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, UK.
- 247 deCODE Genetics/Amgen, Inc., Reykjavik, Iceland.
- 248 Icelandic Heart Association, Reykjavik, Iceland.
- 249 Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden.
- 250 Department of Epidemiology, University of Maryland School of Medicine, Baltimore, MD, USA.
- 251 Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, Glasgow, UK.
- 252 Chair of Genetic Epidemiology, IBE, Faculty of Medicine, LMU Munich, Germany.
- 253 Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan.
- 254 Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan.
- 255 University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany.
- 256 Department of Neurology, Caen University Hospital, Caen, France.
- 257 University of Caen Normandy, Caen, France.
- 258 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands.
- 259 Landspítali University Hospital, Reykjavik, Iceland.
- 260 Survey Research Center, University of Michigan, Ann Arbor, MI, USA.
- 261 University of Virginia Department of Neurology, Charlottesville, VA, USA.