Association Between Neuroticism and the Risk of Developing Dementia

Yaqing Gao

Exeter College, University of Oxford

A thesis submitted for the degree of Doctor of Philosophy

Trinity Term, 2025

Abstract

BACKGROUND: Neuroticism, a personality trait reflecting a tendency towards negative emotions, has been linked to poor health outcomes. Evidence suggests an association between higher neuroticism and dementia risk, although studies have been limited by small samples, short follow-up, and insufficient exploration of underlying pathways.

METHODS: First, a systematic search (up to December 2023) was conducted to identify studies investigating associations of neuroticism with incident dementia, cognitive function, and structural brain outcomes. Second, UK Biobank analyses of 174,164 adults aged ≥60 years (up to 16 years follow-up) used Cox proportional hazards models to assess the association between baseline neuroticism (Eysenck Personality Questionnaire-Revised Short Form) and incident dementia (hospital inpatient and death records), with mediation analyses to explore pathways. Third, EPIC-Norfolk analyses of 19,678 adults aged 40–80 years (up to 26 years follow-up) assessed long-term associations across mid- to later life with dementia risk, and also examined associations with multi-domain cognitive function. Fourth, associations between neuroticism and 249 circulating metabolites were examined in 215,624 UK Biobank participants; neuroticism-linked metabolites were then tested for associations with incident dementia. Significant observational findings were further evaluated using two-sample Mendelian randomisation (MR) to assess their robustness. Finally, associations between neuroticism and 1,747 brain structural outcomes were investigated in 36,901 UK Biobank participants, with mediation and bidirectional MR analyses to assess pathways and directionality.

RESULTS: The systematic search confirmed a consistent association between higher neuroticism and increased dementia risk, and highlighted key evidence gaps. In UK Biobank, neuroticism showed a dose-response association with dementia risk, partly mediated by mental and vascular conditions. EPIC-Norfolk analyses demonstrated that this association persisted across ages 40–80 years and >20 years of follow-up, with higher neuroticism also linked to poorer performance across multiple cognitive domains. Metabolomic analyses revealed that neuroticism was associated with an adverse profile, including lower omega-3 fatty acids, particularly docosahexaenoic acid (DHA), which in turn was related to higher dementia risk; MR supported a pathway from genetically predicted neuroticism to lower DHA and greater cerebrovascular burden. Brain-wide analyses showed that higher neuroticism was associated with smaller frontal grey matter volumes and widespread differences in white matter microstructure. These structural differences were partly mediated by mental and vascular conditions, and MR analyses suggested that they may be a consequence of, rather than a vulnerability to, high neuroticism.

CONCLUSIONS: This thesis provides robust evidence that higher neuroticism is associated with an increased long-term risk of dementia, with pathways involving mental and vascular conditions as well as lower omega-3 fatty acids. Neuroticism is also broadly associated with poorer cognitive performance and structural brain features relevant to ageing and dementia. These findings highlight the potential role of neuroticism in dementia risk stratification and suggest that, while neuroticism itself may be difficult to modify, targeting vascular and mental health factors in individuals with high neuroticism could represent a practical avenue to help reduce dementia burden.

Acknowledgements

I would like to express my deepest gratitude to my supervisors, Thomas Littlejohns, Najaf Amin, Cornelia van Duijn, and David Hunter. Their passion for science has inspired me, and their guidance and encouragement have given me the confidence to challenge myself, explore cutting-edge methods, and uphold the highest standards of research.

I am also grateful to my collaborators, including Carol Brayne, Anya Topiwala, Robert Luben, Shabina Hayat, and Bernd Taschler, from whom I have gained valuable insights into brain health, life-course epidemiology, and neuroimaging. I also thank my DPhil upgrade assessors: Jonathan Emberson, Sarah Floud, and Janet Maccora for their constructive feedback.

I am deeply thankful to the Jardine Foundation for generously funding my DPhil and to the Nuffield Department of Population Health and Exeter College for funding me to present my research at multiple national and international conferences.

I sincerely acknowledge the participants and staff of UK Biobank and EPIC-Norfolk, whose invaluable contributions made this research possible.

Last but not least, I thank my friends for walking beside me through every step of this journey, and my family, especially my parents, for their unwavering support and love.

Statement of contributions

I conceived and developed the research questions addressed in this thesis and designed the pre-specified analysis plans. I conducted all analyses, generated the tables and figures presented, and drafted both the full content of the thesis and the related manuscripts. The research presented in Chapters 3, 4, 5, and 6 forms the basis of publications that have either been published or are currently under review in peer-reviewed journals (see List of publications), for all of which I was the first author. My supervisors, Thomas Littlejohns, Najaf Amin, Cornelia van Duijn, and David Hunter, together with my co-authors on these manuscripts, provided key feedback on each of these aspects.

Thomas Littlejohns and David Hunter played key roles in the acquisition of the data used in this work. This thesis utilised the UK Biobank resource (application number 33952) and the EPIC-Norfolk study, as well as data provided by patients and collected by the National Health Service as part of their care and support. The polygenic risk score for dementia in UK Biobank was derived by the Translational Epidemiology Unit at the University of Oxford, led by David Hunter.

List of publications

1. **Gao, Y.**, Amin, N., van Duijn, C., & Littlejohns, T. J. (2024). Association of neuroticism with incident dementia, neuroimaging outcomes, and cognitive function. *Alzheimer's & dementia: the journal of the Alzheimer's Association*, 20(8), 5578–5589. https://doi.org/10.1002/alz.14071
2. **Gao, Y.**, Luben, R. N., Hayat, S., Brayne, C., Amin, N., van Duijn, C., Hunter, D., & Littlejohns, T. J. (2025). Association of neuroticism with incident dementia and cognitive function: 26-year follow-up of EPIC-Norfolk study. *Age and ageing*, 54(11), afaf339. https://doi.org/10.1093/ageing/afaf339
3. **Gao, Y.**, van Duijn, C., Littlejohns, T. J., & Amin, N. (2025). Neuroticism, omega-3 fatty acids, and risk of incident dementia. *Journal of affective disorders*, 388, 119733. https://doi.org/10.1016/j.jad.2025.119733
4. **Gao, Y.**, Taschler, B., Amin, N., van Duijn, C., Hunter, D. J., Topiwala, A., & Littlejohns, T. J. (2025). Association between neuroticism and brain-wide structural outcomes: Mediation by vascular and mental conditions. *Psychological medicine*, 55, e343. https://doi.org/10.1017/S0033291725102390

TABLE OF CONTENTS

List of abbreviations

AD: Alzheimer's disease

Aβ: amyloid-β

APOE: apolipoprotein E

ACME: average causal mediation effect

ADE: average direct effect

BMI: body mass index

CVD: cardiovascular disease

CSF: cerebrospinal fluid

CI: confidence interval

dMRI: diffusion MRI

DHA: docosahexaenoic acid

EPIC: European Prospective Investigation into Cancer

FA: fractional anisotropy

GC/MS: gas chromatography/mass spectrometry

GWAS: genome-wide association studies

HR: hazard ratio

HDL: high-density lipoprotein

IDP: imaging-derived phenotype

ICD: International Classification of Diseases

IVW: inverse-variance weighted

IHD: ischaemic heart disease

ISOVF: isotropic volume fraction

LDL: low-density lipoprotein

ICVF: lower intracellular volume fraction

λax: axial diffusivity

λrad: radial diffusivity

MRI: magnetic resonance imaging

MD: mean diffusivity

MR: Mendelian randomisation

MMSE: Mini-Mental State Examination

NODDI: neurite orientation dispersion and density imaging

NMR: nuclear magnetic resonance

OR: odds ratio

OD: orientation dispersion

PRS: polygenic risk score

ROI: region-of-interest

EPQ-RS: Eysenck Personality Questionnaire-Revised Short Form

SNP: single nucleotide polymorphism

SD: standard deviation

TDI: Townsend deprivation index

VaD: vascular dementia

VLDL: very-low-density lipoprotein

WMH: white matter hyperintensities

List of tables

List of figures

Chapter 1 Introduction

1.1 DEMENTIA

Definition and burden

Dementia is a syndrome characterized by irreversible brain damage and cognitive decline greater than normal aging.[1] It affects multiple cognitive domains—such as memory, language, visuospatial skills, and executive function—to a degree that interferes with daily functioning.[2] Although some cases begin earlier in life and are often familial, most dementia diagnoses (90–95%) are sporadic and occur after the age of 65.[3]

Dementia is a major global health challenge, affecting an estimated 57.4 million people in 2019—a number projected to reach 152.8 million by 2050 due to population aging.[4] It was the seventh leading cause of death worldwide in 2021, accounting for 1.8 million deaths and 33.6 million disability-adjusted life-years.[5] The economic impact is also substantial, with global costs estimated at US$1.3 trillion in 2019 and expected to rise to US$2.8 trillion by 2030.[6] In the UK, an estimated 982,000 people are currently living with dementia, projected to increase to 1.4 million by 2040, with associated costs rising from £42 billion in 2024 to £90 billion by 2040.[7]

Alzheimer's disease (AD), the most common subtype of dementia (accounting for 60–80% of cases),[8] is characterized by the accumulation of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain. These pathophysiological process begins 10–20 years before symptom onset,[9] with biomarker changes occurring in a temporal sequence, beginning

with reduced cerebrospinal fluid (CSF) Aβ42, followed by increased CSF tau, brain atrophy on structural magnetic resonance imaging (MRI), and eventual cognitive impairment.[10]

Vascular dementia (VaD), the second most common subtype of dementia (15–20% of cases),[11] is characterised by underlying cerebrovascular pathology. Diagnosis requires neuroimaging evidence of vascular lesions, such as infarcts or white matter changes on CT or MRI, sufficient to plausibly explain the observed cognitive impairment.[12] Unlike AD, VaD lacks a well-defined prodromal stage or biomarker cascade, and its clinical presentation is more heterogeneous, with affected cognitive domains depending on the location and extent of vascular injury.[13]

Other major subtypes include dementia with Lewy bodies, characterized by α-synuclein protein accumulation, and frontotemporal dementia, marked by degeneration of the frontal and temporal lobes.[14]

Treatment and prevention

Effective treatments for dementia remain limited. For decades, drugs such as cholinesterase inhibitors provided only temporary symptomatic relief.[2] Recent positive trial results of anti-Aβ monoclonal antibodies represent a long-awaited advance in AD treatment. The US Food and Drug Administration has approved the antibody drugs lecanemab and donanemab, which modestly slow cognitive decline by reducing amyloid burden.[15,16] However, concerns remain regarding their safety, cost, and the clinical significance of their

effects.[17] As a result, public health efforts have increasingly prioritised prevention and early intervention.

Genetic risk

AD shows strong genetic influence, with twin and family studies estimating 60–80% heritability. The apolipoprotein E (*APOE*) genotype represents the strongest established genetic risk factor for late-onset AD. Apo-E regulates lipid metabolism and contributes to processes such as cholesterol transport and Aβ clearance.[18] Its three common alleles—ε2, ε3, and ε4—differ in their effects on AD: ε4 markedly increases risk, ε2 is generally protective, and ε3 is the most prevalent and often used as the reference. Risk estimates have suggested that ε3/ε4 and ε4/ε4 carriers have roughly 2–3-fold and 9–12-fold higher AD risk, respectively, whereas ε2/ε3 carriers have about half the risk of ε3/ε3 individuals.[19] These gradients align with biomarker evidence showing faster amyloid-β accumulation in ε4 carriers and the slowest accumulation in ε2 carriers.[20] Recent ancestry-informed analyses further show that the magnitude of ε4-associated risk varies, being highest in East Asian populations, intermediate in Europeans, and attenuated in African and Hispanic ancestry groups.[21]

An expanding set of genetic loci has been implicated in AD since the introduction of genome-wide association studies (GWAS), which scan the genome for single-nucleotide polymorphisms (SNP) linked to specific disease phenotypes. The most comprehensive GWAS to date, by Kunkle et al.,[22] aggregated data from 63,926 individuals (21,982 cases and 41,994 controls) and identified 25 genome-wide significant variants, 20 of which—

including *APOE*—had been reported as genome-wide significant previously. These loci cluster into several biologically coherent pathways; for example, genes involved in lipid metabolism (*APOE*, *CLU*, *ABCA7*, *SORL1*), immune and inflammatory processes (*CR1*, *MS4A*, *TREM2*), and endocytic trafficking (*PICALM*, *BIN1*).

Compared with AD, GWAS of VaD remain limited and are constrained by small case numbers. The largest GWAS to date—the Mega Vascular Cognitive Impairment and Dementia consortium (753,695 participants, including 8,702 VaD cases)—identified only the *APOE* locus at genome-wide significance.[23] For Lewy body dementia and frontotemporal dementia, existing GWAS are similarly limited, identifying only a small number of robust loci, with *APOE* again the most consistently implicated across studies.[24,25]

Non-genetic risk

A life course approach has become a central framework for dementia prevention, recognising that disease risk is shaped by a range of physical, psychological, and environmental factors acting at different stages of life.[26] As such, identifying and addressing modifiable risk factors—those amenable to effective and accessible interventions—has emerged as a public health priority. The Lancet Commission has progressively expanded its list of such factors from 9[27] to 12[28] and most recently to 14,[17] reflecting the rapidly evolving understanding of modifiable risks and the likelihood of further additions as evidence grows. These 14 factors include low educational attainment in early life, which influences brain development and cognitive reserve; hearing loss, high low-density lipoprotein (LDL) cholesterol, depression, traumatic brain injury, physical inactivity, smoking, diabetes,

hypertension, obesity, and excessive alcohol consumption in midlife, a critical window for vascular and metabolic health; and social isolation, air pollution, and untreated vision loss in later life, when environmental and social exposures become more pronounced. Collectively, these factors are estimated to account for up to 45% of dementia cases worldwide.[17]

Mendelian randomisation (MR) is a method that uses genetic variants associated with an exposure as instrumental proxies to assess its relationship with an outcome. As genetic variants are randomly inherited during meiosis, they should not be associated with potential confounders or influenced by subsequent disease processes. This allows MR to provide less biased estimates of the direction and magnitude of exposure-outcome associations.[29] Valid MR inference relies on three core assumptions: the genetic instruments must be robustly associated with the exposure; they must not share common causes with the outcome (for example, due to population stratification); and they must influence the outcome only via the exposure rather than through alternative biological pathways (i.e., absence of horizontal pleiotropy). These assumptions cannot be proven but can be probed through sensitivity analyses. MR can be implemented using individual-level data or, more commonly, through two-sample MR that combines summary statistics from large, independent GWAS of the exposure and outcome. MR is increasingly used to strengthen evidence for observationally identified modifiable dementia risk factors; to date, educational attainment is the only factor showing a consistently protective association.[30] For most other risk factors, genetically predicted associations are null, and some exhibit paradoxical protective patterns (for example, for obesity, blood pressure and smoking).[31] These counterintuitive findings likely reflect phenotype heterogeneity in dementia GWAS, weak genetic instruments that limit

statistical power, survivor bias (where individuals genetically predisposed to harmful exposures die before reaching dementia age, producing an apparent protective direction), and horizontal pleiotropy, which can distort MR estimates.[30]

Risk factors may also differ across dementia subtypes, although most evidence focuses on AD, with fewer studies on VaD and very limited data for rarer subtypes. Studies that examine AD and VaD simultaneously generally report that many risk factors are shared, but tend to show stronger associations for VaD. Vascular factors, unsurprisingly, display stronger associations with VaD: for example, triglycerides have been associated with higher VaD risk but not AD,[32] and meta-analyses report relative risks of 1.38 for AD and 1.59 for VaD for hypertension.[33,34] In a registry study of 784,434 individuals, type 2 diabetes was associated with hazard ratios of 1.13 for AD and 1.98 for VaD.[35] Psychological factors such as depression and loneliness have also been reported to confer higher risk for VaD than AD,[36,37] likely reflecting their connection to vascular pathways. Consistent with this, MR studies show no clear association between genetically predicted triglycerides, hypertension, or diabetes and AD, [38-40] but do find positive associations with vascular brain injury.[41-43]

Beyond conventional risk factors, molecular profiling offers opportunities for more precise intervention and deeper insight into dementia aetiology. Metabolites—small molecules that are the end products of metabolic pathways—integrate genetic, environmental, and lifestyle influences, making them sensitive indicators of early pathophysiological change.[44] Many metabolites are modifiable through diet, medication, and lifestyle, and several can cross the blood-brain barrier, positioning them as potential targets

for prevention.[45] Lipid subclasses (including sphingolipids, fatty acids, and glycerophospholipids), lipoproteins, and various amino acids have repeatedly been linked to AD, VaD, and related phenotypes, including Aβ aggregation, tau pathology, and differences in brain grey and white matter.[46-49] However, replication has been limited, reflecting small sample sizes, platform heterogeneity, and reliance on cross-sectional designs.

Increasing attention is being paid to upstream factors, particularly those arising early in life, which may interact with or predisposing individuals to downstream risk factors at various stages in the life course, and therefore have long-lasting influence on brain health. Personality traits, defined as relatively stable patterns of thinking, feeling, and behaving,[50] undergo most changes during childhood and adolescence, and tend to stabilize by early adulthood.[51] Certain personality traits have been linked to increased vulnerability to several modifiable dementia risk factors, including depression, cardiovascular disease (CVD), and social isolation,[52] and may therefore represent important targets for further investigation in dementia prevention efforts.

1.2 NEUROTICISM

Definition and measurement

Neuroticism is one of the most extensively studied and empirically validated personality traits,[53] consistently identified across major models, including Eysenck's three-factor model (neuroticism, extraversion, psychoticism)[54] and the five-factor model, or Big Five (openness, conscientiousness, extraversion, agreeableness, neuroticism).[55] Although the term originated in early psychodynamic theory, its contemporary conception is rooted in psychometric and behavioural research. Neuroticism is broadly defined as a stable disposition to experience negative emotions, particularly in response to threat, frustration, or loss.[56] Individuals high in neuroticism tend to exhibit heightened emotional reactivity, often reflected in frequent and disproportionate experiences of irritability, anger, sadness, anxiety, worry, hostility, self-consciousness, and vulnerability. These facets are substantially intercorrelated yet partially distinct, as shown in factor-analytic studies.[57-59]

Neuroticism is commonly measured using a range of well-validated instruments, including the Revised NEO Personality Inventory (NEO-PI-R) and its short form, the NEO Five-Factor Inventory (NEO-FFI),[60] the Eysenck Personality Questionnaire-Revised Short Form (EPQ-RS),[61] the Big Five Inventory (BFI),[62] and the International Personality Item Pool (IPIP).[63] Despite differences in length, format, and theoretical orientation, these tools consistently measure core features such as anxiety, irritability, sadness, self-consciousness, and emotional volatility. All demonstrate strong psychometric properties, including high internal consistency, test-retest reliability, and predictive validity across mental and physical

health outcomes.[61,64-66] Importantly, these instruments conceptualize neuroticism as a continuous, universally present trait rather than a categorical diagnosis.[67] Similar to blood pressure or body mass index (BMI), individuals vary along a spectrum from low to high levels.

Genetic and environmental influences on neuroticism

Neuroticism is a heritable trait, with approximately 40% of its variance attributable to genetic factors, as estimated by twin studies comparing monozygotic and dizygotic twins.[68,69] Recent GWASs, leveraging large-scale data including UK Biobank, 23andMe, and the Genetics of Personality Consortium, have identified over 200 genetic loci associated with neuroticism.[70,71] Notably, some implicated genes, such as *CRHR1*, which influence stress reactivity and have been linked to anxiety and depressive disorders,[72,73] have shown replication across studies.[71,74] However, the proportion of variance explained by all SNPs, known as SNP-based heritability, remains modest (7%–10%).[70,71] This gap between SNP-based and twin-based heritability estimates likely reflects the contribution of non-additive genetic effects and gene-environment interactions not captured by current GWAS approaches. Environmental influences may also shape neuroticism, with retrospective studies linking adverse childhood experiences, such as abuse and neglect, with higher neuroticism in adulthood.[75-77] However, the environmental evidence remains limited and largely correlational; prospective, genetically informed designs are needed to clarify the causality.

Lifespan stability

Given the strong influence of genetic and early life experiences, neuroticism is typically established early. As a personality trait, it demonstrates high rank-order stability, meaning individuals generally maintain their relative level of neuroticism compared to others over time,[78] with a meta-analysis reporting average test-retest correlations of approximately 0.60 even across 15-year intervals.[78] In a large US cohort of 3,850 participants aged 25 to 75, the retest correlation for neuroticism over a nine-year interval was 0.64,[79] a finding replicated across non-Western populations.[79] Analyses stratified by age revealed minimal differences in stability between younger (30–50), middle-aged (50–65), and older adults (>65) over retest intervals ranging from six to 15 years.[80] Notably, neuroticism shows roughly one-third higher stability than symptoms of common mental disorders such as depression and anxiety,[81] and its stability is comparable to that of the other Big Five traits.[51] While individuals tend to maintain their relative standing over time, mean levels of neuroticism modestly decline with age.[82]

Public health significance of neuroticism

Neuroticism is of growing interest in public health research due to its robust and wide-ranging associations with both mental and physical health outcomes. A large meta-analysis of 59 prospective studies (N=443,313) demonstrated that higher neuroticism was significantly associated with increased risk of anxiety, depression, and general psychological distress.[83] These associations remained significant after adjusting for baseline symptoms and psychiatric history, and the magnitudes of short-term (<4 years) and long-term (≥4 years)

associations were comparable. In a 35-year follow-up study of 1,118 adults, higher neuroticism predicted increased risk of clinical diagnoses including anxiety, adjustment, personality, and substance use disorders.[84]

Recent MR studies have shown that genetic liability to neuroticism increases the risk of multiple psychiatric conditions, including depression, anxiety disorders, schizophrenia, attention deficit hyperactivity disorder (ADHD), anorexia nervosa, and bipolar disorder.[70,85] Bidirectional MR analyses suggest potential reciprocal relationships for schizophrenia and ADHD, where genetic liability to these disorders also influences neuroticism.[70,85] No reverse associations were observed for other conditions, supporting a primarily unidirectional influence of neuroticism on psychiatric risk.

A substantial body of research has investigated the role of neuroticism in physical health, particularly in relation to vascular conditions. Prospective studies consistently report significant associations between higher neuroticism and increased risk of incident coronary heart disease and myocardial infarction,[86-89] even after adjustment for traditional risk factors such as hypertension, smoking, depression, and anxiety. Evidence linking neuroticism to stroke remains mixed. A pooled analysis of 58,105 participants across six large longitudinal cohorts reported a positive association,[90] whereas a UK study of 126,255 individuals found no significant link.[87] These observational findings are supported by MR analyses, which suggest that genetic liability to neuroticism increases the risk of CVD, hypertension, and stroke,[91,92] with no evidence that genetic predisposition to these conditions influences neuroticism in the reverse direction. By contrast, evidence for other physical conditions

remains limited. Some studies suggest associations between neuroticism and asthma,[93] atopic eczema,[94] irritable bowel syndrome,[95] and chronic obstructive pulmonary disease,[96] whereas no significant relationship has been observed with cancer.[97]

1.3 NEUROTICISM AND RISK OF DEMENTIA

Current evidence

Given neuroticism's robust associations with a broad range of adverse mental and physical health outcomes, including depression,[83,85] CVD,[86-88] social isolation,[98] and unhealthy behaviours such as smoking and poor diet,[99-102] all of which are recognized risk factors for dementia, there is growing interest in its potential role as an upstream determinant of dementia. A recent meta-analysis of 12 longitudinal studies across the US, Europe, and Australia (N>30,000) found that nine reported significant associations between higher neuroticism and increased dementia risk. Between-study heterogeneity was low, and each standard deviation (SD) increase in neuroticism was associated with a 24% higher risk of dementia.[103] To better understand this association, further research is needed to clarify its directionality, temporality, and potential underlying pathways. Addressing these questions is essential for informing dementia prevention strategies.

Key research goals

Directionality of the association

Dementia typically develops over a long time,[9] which makes it challenging to distinguish between traits that contribute to disease risk and those that may reflect early manifestations of the condition, especially when neuroticism is assessed close to the time of diagnosis, an issue known as reverse causality. Whilst neuroticism is generally considered stable across the life course, dementia is a disease of the brain and may lead to behavioural and psychological symptoms at an early stage, including increased anxiety, irritability, and

sadness—core components of neuroticism.[104] Clarifying whether neuroticism precedes and contributes to dementia risk, rather than reflecting prodromal changes, requires prospective studies with long-term follow-up of 10 years or more, ideally extending beyond 20 years.

Life stage-specific associations

Some downstream factors of neuroticism show age-specific associations with dementia. For instance, midlife hypertension has been consistently linked to increased dementia risk, whereas lowering blood pressure in later life appears to offer less benefit,[17] possibly due to advanced cerebral atherosclerosis or different underlying mechanisms.[30] In contrast, depression is considered a risk factor in both midlife and late life,[105,106] though the association in late life may be partially driven by reverse causality.[107] Given that personality traits are established early in life and remain relatively stable,[78] it is important to determine whether the association between neuroticism and dementia is consistent across the life course or varies by age, to inform how dementia prevention strategies could be tailored to specific age groups and psychological profiles.

Modifiable factors linking the association

Unlike episodic emotional states, neuroticism may be less amenable to short-term modification due to its stability. Most existing interventions have shown only modest effects and are limited by small sample sizes, lack of control groups, and limited long-term follow-up to assess durability of changes.[108-112] Given these challenges, an alternative approach is to identify downstream consequences of neuroticism—such as clinical or molecular risk

factors—that are also associated with increased dementia risk. These intermediate factors may be more responsive to existing behavioural or pharmacological interventions, and thus offer more practical and scalable targets for prevention in individuals with high neuroticism.

Association with broader brain health

Before the clinical onset of dementia, early changes often emerge across multiple cognitive domains and brain structures.[10] Investigating how these changes present in individuals with high neuroticism may help clarify the mechanisms linking neuroticism to dementia risk. For instance, if neuroticism is particularly associated with brain structural markers of cerebrovascular injury, such as increased white matter hyperintensities (WMH),[113] this would support a vascular pathway. In contrast, broad associations spanning multiple cognitive domains and brain regions would point to a multifactorial mechanism. Importantly, comprehensive cognitive testing and neuroimaging can detect preclinical changes less likely to reflect reverse causation, providing a clearer insight into neuroticism's influence on brain health.

1.4 THESIS OBJECTIVES

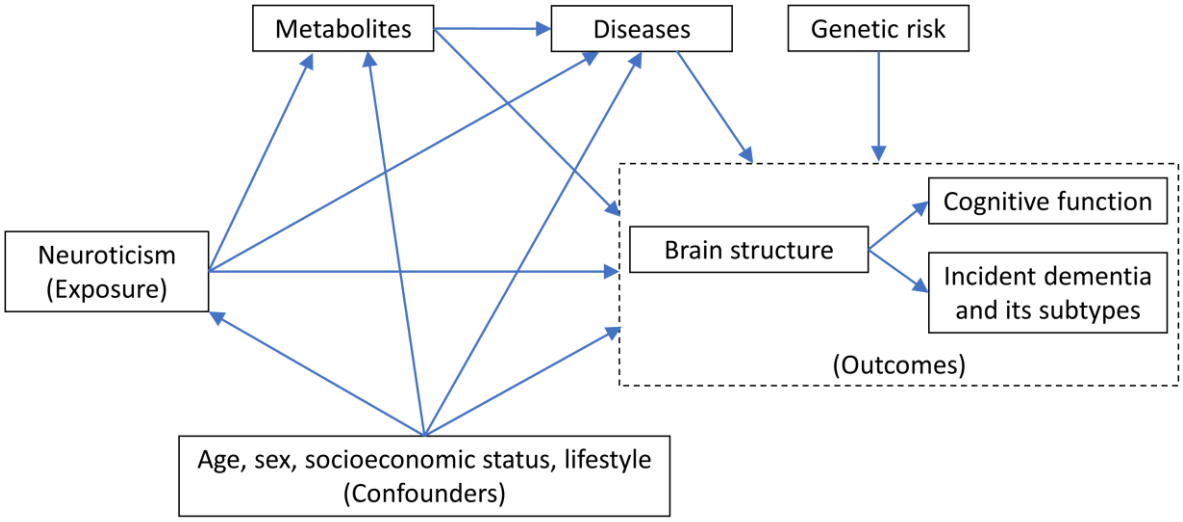
To address critical gaps in current understanding, this doctoral research aims to clarify the relationship between neuroticism and dementia risk, and to investigate the pathways that may underlie this association. The specific objectives are as follows:

1) To conduct a systematic search of the literature on neuroticism in relation to incident dementia, cognitive function, and structural brain outcomes.
    - Purpose: To provide an up-to-date synthesis of prospective studies on neuroticism and incident dementia, as well as relevant cross-sectional and longitudinal studies examining neuroticism's associations with cognitive and structural brain outcomes. This systematic search will identify key gaps in the literature that inform the direction of this thesis.
2) To investigate the associations between neuroticism and incident all-cause dementia and key dementia subtypes in the UK Biobank cohort.
    - Purpose: To leverage a large, richly phenotyped cohort to comprehensively examine the relationship between neuroticism and dementia risk, potential effect modification by genetic risk, mediation through disease histories, and relationship between neuroticism and performance across multiple cognitive domains.
3) To examine the associations between neuroticism and incident all-cause dementia and key dementia subtypes in the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort.
    - Purpose: To leverage a cohort with a broad baseline age range and long follow-up to investigate how neuroticism is associated with dementia risk

from mid- to later life, in the short and long term; extend effect modification and mediation analyses in UK Biobank to this more age-diverse population; and assess the association with cognitive performance using a comprehensive test battery.

4) To explore the metabolomic profile associated with neuroticism and its relevance to dementia risk.
    - Purpose: To conduct hypothesis-free analyses using UK Biobank metabolomics data to identify metabolites associated with neuroticism, and to examine whether these neuroticism-linked metabolites are associated with incident dementia and its subtypes. This will provide insight into the potential molecular pathways underlying the association.
5) To investigate the association between neuroticism and brain-wide structural outcomes.
    - Purpose: To use UK Biobank neuroimaging data to assess the association between neuroticism and grey and white matter structure in a hypothesis-free, causal inference framework, and evaluate mediation through disease histories examined in Objective 2 and 3. These findings will provide insight into neuroticism's role in broader brain health.

Figure 1.1: Directed acyclic graph of hypothesised neuroticism and dementia-related pathways



This directed acyclic graph illustrates the conceptual framework underpinning the thesis objectives. Neuroticism may influence dementia risk and cognitive function directly or indirectly through metabolites, diseases, and brain structural differences. Genetic susceptibility to dementia may modify these relationships. Sociodemographic and lifestyle factors act as covariates and are adjusted for in all analyses.

Chapter 2 A systematic search of the literature on the associations between neuroticism and incident dementia, cognitive function, and structural brain outcomes

2.1 CHAPTER SUMMARY

This chapter presents a systematic search of the current evidence on neuroticism and its association with incident dementia, cognitive function, and structural brain outcomes in mid- to later life. PubMed searches were conducted to December 2023, extending a 2020 meta-analysis for dementia, summarising all available studies on cognition, and updating a 2022 review on grey matter and newly assessing white matter outcomes.

Pooled results from 12 prospective studies showed that higher neuroticism was associated with an increased risk of dementia. Most studies assessed all-cause dementia, relatively few specifically examined AD or VaD. Thirty-one studies assessed cognition, most reporting poorer global function and episodic memory, with less consistent findings for other domains. Structural imaging evidence was limited: studies on grey matter showed smaller frontal volumes, and the few available white matter studies suggested reduced fractional anisotropy (FA) and increased diffusivity.

Overall, neuroticism appears to be associated with greater dementia risk, poorer cognition, and adverse brain structural outcomes. However, small samples, short follow-up, restricted age ranges, and limited coverage of cognitive and structural brain outcomes constrain interpretation, and effect modification and pathways remain largely unexplored.

2.2 OBJECTIVES

The objectives of this systematic search of the literature were to identify, summarise, and appraise published evidence on the association between neuroticism and incident dementia, with a focus on direct associations, potential effect modification, and underlying pathways. As outlined in the previous chapter, early changes in brain health, reflected in cognitive performance and structural brain differences, often precede the clinical onset of dementia. To better capture cases of late-onset dementia (typically manifesting after age 65) and to examine associations between neuroticism and age- or dementia-related changes in cognitive function and brain structure, this systematic search focused on studies involving mid- to later-life participants.

2.3 METHODS

Incident dementia

In this chapter, the systematic search of the literature on the association between neuroticism and incident dementia was based on the most up-to-date meta-analysis available at the time of the literature search, conducted in December 2023.[103] This meta-analysis, published in February 2021, had systematically reviewed prospective studies published up to June 2020. To identify more recent evidence, an updated literature search was conducted on PubMed for studies published from July 2020 to December 2023. This search followed the same strategy and inclusion criteria as the meta-analysis.[103]

The search terms used were: (dement*[Title] OR Alzheimer*[Title]) AND (personality[Title] OR neuroticism[Title] OR five factor[Title] OR five-factor[Title] OR big five[Title]). Studies were included if they met the following criteria: (1) human studies; (2) published in peer-reviewed journals and written in English; (3) reported how neuroticism and dementia were assessed; and (4) provided risk estimates (e.g., hazard ratios [HRs] or odds ratios [ORs]) along with confidence intervals (CIs) and/or p-values.

Cognitive function

At the time of the literature search (December 2023), only one meta-analysis had examined the association between neuroticism and cognitive function, based on studies published up to April 2014.[114] However, it included only longitudinal studies and focused exclusively on global cognition, without synthesizing evidence on specific cognitive domains. To address this gap, a literature search was conducted on PubMed for (longitudinal or cross-sectional) studies published at any time up to December 2023.

The search terms used were: (cognitive[Title] OR cognition[Title] OR (intelligence[Title] NOT "artificial intelligence"[Title]) OR memory[Title] OR "executive function"[Title]) AND (personality[Title] OR neuroticism[Title] OR five factor[Title] OR five-factor[Title] OR big five[Title]). Studies were included if they met the following criteria: (1) conducted in human populations aged 45 years and older, excluding studies focused exclusively on populations with specific conditions (e.g., depression, subjective cognitive decline); (2) published in peer-reviewed journals and written in English; (3) reported how neuroticism and cognitive function were assessed; (4) used objective cognitive measures

based on test performance rather than informant or self-reported cognitive problems; and (5) provided risk estimates (e.g., HRs or ORs) along with CIs and/or p-values.

Structural brain outcomes

To examine the associations between neuroticism and structural brain outcomes in mid- to later life, studies were first identified from the most recent systematic review (published August 2022),[115] which evaluated grey matter volume, cortical surface area, and cortical thickness based on publications up to 2020. Since that review applied no age restrictions, only studies including participants aged 45 or older were retained. An updated PubMed search was then conducted: for cortical and subcortical structures, the same search strategy from the previous review[115] was used to identify studies published between January 2020 and December 2023; for white matter structures, studies were searched without date restrictions through December 2023.

Search terms for cortical/subcortical structure studies included: (MRI[Title/abstract] OR gray matter volume[Title/abstract] OR GMV[Title/abstract] OR VBM[Title/abstract] OR voxel-based morphometry[Title/abstract] OR SBM[Title/abstract] OR surface-based morphometry[Title/abstract] OR cortical thickness[Title/abstract] OR cortical thinning[Title/abstract] OR surface area[Title/abstract] OR cortical folding[Title/abstract] OR brain structure[Title/abstract] OR neuroimaging[Title/abstract] OR imaging[Title/abstract]) AND (personality[Title] OR neuroticism[Title] OR five factor[Title] OR five-factor[Title] OR big five[Title]). For white matter studies: (DTI[Title/abstract] OR diffusion[Title/abstract] OR white matter

hyperintensities[Title/abstract]) AND (personality[Title] OR neuroticism[Title] OR five factor[Title] OR five-factor[Title] OR big five[Title]). Studies were included if they (1) involved participants aged 45 or older, excluding studies focused exclusively on populations with specific conditions (e.g., depression, subjective cognitive decline); (2) published in peer-reviewed journals and written in English; and (3) reported neuroticism assessment methods and neuroimaging protocols.

2.4 RESULTS

Neuroticism and incident dementia

Prospective evidence

This systematic search identified 13 prospective cohort studies examining the association between neuroticism and incident dementia. Twelve were included in the most recent meta-analysis available as of December 2023,[103] and one additional study was published subsequently (**Table 2.1**).[116] All studies were conducted in Western, community-based populations, predominantly involving White participants. The studies were based in seven cohorts from the US,[117-123] three from the UK,[116,124,125] two from Sweden,[126,127] and one from Australia.[125]

Neuroticism was assessed using various validated instruments. The most commonly used tool was the NEO Personality Inventory (NEO-FFI or NEO-PI-R), applied in six studies.[117-121,123] Other instruments included the Mini-Markers by Saucier,[125] the EPQ-RS,[116,126,127] and the Midlife Development Inventory (MIDI).[122,124,125] Dementia outcomes, including all-cause dementia and specific subtypes such as AD and VaD, were identified using neuropsychiatric examinations (used alone in six studies),[117-121,123] cognitive cut-off scores,[122,125] clinical diagnoses,[116,124] or a combination of these methods.[126,127]

Among the seven studies investigating all-cause dementia, five reported statistically significant positive associations between higher neuroticism and increased dementia risk (**Table 2.2**), with most adjusting for age, sex, ethnicity, and education. Three large cohort

studies conducted in the US and UK, with baseline mean ages in the mid-60s to early 70s, mean follow-up periods of approximately six years, incident dementia cases ranging from 231 to 433, reported similar HRs per 1-SD increase in neuroticism: HR 1.18 (95% CI 1.07 to 1.30),[122] 1.20 (1.05 to 1.36),[125] and 1.32 (1.17 to 1.49).[124] Two additional studies with longer follow-up periods also found significant associations: one followed 2,778 participants for 11 years and identified 52 incident cases, reporting a stronger association (1.64, [1.14 to 2.35]);[125] the other followed over 400,000 participants for nine years, with 1,798 incident cases, and reported an HR of 1.22 (1.17 to 1.28).[116] This study also examined dementia subtypes and found that neuroticism was more strongly associated with VaD (1.24, [1.13 to 1.38]) than with AD (1.15, [1.06 to 1.24]).[116]

In contrast, a study involving a small sample of older adults (N=506; mean age=83) found no association (0.98, [0.93 to 1.03]) after comprehensive adjustment for age, sex, education, *APOE* ε4 status, cognitive function, vascular disease, and depressive symptoms.[126] Another study of 800 women aged 38–54 at baseline, followed for up to 38 years, also reported a non-significant association (1.02, [0.99 to 1.06]), even when adjusting for age only.[127] However, a modest but significant association was observed for AD (1.04, [1.00 to 1.08]) but not VaD (0.95, [0.88 to 1.03]).

Table 2.1: Characteristics of studies examining neuroticism and incident dementia

Authors, Year	Country (data source)	Race	N_{tot}	Age M (SD)	Female %	Neuroticism measure	Outcome	Outcome measure
Wilson, 2005 [117]	US (Rush Biracial)	50.2% White; 49.8% African American	1,064	73.8 (9.6)	61.9	NEO-FFI	AD	Adjudicated based on NINCDS-ADRDA
Wilson, 2006 [118]	US (Rush MAP)	93.7% White	648	80.6 (6.9)	73.5	NEO-FFI	AD	Adjudicated based on NINCDS-ADRDA
Wilson, 2007 [119]	US (Rush ROS)	NR	904	73.5–80.0 (6.5)[a]	68.0–71.0[a]	NEO-FFI	AD	Adjudicated based on NINCDS-ADRDA
Wang, 2009 [126]	Sweden (KPS)	NR	506	83.0 (3.2)–83.9 (3.7)[a]	69.6–76.4[a]	EPI	All-cause dementia	Adjudicated based on DSM-III-R; hospital records and death certificates
Duberstein, 2011 [120]	US (GEM)	91.8% White	767	78.6 (3.1)	41.9	NEO-FFI	AD	Adjudicated based on DSM-IV, NINCDS ADRDA, NINDS AIREN
Terracciano, 2014 [121]	US (BLSA)	70.7% White	1,671	56.5 (16.0)	49.4	NEO-PI-R	AD	Adjudicated based on DSM-III-R, NINCDS ADRDA
Johansson, 2014 [127]	Sweden (PPSW)	NR	800	38–54	100	EPI	All-cause dementia, AD, VaD	For all-cause dementia: neuropsychiatric examinations, close informant interviews, medical records (compatible with DSM-III-R); For AD and VaD: NINCDS ADRDA, NINDS AIREN
Terracciano, 2017 [122]	US (HRS)	85% White	10,457	67.17 (9.23)	60	MIDI	All-cause dementia	Adjudicated based on TICSm
Duchek, 2020 [123]	US (WashU)	NR	436	65.9 (9.2)	57	NEO-FFI	AD	Adjudicated based on NINCDS-ADRDA, CDR≥0.5
Singh-Manoux, 2020 [124]	UK (Whitehall II)	92.8% White	6,135	69.59 (5.78)–75.38 (4.97)[a]	30	MIDI	All-cause dementia	Hospital inpatient data, mental health service data, death records (ICD-10 codes F00-F03, F05.1, G30 and G31)
Aschwanden, 2020 [125]	UK (ELSA)	97.5% White	6,887	65.65 (8.31)	56.2	MIDI	All-cause dementia	Adjudicated based on TICSm; self-report
Aschwanden, 2020 [125]	Australia (HILDA)	98.7% White	2,778	60.90 (8.08)	54.7	Mini-Markers Saucier	All-cause dementia	Adjudicated based on SDMT and BDS
Terracciano, 2021[b] [116]	UK (UK Biobank)	NR	401,422	56.41 (8.07)	53.7	EPQ-RS	All-cause dementia, AD, VaD	Hospital inpatient data and death records

Rush Biracial, Rush Memory and Aging Biracial (White, African Americans); Rush MAP, Rush Memory and Aging Project; Rush ROS, Rush Religious Order Study; KPS, Kungsholmen Project Stockholm; GEM, Ginkgo Evaluation of Memory Study; BLSA, Baltimore Longitudinal Study of Aging; PPSW, Prospective Population Study of Women; HRS, Health Retirement Study; HABC, Health, Aging and Body Composition Study; WashU, Study conducted at Washington University in St. Louis; Whitehall II, Whitehall II Study; ELSA, English Longitudinal Study of Ageing; HILDA, Household, Income and Labour Dynamics in Australia; UK Biobank, UK Biobank; NEO-FFI, NEO Five Factor Inventory; NEO-PI-R, Revised NEO Personality Inventory; MIDI, Midlife Development Inventory; EPI, Eysenck's Personality Inventory; EPQ-RS, Eysenck Personality Questionnaire - Revised Short Form; ICD, International Classification of Diseases; CDR, Clinical Dementia Rating;

DSM, Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; TICSm → Telephone Interview for Cognitive Status - modified; SDMT, Symbol Digit Modalities Test; BDS, Backward Digit Span; NR, not reported; AD, Alzheimer's disease; VaD, vascular dementia; N_{tot}, total sample size; M, mean; SD, standard deviation

[a] Age was not provided for the total sample (participants were categorized into groups in descriptive statistics).

[b] This investigation was not included in the meta-analysis but resulted from the literature search for subsequent investigations.

Table 2.2: Associations between neuroticism and incident dementia in included studies

Authors, Year	$N_{all-cause}$	N_{AD}	N_{VaD}	Follow-up M	Covariates (main model)	Effect sizes (main model)
Wilson, 2005 [117]	NR	170	NR	NR (max=6)	Age, sex, race, education, *APOE* ε4 status, follow-up time	Per 1-point increase: OR=1.060; 95% CI 1.012–1.109
Wilson, 2006 [118]	58	55	NR	2.7	Age, sex, education	Per 1-point increase: RR=1.056; 95% CI 1.019–1.095
Wilson, 2007 [119]	NR	176	NR	NR (max=12)	Age, sex, education	Per 1-point increase: HR=1.033; 95% CI 1.005–1.063
Wang, 2009 [126]	144	NR	NR	NR (max=6)	Age, sex, education, *APOE* ε4 status, cognitive functioning (MMSE score ≥27 vs ≤26), vascular diseases (heart disease, stroke, and diabetes), depressive symptoms or diagnosis	Per 1-point increase: HR=0.98; 95% CI 0.93–1.03
Duberstein, 2011 [120]	NR	116	NR	6	Age, gender, education, race	Per 1-SD increase: HR=1.39, 95% CI 1.16–1.67
Terracciano, 2014 [121]	NR	90	NR	12	Age, sex, ethnicity, education	Per 1-SD increase: HR=1.37, 95% CI 1.09–1.73
Johansson, 2014 [127]	153	104	35	NR (max=38)	Age	Per 1-SD increase: HR=1.02, 95% CI 0.99–1.06 (all-cause); HR=1.04, 95% CI 1.00–1.08 (AD); HR=0.95, 95% CI 0.88–1.03 (VaD)
Terracciano, 2017 [122]	433	NR	NR	6.29	Age, sex, race, ethnicity, education	Per 1-SD increase: HR=1.18, 95% CI 1.07–1.30
Duchek, 2020 [123]	NR	47	NR	6.95	Age	Per 1-SD increase: OR=1.25, 95% CI 0.89–1.74 (self-report); OR=1.05, 95% CI 0.70–1.56 (informant report)
Singh-Manoux, 2020 [124]	231	NR	NR	6.18	Age, sex, ethnicity, marital status, education	Per 1-SD increase: HR=1.32, 95% CI 1.17–1.49
Aschwanden, 2020 [125]	252	NR	NR	5.68	Age, gender, ethnicity, education	Per 1-SD increase: HR=1.20, 95% CI 1.05–1.36
Aschwanden, 2020 [125]	52	NR	NR	10.96	Age, gender, ethnicity, education	Per 1-SD increase: HR=1.64, 95% CI 1.14–2.35
Terracciano, 2021[a] [116]	1,798	675	376	8.88	Age, sex	Per 1-SD increase: HR=1.22, 95% CI 1.17–1.28 (all-cause); HR=1.15, 95% CI 1.06–1.24 (AD); HR=1.24, 95% CI 1.13–1.38 (VaD)

$N_{all-cause}$, number of all-cause dementia cases; N_{AD}, number of incident AD cases; N_{VaD}, number of incident VaD cases; M, mean; AD, Alzheimer's disease; VaD, vascular dementia; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; NR, not reported; SD, standard deviation; OR, odds ratio; HR, hazard ratio; CI, confidence interval

[a] This investigation was not included in the meta-analysis but resulted from the literature search for subsequent investigations.

Effect modification and mediation

Certain studies examined whether the association between neuroticism and dementia risk varied by age,[122,125] sex,[121,122,125] or education.[122,125] None of these found significant interactions. Interaction with *APOE* ε4 status,[121] and household income was each examined in a single study,[116] but neither showed statistically significant modification of the association.

No study conducted formal mediation analysis. However, several used multivariable models to assess whether the observed associations persisted after adjusting for various covariates, without specifying whether these factors were confounders or mediators. Depression was the most commonly adjusted psychological factor. In most studies, depressive symptoms were assessed using questionnaires or structured interviews, and adjusting for them generally left the association between neuroticism and dementia unchanged[117,118] or only slightly attenuated,[120] with the association remaining significant. However, in one study that incorporated a broader definition of depression—combining symptom scores, clinical diagnoses, and antidepressant use—the previously significant associations were attenuated to null.[124] Apart from depression, another study reported that adjusting for self-reported distress related to daily life (e.g., work, health, or family issues) experienced during the previous five years attenuated the significant association with AD to null.[127]

Certain studies also explored whether physical health explained the observed association between neuroticism and dementia. These analyses typically adjusted for

prevalent chronic conditions such as diabetes,[116,120,122,124] heart disease,[116,120,124,127] and hypertension.[116,120,122,124,127] In studies that assessed chronic conditions using field measurements (e.g., blood pressure for hypertension)[127] or self-reported diagnoses,[116,120,122] adjusting for health conditions did not substantially change the results. In contrast, the study that used medical records to ascertain diagnoses reported attenuation of the association after adjustment for physical health.[124]

Neuroticism and cognitive function

This systematic search identified 31 studies examining the association between neuroticism and cognitive function in mid- to later life (**Table 2.3**). Nearly all were conducted in North America or Europe, with predominantly White samples. A few US studies included partial representation of African American participants,[128-130] while only three studies were conducted in predominantly non-White populations, based in Japan[131,132] and Malaysia.[133] Thirteen studies had fewer than 1,000 participants, and 15 included between 1,000 and 8,000. Only three studies exceeded 10,000 participants,[114,134,135] the largest being an individual-level meta-analysis of nine international cohorts (N=120,640).[134]

Thirteen studies assessed global cognitive function or used composite scores derived from multiple cognitive domains (**Table 2.4**).[128-133,136-142] Nine of these focused solely on global cognition or summary indices without evaluating domain-specific outcomes.[130,131,133,136-141] Nearly all reported significant cross-sectional associations between higher neuroticism and poorer global or composite cognitive performance. Longitudinal analyses also consistently found that higher baseline neuroticism predicted lower global

cognitive performance measured up to 10–20 years later.[129,131,137] However, associations with the rate of cognitive decline were observed only among participants with older baseline ages (mean age >72 years),[130,141] and were generally null in younger cohorts.[136,139]

Episodic memory is the most frequently assessed cognitive domain in studies of neuroticism and cognition, commonly measured using immediate or delayed word recall tasks. Seven studies focused exclusively on this domain,[114,134,143-145] particularly those based on large, harmonized data from multi-country cohorts.[114,134] These studies consistently found that higher neuroticism was associated with poorer memory performance[114,134] and greater decline over time.[134]

Nine studies assessed at least three cognitive domains,[128,146-152] most commonly memory and executive function, with some also evaluating reasoning,[147] visuospatial skills,[149,150,152] and verbal fluency.[146,147,150,152,153] Large cohort studies (N=7,685;[128] N=2,865[149]) consistently found negative cross-sectional associations between neuroticism and baseline performance across global cognition, memory, and executive function, with similar effect sizes across domains. In contrast, smaller studies (N<600) showed less consistent findings: some reported associations only with global cognition,[129,132,142] while others found domain-specific associations that varied across studies. For example, some reported a negative association between neuroticism and executive function at baseline[150] and over time,[152] while others found no significant associations.[148]

Table 2.3: Characteristics of studies examining neuroticism and cognitive function

Authors, Year	Country (data source)	Design	Race	N_{tot}	Age M (SD)	Female %
Olaru, 2023[136]	Sweden (SNAC-K)	Longitudinal	NR	506	83.0 (3.2)–83.9 (3.7)[a]	69.6–76.4[a]
Stephan, 2023[143]	UK (ELSA)	Longitudinal	98% White	3,584	67.63 (6.89)	53
Stephan, 2023[143]	US (HRS)	Longitudinal	6% Hispanic, 10% African American	4,109	70.51 (6.32)	58
Desai, 2023[128]	US (CHAP)	Longitudinal	36% White; 64% African American	7,685	72.2 (6.2)	62
Bethell, 2023[135]	Canada (CLSA)	Cross-sectional	NR	27,765	65.44 (10.08)–65.78 (10.08)[a]	49
Iwasa, 2022[132]	Japan (Tokyo community)	Cross-sectional	NR	373	61.9 (12.1)	55.2
Terracciano, 2022[137]	Italy (SardiNIA)	Longitudinal	NR	1,668	61.48 (8.00)	56.4
Beaudreau, 2022[146]	US (WLS)	Longitudinal	NR	6,133	53.2 (0.6)	54.2
Sutin, 2022[134]	US, UK, Europe (HRS, MIDUS, WLSG, WLSS, NHATS, NSHAP, ELSA, SHARE, CFAS)	Longitudinal	72.47%–100%[b]	120,640	56.01 (12.33)–79.22 (7.36)	51.78–59.07
Montoliu, 2021[138]	Spain (University of Valencia)	Longitudinal	NR	87	65.08 (4.54)	49.4
Stephan, 2021[144]	US (MIDUS)	Longitudinal	95% White	2,411	45.78 (11.11)	55
Stephan, 2021[144]	US (WLS)	Longitudinal	100% White	5,446	53.18 (0.60)–52.44 (6.90)[a]	54
Simon, 2020[147]	US (RANN, CR)	Cross-sectional	NR	422	54.0 (16.7)	54.6
Simon, 2020[147]	US (NKI-RSI)	Cross-sectional	NR	549	49.5 (18.8)	67.9
Wettstein, 2019[148]	Germany (ILSE)	Longitudinal	NR	500	62.87 (0.89)	48
Sutin, 2019[149]	US (HRS)	Cross-sectional	82% White; 14% African American	2,865	76.49 (7.36)	60
Crook, 2018[139]	UK (LBC1936)	Longitudinal	NR	1,028	69.5 (0.8)	49.8
Foong, 2018[133]	Malaysia (LRGS TUA)	Cross-sectional	NR	2,322	69.1 (6.23)	52
Chapman, 2017[150]	US (R/OCAS)	Cross-sectional	NR	179	82.09 (4.37)	53
Wettstein, 2017[151]	Germany (ILSE)	Longitudinal	NR	1,002	44.2 (0.91)–62.9 (0.89)[a]	48.1
Klaming, 2017[145]	Netherlands (LASA)	Longitudinal	NR	1,966	76.18 (6.83)	53.8
Luchetti, 2016[114]	Europe & Israel (SHARE)	Cross-sectional	NR	71,566	67.9 (9.5)	57

Caselli, 2016[152]	US (Maricopa County)	Longitudinal	81% White	510	57.6 (10.6)	70
Nishita, 2016[131]	Japan (NILS-LSA)	Longitudinal	NR	594	68.23 (5.63)	48.82
Hock, 2014[129]	US (ECA)	Longitudinal	60.4% White	561	45.2 (10.78)	64.9
Dar-Nimrod, 2012[140]	US (GEM)	Cross-sectional	91.8% White	597	78.6 (3.1)	41.9
Chapman, 2012[141]	US (GEM)	Longitudinal	NR	602	75 (6.6)	62
Hagger-Johnson, 2012[154]	UK (HALS)	Longitudinal	NR	4,260	44.19 (15.36)	55.4
Boyle, 2011[142]	US (primary care patients)	Cross-sectional	NR	488	75.0 (6.5)	62.3
Sutin, 2011[153]	Italy (SardiNIA)	Longitudinal	NR	4,790	42.59 (16.32)	58
Wilson, 2005[130]	US (CHAP)	Longitudinal	62% Black	4,983	73.9 (6.5)	62

N_{tot}, total sample size; M, mean; SD, standard deviation; NR, not reported; CLSA, Canadian Longitudinal Study on Aging; TIPI, Ten Item Personality Inventory; CHAP, Chicago Health and Aging Project; SNAC-K, Swedish National Study on Aging and Care in Kungsholmen; R/OCAS, Rochester/Orange County Aging Study; SHARE, Survey of Health, Ageing and Retirement in Europe; HRS, Health and Retirement Study; ELSA, English Longitudinal Study of Ageing; WLS, Wisconsin Longitudinal Study; WLSG/WLSS, Wisconsin Longitudinal Study Graduate/ Sibling samples; MIDUS, Midlife in the United States Study; NHATS, National Health and Aging Trends Study; NSHAP, National Social Life, Health, and Aging Project; CFAS, Cognitive Function and Ageing Studies in Wales; RANN, Reference Ability Neural Network; CR, Cognitive Reserve; NKI-RSI, Nathan Kline Institute-Rockland Sample Initiative; ILSE, Interdisciplinary Longitudinal Study of Adult Development; LRGS TUA, the longitudinal study on the neuroprotective model for healthy longevity; LBC1936, Lothian Birth Cohort 1936; LASA, Longitudinal Aging Study Amsterdam; NILS-LSA, National Institute for Longevity Sciences - Longitudinal Study of Aging; ECA, Epidemiologic Catchment Area study; GEM, Ginkgo Evaluation of Memory; HALS, Health and Lifestyle Survey

[a] Age was not provided for the total sample (participants were categorized into groups in descriptive statistics).

[b] Individual participant data meta-analyses.

Table 2.4: Associations between neuroticism and cognitive function in included studies

Authors, Year	Neuroticism measure	Outcome (measure)	Covariates (main model)	Main findings [a]
Olaru, 2023[136]	EPI	Composite score based on: Episodic memory (word recall and word recognition); Perceptual speed (digit cancellation and pattern comparison); Semantic memory (30 item vocabulary test); Verbal fluency (letter fluency, category fluency)	Age, gender, education, and number of chronic diseases	In young−old (60–72 years old) group: Neg. Baseline cognition; Nsig. Cognitive decline; In old−old (78 years or older) group: Neg. Baseline and decline of cognition
Stephan, 2023 [143]	MIDI	Episodic memory (word recall)	Age, gender, education, race	Neg. Episodic memory
Stephan, 2023[143]	MIDI	Episodic memory (word recall)	Age, gender, education, race	Neg. Episodic memory
Desai, 2023[128]	NEO-FFI	Memory (EBMT); Executive function (Symbol Digit); Global cognition (MMSE)	Age, race, sex, education, medical conditions, depressive symptoms	Neg. Baseline memory (−0.042), executive function (−0.033), global cognition (−0.036); Nsig. Rate of change of memory, executive function, global cognition
Bethell, 2023[135]	TIPI	Memory (RAVL); Executive function (AFT, MAT, COWAT, Stroop Test)	None	For female, Neg. RAVL2 (−0.043), AFT (−0.131), MAT (−0.181), COWAT (−0.170); Nsig. RAVL1, Stroop; for male, Neg. RAVL (−0.067, −0.054), MAT (−0.307); Nsig. AFT, Stroop, COWAT
Iwasa, 2022[132]	TIPI-J	Global cognition (SIML); Memory (PRMQ)	Age, gender, educational attainment, paid work, social network, chronic disease, self-rated sleep quality, and the five personality traits	Nsig. Memory; Neg. Global cognition
Terracciano, 2022[137]	NEO-PI-R	Global cognition (MMSE)	Age, sex, and personality assessment method	Nsig. Time, registration, spatial; Neg. Place (−0.09), recall (−0.06), attention (−0.09), language (−0.05), total (−0.12)
Beaudreau, 2022[146]	BFI (54-item)	Executive functioning (abstract reasoning, working memory); Verbal fluency; Semantic memory	Sex, education, and health status	Nsig. Baseline or rate of change in any domain
Sutin, 2022[134]	MIDI (HRS, ELSA, MIDUS [26-item]; NSHAP [21-item]; NHATS [10-item]), BFI (WLS [29-item], SHARE [10-item]), TIPI (CFAS)	Episodic memory (word recall)	Age, sex, race, and education	Neg. Average and decline of episodic memory

Montoliu, 2021[138]	NEO-FFI	Composite score based on: RAVL; Digit Span Forward; Digit Span Backward; Letter-Number Sequencing	Age, gender, educational level, medication/disease	Neg. Baseline and change of cognition
Stephan, 2021[144]	MIDI	Memory (word recall)	Age, sex, education, and race	Neg. Memory
Stephan, 2021[144]	BFI (29-item)	Memory (word recall)	Age, sex, and education	Neg. Memory
Simon, 2020[147]	IPIP	Reasoning (WAIS); Language (WAIS, WTAR, AMNART); Memory (SRT); Executive function (WAIS, Stroop Test, TMT-A)	Age, gender	Nsig. Reasoning, language, memory, executive function
Simon, 2020[147]	NEO-FFI	Reasoning (WASI, TMT); Language (WASI, WIAT); Memory (RAVL, list B and delayed recall); Executive function (Stroop Test)	Age, gender	Neg. Reasoning; Nsig. Language, memory, executive function
Wettstein, 2019[148]	NEO-FFI	Crystallized abilities (WAIS); Fluid abilities (picture completion, block design, spatial ability); Executive function (Number-Connecting Test, Symbol Digit)	Age, education	Neg. Baseline crystallized abilities (–0.015), fluid abilities (–0.017); Nsig. Baseline executive function; Rate of change in any domain
Sutin, 2019[149]	MIDI	Memory (CERAD; Brave Man; Logical Memory); Executive function (Letter Cancellation, Backward Count, Symbol Digit, TMT-A, TMT-B); Visuospatial (Constructional Praxis; Raven Matrice); Verbal fluency; Numeric reasoning (Number series)	Age, sex, race, ethnicity, and education	Neg. Memory (−0.1), executive function (−0.1), visuospatial ability (−0.1), verbal fluency (−0.06), numeric reasoning (−0.07)
Crook, 2018[139]	IPIP	Composite score based on WAIS	Age, sex, a count of medical conditions	Neg. Baseline cognition; Nsig. Cognitive decline
Foong, 2018[133]	EPQ-RS	Global cognition (MMSE)	Age, sex, marital status, educational achievement and household income	Neg. Global cognition
Chapman, 2017 [150]	NEO-FFI	Executive function (TMT-A, TMT-B, Digit Span); Language (BNT, category fluency); Memory (RAVL); Visuospatial (HVOT)	Age, gender, education	Neg. Executive function, visuospatial ability, verbal fluency; Nsig. Memory
Wettstein, 2017[151]	NEO-FFI	Crystallized abilities (WAIS); Fluid abilities (picture completion, block design, spatial ability); Executive function (Number-Connecting Test, Symbol Digit)	Age, education, self-rated and physician-rated health	Nsig. Change in any domain
Klaming, 2017[145]	DPQ	Episodic memory (RAVL)	Age, sex, income, number of chronic diseases, functional limitations, depressive symptoms, verbal intelligence	Neg. Baseline delayed recall (−0.024), retention (−0.216); Nsig. Baseline immediate recall (−0.011), rate of change in any domain
Luchetti, 2016 [114]	BFI (10-item)	Memory (immediately word recall)	Age, age squared, sex, and education	Neg. Memory
Caselli, 2016[152]	NEO-PI-R	Memory (RAVL, FCSRT, CFT, VRT); Executive function (PASAT, WCST, WAIS, Symbol Digit, Digit Span); Language (BNT, COWAT, Token Test, WAIS); Visuospatial (JLO, Facial Recognition Test, CFT, WAIS); General (DRS)	Age (baseline and follow-up)	Neg. Decline of memory (−0.8% to 1.7% per year), executive function decline (−0.6% to 1.3% per year); Nsig. Decline of language, visuospatial, general

Nishita, 2016[131]	NEO-FFI	Global cognition (MMSE)	Age, sex, follow-up years, and MMSE score at baseline	Neg. Global cognition
Hock, 2014[129]	NEO-PI-R	Global cognition (MMSE); Memory (Word Recall Tasks)	Age, sex, education, race, baseline cognitive test score, heart problems, hypertension, diabetes, stroke, number of depressive symptoms, and psychotropic medication use in the past week	Neg. Change in global cognition; Nsig. Change in memory
Dar-Nimrod, 2012[140]	NEO-FFI	Global cognition (ADAS-Cog)	Age, gender, race, education, self-rated health, and self-reported major diseases in the last five years, depressive symptoms, BMI, waist circumference, smoking status, alcohol consumption, and treatment group membership	Overall: Nsig. Global cognition; *APOE* ε4 carrier: Neg. Global cognition; *APOE* ε4 non−carrier: Nsig. Global cognition
Chapman, 2012[141]	NEO-FFI	Global cognition (MMSE)	Age, gender, race, education, self-rated health, and self-reported major diseases in the last five years, depressive symptom, BMI, waist circumference, smoking status, and *APOE* ε4 status	Neg. Average and decline of global cognition
Hagger-Johnson, 2012[154]	EPI	Executive function (reaction time)	Age, sex	For female, Neg. Baseline and decline of executive function; for male, Nsig. Baseline and decline of executive function
Boyle, 2011[142]	NEO-FFI	Global cognition (MMSE); Executive function (DRS, TMT-A, TMT-B)	Age, gender, years of education, medical illness burden	Neg. Global cognition; Nsig. Executive function
Sutin, 2011[153]	NEO-PI-R	Verbal fluency (category fluency)	Sex, age, age squared, education, and test administration	Neg. Verbal fluency
Wilson, 2005[130]	NEO-FFI	Composite score based on: Memory (EBMT); Executive function (Symbol Digit); Global cognition (MMSE)	Age, sex, race, and education	Neg. Baseline and decline of cognition

NEO-FFI, NEO Five Factor Inventory; NEO-PI-R, Revised NEO Personality Inventory; MIDI, Midlife Development Inventory; BFI, Big Five Inventory; TIPI-J, Ten-Item Personality Inventory; IPIP, International Personality Item Pool; EPQ-RS, Eysenck Personality Questionnaire - Revised Short Form; DPQ, Dutch Personality Questionnaire; EPI, Eysenck Personality Inventory; RAVL, Rey Auditory Verbal Learning; AFT, Animal Fluency Test; MAT, Mental Alternation Test; HVOT, Hooper Visual Organization Test; COWAT, Controlled Oral Word Association Test; EBMT, East Boston Memory Test; MMSE, Mini-Mental State Examination; SIML, Short Inventory of Minor Lapses; PRMQ, Prospective and Retrospective Memory Questionnaire; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; TMT, Trail-making tests; WAIS, Wechsler Adult Intelligence Scale; FCSRT, Free and Cued Selective Reminding Test; CFT, Rey-Osterrieth Complex Figure Test; VRT, Benton Visual Retention Test; PASAT, Paced Auditory Serial Addition Test; WCST, Wisconsin Card Sorting Test; BNT, Boston Naming Test; JLO, Judgment of Line Orientation; DRS, Mattis Dementia Rating Scale; ADAS-Cog, The Alzheimer's Disease Assessment Scale-Cognitive Subscale; WTAR, Wechsler Test of Adult Reading; AMNART, American National Adult Reading Test; SRT, Selective Reminding Test; WIAT, Wechsler Individual Achievement Test; BMI, body mass index; Nsig, no significant association; Neg, negative association

[a] For studies reporting significant associations across multiple cognitive domains with standardised outcome scores, values in brackets represent beta coefficients from regression models.

Neuroticism and structural brain outcomes

Since the last major literature review in 2022,[115] no new studies have examined the association between neuroticism and cortical or subcortical brain structures in mid- to later-life populations. Grey matter volume remains the most frequently assessed outcome, reported in 12 studies with sample sizes ranging from 29 to 578 (**Table 2.5**),[155-166] seven of these included fewer than 100 participants.[157,159,161,163-166] Studies were conducted in diverse populations across the UK,[155,159] US,[161,164-166] China,[156] Japan,[157,162] Norway,[160] Netherlands,[163] and Australia.[158]

Five studies used whole-brain analysis, typically adjusting for age, sex, intracranial volume, and other personality traits. Three studies involving younger populations (mean age 40,[156] 51,[157] and 73 years[155]) reported no significant associations between neuroticism and brain volume in any region (**Table 2.6**). In contrast, two studies including older adults (up to age 90) reported significant findings: both identified negative associations between neuroticism and right middle frontal gyrus volume,[158,161] one of these studies also found a negative association with orbitofrontal cortex volume,[161] which was later replicated in a region-of-interest (ROI) study.[164] However, findings across other brain regions were inconsistent. Significant associations reported in individual studies included negative associations with volumes in the right cerebellum, left superior occipital gyrus, inferior temporal gyrus, temporal poles, bilateral superior frontal gyrus,[158] as well as right Rolandic opperculum, middle temporal gyrus, and parahippocampal gyrus.[161]

Few studies have investigated cortical surface area or thickness, and only one had a sample size exceeding 500 participants.[155] Four whole-brain studies were identified: two reported no significant associations,[155,156] one found negative associations between neuroticism and surface area in the middle frontal gyrus, anterior cingulate cortex, and superior temporal gyrus,[160] and another reported reduced thickness in the inferior and superior frontal gyri and increased thickness in the anterior temporal cortex.[165] One ROI-based cortical thickness study found no significant associations across major lobes or in the orbitofrontal cortex.[167]

Regarding white matter macrostructure, two studies with relatively small sample sizes (N=617[168]; N=397[169]) reported no significant associations, whereas a much larger study (N=40,602)[170] found that higher neuroticism was positively associated with greater WMH volume, even after adjusting for a wide range of lifestyle and vascular risk factors.

White matter microstructure has been examined in only four studies, with sample sizes ranging from 51 to 668. One study including participants up to age 85 reported that higher neuroticism was associated with widespread reductions in FA across major white matter tracts, including long association fibers linking cortical lobes, fiber tracts connecting thalamic nuclei with the frontal lobes, and the corpus callosum, accompanied by increased diffusivity in overlapping regions.[160] Another study (mean age 29.6; range 18–54) found similar patterns, showing increased diffusivity in the corpus callosum, long association fibers (e.g., uncinate, fronto-occipital, and longitudinal fasciculus), thalamic radiations, and

cingulum.[171] A third study, focusing on a narrower age range around 73 years, also identified decreased FA in the uncinate fasciculus and cingulum.[172]

Table 2.5: Characteristics of studies examining neuroticism and structural brain outcomes

Authors, Year	Country (data source)	N_{tot} (Female/Male)	Age M (SD, range)
Grey matter volume			
Lewis, 2018 [155]	UK (LBC1936)	578 (268/310)	72.73 (0.72, NR)
Li, 2017 [156]	China (community)	108 (64/44)	40.28 (11.43, 19–60)
Kitamura, 2016 [157]	Japan (community)	41 (17/24)	50.1 (17.8, 22–77)
Tuerk, 2016 [158]	Australia (SMAS)	281 (150/131)	77.8 (4.5, 70–90)
Krishnadas, 2014 [159]	UK (PSoBiD)	37 (0/37)	50.79 (8.19, NS)
Bjørnebekk, 2013 [160]	Norway (CPLS)	265 (150/115)	49.8 (17.4, 20–85)
Kapogiannis, 2013 [161]	US (BLSA)	87 (42/45)	72.0 (7.70, 59–85)
Taki, 2013 [162]	Japan (ABIP)	274 (161/113)	51.2 (11.80, 21–80)
Cremers, 2011 [163]	Netherlands (NESDA)	65 (42/23)	40.5 (9.7, 21–56)
Jackson, 2011 [164]	US (WashU)	79 (59/20)	66 (12.5, 44–88)
Wright, 2007 [165]	US (community)	29 (17/12)	70.3 (6.6, 61–84)
Knutson, 2001 [166]	US (community)	86 (48/38)	30.52 (7.23, 19–45)
Cortical surface area			
Lewis, 2018 [155]	UK (LBC1936)	578 (268/310)	72.73 (0.72, NR)
Li, 2017[156]	China (community)	108 (64/44)	40.28 (11.43, 19–60)
Bjørnebekk, 2013[160]	Norway (CPLS)	265 (150/115)	49.8 (17.4, 20–85)
Cortical thickness			
Sweeney, 2019[167]	US (RANN, CR)	450 (247/203)	53 (17, 19–80)
Lewis, 2018 [155]	UK (LBC1936)	578 (268/310)	72.73 (0.72, NR)
Li, 2017[156]	China (community)	108 (64/44)	40.28 (11.43, 19–60)
Bjørnebekk, 2013[160]	Norway (CPLS)	265 (150/115)	49.8 (17.4, 20–85)
Wright, 2007[165]	US (community)	29 (17/12)	70.3 (6.6, 61–84)
White matter hyperintensities			
Booth, 2014[168]	UK (LBC1936)	617 (NR)	72.7 (0.7, NR)
Byun, 2020[169]	Korea (KBASE)	397 (221/176)	70.5 (7.9, NR)
Terracciano, 2023[170]	UK (UK Biobank)	40,602 (21,465/19,137)	63.97 (7.66, 45–82)
White matter microstructure			
Rodriguez, 2019[173]	Switzerland (community)	163 (99/64)	72.3 (5.4, NR)
Bjørnebekk, 2013[160]	Norway (CPLS)	265 (150/115)	49.8 (17.4, 20–85)
Xu, 2012[171]	US (community)	51 (21/30)	29.6 (10.0, 18–54)
McIntosh, 2012[172]	UK (LBC1936)	668 (356/312)	72.7 (0.7, NR)

N_{tot}, total sample size; M, mean; SD, standard deviation; NR, not reported; LBC1936, Lothian Birth Cohort 1936; SMAS, Sydney Memory and Ageing Study; PSoBiD, Psychological, social and biological determinants of ill health; CPLS, Cognition and Plasticity through the Life-Span; BLSA, Baltimore Longitudinal Study of Aging; ABIP, Aoba Brain Imaging Project; NESDA, Netherlands Study of Depression and Anxiety; WashU, Washington University Alzheimer's Disease Research Center; RANN, Reference Ability Neural Network; CR, Cognitive Reserve; UK Biobank, UK Biobank; KBASE, Korean Brain Aging Study for the Early Diagnosis & Prediction of Alzheimer's disease

Table 2.6: Associations between neuroticism and structural brain outcomes in included studies

Authors, Year	Neuroticism measure	Outcome (Atlas)	Covariates	Threshold (Correction)	Main findings
Grey matter volume					
Lewis, 2018 [155]	IPIP	VBM	Age, sex, ICV, other four personality traits, intelligence	0.05 (vertex, FDR)	Nsig
Li, 2017 [156]	NEO-FFI	SBM	Age, sex, ICV	0.05 (voxel, FDR)	Nsig
Kitamura, 2016 [157]	NEO-FFI	CAD, l PSC, l CRB, l STG, r PCC, PCN, r PHC (ROI from voxel-wise age-related results)	Age	0.05 (Bonf)	Nsig
Tuerk, 2016 [158]	NEO-FFI	VBM	Age, gender, ICV, scanner, cardiovascular risk	0.05 (cluster, FWE)	Neg. l/r medSFG, l SOG/ITG/TP, r CRB, r MFG
Krishnadas, 2014 [159]	EPQ-RS	ACC, AINS (Freesurfer Destrieux)	Age, ICV	0.05 (Bonf)	Nsig
Bjørnebekk, 2013 [160]	NEO-PI-R	Subcortical structure (AMY, NAc, CAD, PUT) (FreeSurfer Subcortical Segmentation)	Age, sex, TBV, other four personality traits	0.01 (Bonf)	Nsig
Kapogiannis, 2013 [161]	NEO-PI-R	VBM	Age, sex, ICV, education, other four personality traits	0.05 (cluster, FWE)	Pos. r LNG, r FSF, r MOG, r PRC, r CAL Neg. r infOFC, r RLO, r MFG, r PHC, r MTG
Taki, 2013 [162]	NEO-PI-R	VBM	Age, gender, ICV, other four personality traits	0.05 (voxel, FWE)	Nsig
Cremers, 2011 [163]	NEO-FFI	TGMV	Age, alternative trait (E), scan centers	0.05 (voxel, FWE)	Nsig
Jackson, 2011 [164]	NEO-FFI	Cerebral GW, SFG, VLPFV, DLPFC, OFC, PHC, HCP, AMY (Freesurfer)	Age, education	0.05	Neg. Cerebral GM, VLPFC/DLPFC, OFC
Wright, 2007 [165]	NEO-FFI	AMY (manually traced)	Age, sex, mean GMV	0.05	Nsig
Knutson, 2001 [166]	NEO-PI-R	GM ratio [a]	Age, sex	0.05	Nsig
Cortical surface area					
Lewis, 2018 [155]	IPIP	SBM	Age, sex, ICV, other four personality traits, intelligence	0.05 (vertex, FDR)	Nsig
Li, 2017[156]	NEO-FFI	SBM	Age, sex, ICV	0.05 (voxel, FDR)	Nsig
Bjørnebekk, 2013[160]	NEO-PI-R	SBM	Age, sex, other four personality traits	0.05 (cluster, MCS)	Neg. l/r STG, r cauMFG/rosMFG, r ACC
Cortical thickness					
Sweeney, 2019[167]	IPIP	Total CT, frontal, temporal, parietal, ACC, OFC (Freesurfer Desikan)	Age, sex, ICV, age * neuroticism, sex * neuroticism, age * sex * neuroticism, education	0.05	Nsig

Lewis, 2018 [155]	IPIP	SBM	Age, sex, ICV, other four personality traits, intelligence	0.05 (vertex, FDR)	Nsig
Li, 2017[156]	NEO-FFI	SBM	Age, sex, ICV	0.05 (voxel, FDR)	Nsig
Bjørnebekk, 2013[160]	NEO-PI-R	SBM	Age, sex, other four personality traits	0.05 (cluster, MCS)	Nsig
Wright, 2007[165]	NEO-FFI	SBM	Age, sex, mean GMV	PFC: 0.001 Non-PFC: 0.0001	Neg. r IFG, r SFG Pos. r ATC
White matter hyperintensities					
Booth, 2014[168]	IPIP	WMH (FLAIR)	Age, sex, other four personality traits	0.05	Nsig
Byun, 2020[169]	NEO-FFI	WMH (FLAIR)	Age, sex, education level, apolipoprotein E ε4 status, vascular risk factor score, depressive symptom, and clinical diagnosis	0.05 (Bonf)	Nsig
Terracciano, 2023[170]	EPQ-RS	WMH (FLAIR)	Age and sex, education, Townsend deprivation index, self-reported diabetes, high blood pressure, heart attack, angina, and stroke, BMI, smoking	0.05	Neg. WMH
White matter microstructure					
Rodriguez, 2019[173]	NEO-PI-R	FA (TBSS)	Age, gender	0.05	Nsig
Bjørnebekk, 2013[160]	NEO-PI-R	FA, MD, λ_{ax}, and λ_{rad} (TBSS)	Age, sex, other four personality traits	0.05 (cluster, FWE)	Pos. MD, λ_{rad} (widespread); Neg. FA (widespread)
Xu, 2012[171]	NEO-PI-R	FA, MD, λ_{ax}, and λ_{rad} (TBSS)	Age, gender	0.05 (cluster, FWE)	Pos. r forceps minor, CC body, CR, A cingulum and IFOF (MD, λ_{ax}, and λ_{rad}); l CR and SLF (MD, λ_{ax}, and λ_{rad}); l forceps minor and A cingulum (MD, λ_{ax}, and λ_{rad}); l SLF and CR (MD, λ_{ax}, and λ_{rad}); l IFOF and uncinate (MD, λ_{ax}, and λ_{rad}); l CR, P cingulum and CC body (MD, λ_{ax}); Neg. l forceps minor and A cingulum (FA)
McIntosh, 2012[172]	NEO-FFI	FA (12 major WM tracts)	Age, sex, and later antidepressant use, stroke history, and smoking	0.05 (FDR)	Neg. l CCG, l Unc

N_{tot}, total sample size; M, mean; SD, standard deviation; NR, not reported; CLSA, Canadian Longitudinal Study on Aging; TIPI, Ten Item Personality Inventory; CHAP, Chicago Health and Aging Project; SNAC-K, Swedish National Study on Aging and Care in Kungsholmen; SHARE, Survey of Health, Ageing and Retirement in Europe; HRS, Health and Retirement Study; ELSA, English Longitudinal Study of Ageing; WLS, Wisconsin Longitudinal Study; MIDUS, Midlife in the United States Study; NHATS, National Health and Aging Trends Study; NSHAP, National Social Health and Aging Project; CFAS, Cognitive Function and Ageing Studies in Wales; RANN, Reference Ability Neural Network; CR, Cognitive Reserve; NKI-RSI, Nathan Kline Institute-Rockland Sample Initiative; ILSE, Interdisciplinary Longitudinal Study of Adult Development; LRGS TUA, The longitudinal study on neuroprotective model for healthy longevity; LBC1936, Lothian Birth Cohort 1936; LASA, Longitudinal Aging Study Amsterdam; NILS-LSA, National Institute for Longevity Sciences - Longitudinal Study of Aging; ECA, Epidemiologic Catchment Area study; GEM, Ginkgo Evaluation of Memory; HALS, Health and Lifestyle Survey; NEO-FFI, NEO Five Factor Inventory; NEO-PI-R, Revised NEO Personality Inventory; IPIP, International Personality Item Pool; EPQ-RS, Eysenck Personality Questionnaire - Revised Short Form; VBM, voxel-based morphometry; SBM, surface-based morphometry; ROI, region-of-interest; CT, cortical thickness; GW, grey matter; GMV, grey matter volume; TGMV, total grey matter volume; WMH, white matter hyperintensities; FA, fractional anisotropy; MD, mean diffusivity; λ_{ax}, axial diffusivity; λ_{rad}, radial diffusivity; TBSS,

tract-based spatial statistics; WM, white matter; GM ratio, grey matter ratio; CC, corpus callosum; A cingulum, anterior cingulum; P cingulum, posterior cingulum; ACC, anterior cingulate cortex; AINS, anterior insula; AMY, amygdala; ATC, anterior temporal cortex; CAL, calcarine gyrus; CAD, caudate; CR, corona radiata; CRB, cerebellum; CCG, cingulum cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; FSF, fusiform gyrus; HCP, hippocampus; IFG, inferior frontal gyrus; ICV, intracranial volume; infOFC, inferior orbitofrontal cortex; IFOF, inferior fronto-occipital fasciculus; ITG, inferior temporal gyrus; LNG, lingual gyrus; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PCN, precuneus; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PHC, parahippocampal gyrus; PRC, precentral gyrus; PSC, postcentral gyrus; PUT, putamen; RLO, rolandic operculum; rosMFG, rostral middle frontal gyrus; SFG, superior frontal gyrus; SLF, superior longitudinal fasciculus; SOG, superior occipital gyrus; STG, superior temporal gyrus; TP, temporal pole; Unc, uncinate fasciculus; VLPFC, ventrolateral prefrontal cortex; Nsig, no significant association; Neg, negative association; Pos, positive association

[a] Tissue ratios were calculated as tissue volume/(ICV−tissue volume).

2.5 DISCUSSION

Gaps in understanding the direction, timing, and underlying pathways

Studies examining neuroticism and incident all-cause dementia consistently report a positive association in predominantly White, Western populations. However, the effect sizes vary widely, with risk increases per one SD ranging from 3% to 64%. A major limitation is sample size: most studies had small cohorts (N<10,000), limiting statistical power and precision. Even the largest study (N=401,422) had an average baseline age under 60 and follow-up periods shorter than 10 years, resulting in relatively few incident dementia cases (1,798 cases, 0.4% of the total sample).[116] Subtype-specific cases (AD and VaD) were even fewer—often fewer than 100—yielding imprecise estimates and limiting robust comparisons between subtypes.

Most studies had relatively short follow-up periods, with at least nine of the 13 included studies reporting mean durations under 10 years. This is a critical limitation because, as outlined in Chapter 1, pathological changes such as Aβ accumulation can precede clinical diagnosis of dementia—used as the outcome in these studies—by more than a decade.[10] Moreover, certain components of neuroticism may represent early symptoms of dementia.[104] A few studies attempted to address this by excluding dementia cases diagnosed within two,[121] three,[126] or five years of follow-up,[116] and the associations remained consistent. However, these exclusion windows may still be too short to fully account for early cases, and none of the studies conducted time-stratified analyses to test whether associations attenuated over time, which might reflect reverse causation.

Few studies are positioned to examine life-course variation in the neuroticism–dementia association, which is crucial for identifying at-risk populations. Among the 12 cohorts included in the most recent meta-analysis,[103] most had narrow baseline age ranges, focusing primarily on later-life samples (mean age >75)[117-119] or midlife samples.[116] Both age groups generally showed significant associations; however, midlife studies were often underpowered due to short follow-up and few incident cases, while late-life studies may capture early symptoms of dementia. None of these studies conducted age-stratified analyses, likely due to limited power arising from their narrow baseline age ranges.

Effect modification remains understudied. Studies that tested interactions with age, sex, or education have consistently found no significant results.[121,122,125] Interactions with genetic risk factors *APOE* ε4 have been examined only rarely. This is an important gap because *APOE* ε4 carriers already have elevated dementia risk, and if neuroticism confers additional risk in this group, they could represent a particularly high-risk subgroup. One study tested the interaction between neuroticism and *APOE* ε4 but found no significant result; however, the analysis was likely underpowered (N=1671, incident AD cases=90).[121] Apart from *APOE*, no studies have examined interactions with other genetic risk variants for AD, further highlighting the need for well-powered investigations in this area.

The pathways underlying the association between neuroticism and dementia remain poorly understood. As discussed in Chapter 1, neuroticism is generally stable in adulthood and difficult to modify directly, making it crucial to identify modifiable factors that may

mediate this association to inform targeted public health strategies. Evidence for chronic conditions (e.g., depression, hypertension) as mediators is mixed. While one study using hospital diagnoses, which are more likely to capture severe or persistent cases, reported attenuation of the neuroticism–dementia association after adjustment,[124] most studies relied on self-reported or field-based measures (e.g., blood pressure or depressive symptoms) and typically did not show such attenuation,[116-118,120,127] possibly reflecting differences in disease severity or misclassification. Moreover, no study applied formal mediation methods, such as structural equation modeling or counterfactual-based approaches.[174]

There is growing interest in examining molecular pathways, such as inflammation, lipid metabolism, and amino acid profiles, which may precede chronic conditions and offer earlier, more precise intervention targets. However, only two studies to date have adjusted for multiple blood biomarkers simultaneously (Hemoglobin A1c, C-reactive protein, and LDL) and observed no attenuation of the neuroticism–dementia association.[116,122] No study has examined these or other molecular mediators individually to assess their specific contributions.

Toward robust evidence on how neuroticism relates to specific cognitive domains

Findings across studies consistently support a link between higher neuroticism and poorer cognitive performance in mid- to later life, particularly for global cognition and episodic memory. In most studies, global cognition was measured using the Mini-Mental State Examination (MMSE), a widely used brief screening tool for dementia with good diagnostic accuracy (area under the curve = 0.92) and better performance than many

single-domain tests;[175] one study used the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), a screening tool more specific to AD,[176] and found no overall association but did observe a significant difference among *APOE* ε4 carriers.[140] The associations observed with MMSE and ADAS-Cog scores support that neuroticism may be involved in dementia-related pathways.[176]

This is further supported by neuroticism's consistent link to episodic memory deficits, a core clinical feature of AD that emerges in the earliest stages.[177] Longitudinal studies show that episodic memory decline is a strong predictor of dementia, emerging 10–15 years before diagnosis and more pronounced than the decline observed on the MMSE.[178] Far fewer studies have examined executive function, reasoning, visuospatial skills, or language, and domain-specific associations remain unclear due to small sample sizes and limited test batteries.[148,150,152] Clarifying these associations would help understand whether neuroticism broadly influences cognition or targets specific domains, and would further support its relevance to dementia, which typically involves impairments across multiple cognitive domains.[179]

The need for well-powered brain-wide association studies

Studies linking neuroticism with neuroimaging outcomes in mid- to later-life adults remain limited. Most brain-wide association studies to date have focused on grey matter volume, but sample sizes have been small, ranging from 29 to 578, with over half including fewer than 100 participants. This is problematic because brain-wide association studies conducted in small samples often yield inflated and non-replicable findings, given the high

variability and low signal-to-noise. Reliable results generally require sample sizes in the thousands.[180]

Participant age range is another concern, as many studies included individuals from early adulthood to later life without stratified analysis. Neuroticism is stable across adulthood,[51] therefore its potential impact on brain structure may accumulate with age. Indeed, the few studies focused on older adults (mean age over 70)[158,161] reported stronger associations than those combining younger and older participants.

Most studies have focused on grey matter, with consistent evidence linking higher neuroticism to reduced volume, surface area, and thickness in frontal regions critical for higher-order cognition.[158,160,161,164,165] These findings support a potential role for neuroticism in age-related cognitive vulnerability. However, a comprehensive understanding of brain health also requires examination of white matter, which indexes cerebrovascular health[113] and subtle changes in neural integrity and connectivity that are associated with cognition.[181] A positive association between neuroticism and WMH has been reported in an ROI study,[170] and three smaller, hypothesis-free studies (largest N=668) consistently found reduced FA and increased diffusivity across overlapping tracts, though the specific tracts most strongly implicated varied.[160,171,172] These findings underscore the need for well-powered, comprehensive investigations of both grey and white matter structures.

Conclusion

This systematic search comprehensively summarised current evidence on the association between neuroticism and incident dementia, demonstrating a consistent link between higher neuroticism and increased dementia risk. However, most studies have short follow-up periods and narrow baseline age ranges, resulting in fewer incident cases. As a result, effect estimates may be underpowered, prone to reverse-causality bias, and provide limited insight into life-course variation. Evidence for associations with cognitive function and brain structure is more mixed and limited, primarily due to small sample sizes and a lack of comprehensive assessment across multiple cognitive domains and neuroimaging modalities.

Chapter 3 Association of neuroticism with incident dementia and cognitive function in the UK Biobank

3.1 CHAPTER SUMMARY

The systematic search in Chapter 2 suggested that higher neuroticism might be associated with an increased risk of dementia, but prior studies were limited by small case numbers and short follow-up. This chapter investigated the association in the UK Biobank, a cohort of ~500,000 adults aged 40–69 years with up to 16 years of follow-up. Neuroticism was assessed using the Eysenck Personality Questionnaire-Revised Short Form, dementia diagnoses from hospital and death records, and cognition through touchscreen tests. Associations were estimated using Cox models for incident dementia, linear regression for cognition, and bidirectional two-sample MR for neuroticism, AD, and WMH burden, a key marker of VaD.

Among 174,164 dementia-free participants aged ≥60 years, 5,974 developed dementia (2,741 AD, 1,364 VaD) over a median 13.5 years. Higher neuroticism was associated with increased dementia risk (HR 1.11, 95% CI [1.08 to 1.14]), with stronger associations observed for VaD (1.15, [1.09 to 1.21]) than for AD (1.06, [1.02 to 1.10]). Associations with all-cause dementia and VaD persisted beyond 10 years and did not differ by genetic risk. Mental and vascular conditions partially mediated these associations. Neuroticism was also linked to poorer cognitive performance and, in MR analyses, to greater WMH burden, but not to AD.

This study demonstrates that higher neuroticism is associated with greater dementia risk and poorer cognitive function, partly mediated by mental and vascular health.

3.2 BACKGROUND

Most studies identified in the systematic search in Chapter 2 reported a significant positive association between neuroticism and dementia risk, including the most recent meta-analysis of 12 longitudinal studies (N=33,054; 1,806 dementia cases)[103] and the largest individual study to date (N=401,422; 1,798 cases).[116] However, the majority of existing studies had relatively short follow-up durations (mean <10 years in at least eight of 12 studies in the meta-analysis; 8.9 years in the subsequent large-scale study), limiting the ability to determine whether neuroticism only reflects an early symptom or a contributing factor for dementia. Longer follow-up is needed to disentangle these possibilities, as reverse causality is most likely to inflate effect estimates during shorter intervals.

Understanding effect modification by genetic risk may help identify subgroups in which neuroticism confers particularly high dementia risk, thereby improving risk stratification. Beyond *APOE* ε4, polygenic risk scores (PRS), which aggregate multiple AD-associated SNPs, provide a broader measure of genetic vulnerability.[182] There is a need to comprehensively assess whether neuroticism interacts with both *APOE* ε4 and non-*APOE* genetic risk.

As highlighted in earlier chapters, neuroticism itself is difficult to modify,[183] but it has been linked to a range of modifiable health conditions, including depression,[184] anxiety disorders,[184] CVD,[86] and hypertension.[185] MR studies suggest genetically predicted neuroticism increases risk for these conditions but not vice versa.[70,85,91] Mental and vascular

health conditions are well-established risk factors for dementia and are more directly modifiable than neuroticism,[28] but no study has formally tested whether they may partially mediate the association.

Further insight can be gained by examining intermediate cognitive outcomes. Neuroticism has been associated with poorer episodic memory,[114,134] an early hallmark of dementia, as well as deficits in verbal fluency, visuospatial skills, and executive function,[150] but evidence is limited and inconsistent. Well-powered studies assessing neuroticism in relation to multiple cognitive domains can help clarify whether its associations are global or domain-specific.

This study first investigated the association between neuroticism and the risk of incident dementia in a large population-based cohort followed-up for up to 16 years. Next, it assessed whether and how much this association is mediated through modifiable health conditions and then explored associations with cognitive outcomes across multiple domains. Finally, this study triangulated these findings using a two-sample bidirectional MR approach, which uses genetic variants as instruments for neuroticism that are fixed at conception and less susceptible to confounding or reverse causation,[29] to test the directionality of the association.

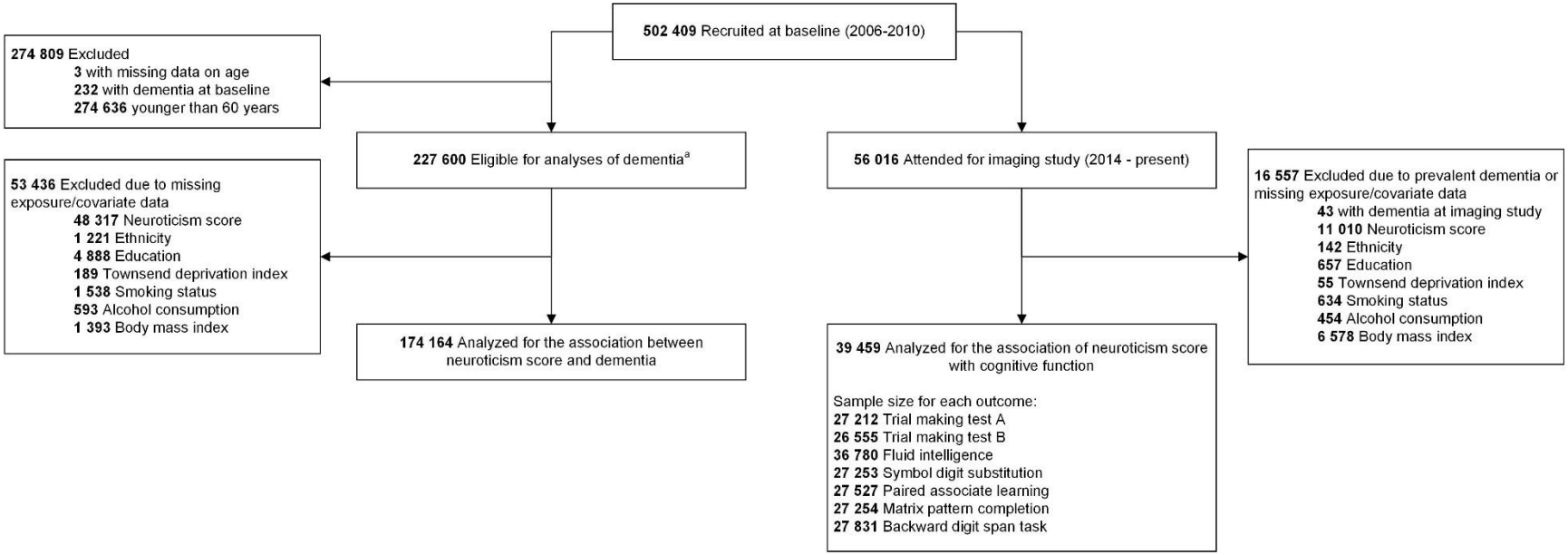
3.3 METHODS

Study population

This study used data from the UK Biobank, which is a population-based cohort that recruited more than 500,000 individuals aged 40–69 years from England, Scotland, and Wales between 2006 and 2010.[186] Baseline assessments included touchscreen questionnaires, verbal interviews, and physical measurements to collect sociodemographic, lifestyle, and health-related data. Blood samples were collected for additional assays, including genotyping. Follow-up data were obtained by cohort-wide linkage to electronic health records. UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (Ref: 11/NW/0382). All participants provided informed consent via electronic signature through the touchscreen.

This study excluded participants aged less than 60 years old at baseline (n=274,636) to ensure that the analytic sample was restricted to those at high risk of developing late-onset dementia (typically defined as onset after age 65 and accounting for 90%–95% of all dementia cases[3]) during the 16 year follow-up period. This study further excluded participants with self-reported prevalent cognitive impairment or dementia or hospital-diagnosed dementia at baseline (n=232), missing neuroticism (n=48,317) or covariate (n=7,992) data. The final sample size consisted of 174,164 participants (**Figure 3.1**).

Figure 3.1: Flow diagram of analyses



[a] Sensitivity analysis was conducted in this population using multiple imputation to account for missing data on the exposure and covariates.

Cognitive function was initially assessed at baseline in UK Biobank. While all participants completed brief tests of visuospatial memory and processing speed, additional tests assessing memory and reasoning were introduced partway through recruitment and therefore completed by only a subset of the participants.[186] In 2014, UK Biobank launched a large-scale imaging study as a repeat follow-up, inviting participants from the original cohort to undergo comprehensive brain and body imaging alongside repeated cognitive and health assessments.[187] The imaging assessment included a more comprehensive, standardized cognitive battery targeting age-sensitive domains, administered via fully automated touchscreen interface in dedicated assessment centres. Accordingly, cognitive analyses in this study were based on participants who attended the imaging study and completed this enhanced cognitive assessment.[188] Of 56,016 participants who underwent imaging assessment, exclusions were made for those with prior diagnoses of cognitive impairment or dementia (n=43), as well as those with missing neuroticism (n=11,010) or covariate data (n=4,372). As this study aimed to investigate the association between neuroticism and cognitive outcomes in dementia-free individuals, it did not exclude participants based on age. This resulted in a final sample size of 39,459 participants (**Figure 3.1**).

Assessment of neuroticism

Neuroticism was assessed using the EPQ-RS.[61] The EPQ-RS shows high reliability (Cronbach's alpha 0.80–0.84)[61] and correlates strongly (r=0.85)[189] with neuroticism score on the NEO Five Factor Inventory, another well-established measurement tool. Its psychometric properties remain consistent across cultures and age groups.[190,191] The EPQ-RS consists of 12 items, with each item measuring a single neurotic trait (**Table 3.1**).

Table 3.1: Questions and corresponding neurotic traits in the Eysenck Personality Questionnaire-Revised Short Form

Neurotic trait	Item
Mood swings	Does your mood often go up and down?
Miserableness	Do you ever feel 'just miserable' for no reason?
Irritability	Are you an irritable person?
Sensitivity	Are your feelings easily hurt?
Fed-up feelings	Do you often feel 'fed-up'?
Nervous feelings	Would you call yourself a nervous person?
Worry	Are you a worrier?
Tense	Would you call yourself tense or 'highly strung'?
Persistent worry after embarrassment	Do you worry too long after an embarrassing experience?
Suffer from nerves	Do you suffer from 'nerves'?
Loneliness	Do you often feel lonely?
Guilty feelings	Are you often troubled by feelings of guilt?

Response options were “No” and “Yes”, which were recoded as 0 and 1, respectively. An overall neuroticism score ranging from 0 to 12 was derived by summing up the responses to all items. A higher score indicates higher levels of neuroticism. Finally, the neuroticism score was standardized to have a mean of 0 and an SD of 1 to create a neuroticism z-score. Neuroticism measured through the touchscreen questionnaire at baseline was used as the exposure in the dementia analyses, and neuroticism measured through the touchscreen questionnaire at the imaging assessment was used as the exposure in the cognitive function analyses.

Incident dementia outcomes

Incident dementia was defined as the first hospital inpatient primary or secondary diagnosis of dementia or dementia as an underlying or contributory cause of death. The

sensitivity and specificity for identifying all-cause dementia using England hospital inpatient data are 78.0% and 92.0%,[192] respectively, with potential further improvement through the use of death register data. Both hospital inpatient data and death registers employed the International Classification of Diseases (ICD) coding system to encode diagnostic information. The ICD code list for dementia and its subtypes (AD and VaD) was developed and validated by the UK Biobank Outcome Adjudication group (**Table 3.2**).[193]

Table 3.2: International Classification of Diseases codes for dementia in hospital inpatient records and death registries

Disease	ICD-9 codes	ICD-10 codes
All-cause dementia	2902, 2903, 2904, 2912, 2941, 3310, 3311, 3312, 3315	A810, F00, F01, F02, F03, F051, F106, G30, G310, G311, G318, I673
AD	3310	F00, G30
VaD	2904	F01, I673

ICD, International Classification of Diseases

Cognitive outcomes

This study selected cognitive tests with demonstrated reliability and validity and covering different domains,[188] including executive function (Trail Making Test A and B), verbal and numerical reasoning (Fluid Intelligence), working memory (Backward Digit Span task), complex processing speed (Symbol Digit Substitution), verbal declarative memory (Paired Associate Learning), and non-verbal reasoning (Matrix Pattern Completion). The brief description and performance score for each test were summarised below.

The Trail Making Test included Part A (connect numbers 1–25 sequentially) and Part B (alternate between numbers and letters, e.g., 1-A-2-B). Errors required restarting from the

last correct point. Performance was scored by completion time (seconds), with longer times indicating poorer function.

The Fluid Intelligence test comprised 13 multiple-choice questions assessing verbal analogies and numerical patterns. Participants had two minutes to respond. The score reflected the number of correct answers.

Backward Digit Span task required participants to recall and enter digit sequences in reverse order, with increasing difficulty. The score was the length of the longest sequence correctly recalled.

The Symbol Digit Substitution Test required matching symbols to digits using a keypad within 60 seconds. The score was the number of correct matches, reflecting speed and accuracy.

Paired Associate Learning test required participants to memorize 12 word pairs and later identified the correct pairings from four options. The score was the number of correct responses out of 10.

The Matrix Pattern Completion test involved selecting the missing piece in a visual matrix from 6–8 options. Participants completed up to 15 items in three minutes. The score was the number of correct answers.

Appendix 3.1 presents raw and transformed distributions of the cognitive outcomes. Due to skewed distributions, Trail Making Test A and B scores were log-transformed, with higher values reflecting poorer performance (i.e., longer completion times). For all other tests, lower scores indicated poorer function. Participants with a Trail Making Test score of 0 (incomplete trials) were treated as missing. To ensure comparability across tests and age groups, raw scores were standardized into z-scores within 5-year age bands. For the Trail Making Tests, the negative of the log-transformed score was used so that higher z-scores uniformly reflected better cognitive performance.

Covariates and mediators

Covariates were selected a priori based on robust evidence of their associations with dementia risk and their potential to confound the relationship between neuroticism and later-life cognitive outcomes. Dementia incidence increases exponentially with age,[194] and women have a greater risk than men;[195] both age and sex also show established associations with neuroticism (older adults reporting lower levels,[196] women reporting higher levels[197]). Modifiable factors highlighted in the 2024 Lancet Commission on Dementia Prevention, Intervention and Care[17]—education, smoking, alcohol consumption, and obesity—were additionally adjusted for, as these are well-recognised dementia risk factors, are correlated with neuroticism,[198-201] and are measured with relatively high accuracy in the UK Biobank. Categorisation of lifestyle-related covariates followed widely adopted conventions in UK Biobank epidemiological studies to ensure comparability with the broader literature.[202]

The following covariates were measured at baseline: sex (female and male), ethnicity (White and non-White), and Townsend deprivation index (TDI, in quintiles). TDI is a summary measure of material deprivation that takes into account factors such as unemployment, overcrowding, non-car ownership, and non-home ownership.[203] Age, education (primary, secondary, post-secondary non-tertiary, and tertiary), smoking status (never, previous, and current smoker), alcohol consumption (≤4 times/week, daily or almost daily), and BMI (normal [<25 kg/m^2], overweight [≥25–<30 kg/m^2], and obese [≥30 kg/m^2]) were measured both at baseline (adjusted for in the dementia analyses) and at the imaging assessment (adjusted for in the cognitive function analyses).

To ensure the temporal sequence of neuroticism preceding mediators, health conditions identified in MR studies as influenced by neuroticism, rather than the reverse, were selected. Specifically, mental conditions (depression, anxiety and stress-related disorders) and vascular conditions (ischaemic heart disease [IHD], hypertension) were included as mediators, as neuroticism increased their risk without evidence that these conditions significantly influence neuroticism levels.[70,85,91] Additionally, diabetes was included as a negative control mediator, given its established association with poor brain health but limited evidence of an association with neuroticism.[91,204] A smaller or null mediation effect was anticipated for diabetes relative to mental and vascular conditions. Disease histories were obtained from two sources: self-reported medical conditions obtained during the verbal interview at baseline and hospital diagnoses of diseases prior to the baseline. **Table 3.3** provides detailed information on measurement, definition, and classification of the covariates and mediators.

Table 3.3: Definitions of covariates and mediators

Variable	Definition/categorization	Measurement
Age	Age=year of assessment−year of birth	Acquired from central registry at recruitment
Sex		
TDI	A greater Townsend index score implies a greater degree of deprivation. The entire UK Biobank sample was categorized into quintiles based on their TDI, with quintile 1 representing the richest and quintile 5 representing the poorest.	The TDI was computed for each participant using the national census data preceding their enrolment in UK Biobank. The score was assigned based on the output area of the participant's postcode.
Ethnicity	1) White; 2) Non-White (Asian or Asian British, Black or Black British, Chinese, Mixed, and other ethnic group)	Self-reported using the touch-screen questionnaire
Education	Participants with multiple qualifications were assigned the highest qualification attained, which was subsequently converted to the International Standard Classification for Education (ISCED) code representing years of education:[205,206] 1) Tertiary: College/University Degree, National Vocational Qualification (NVQ)/Higher National Diploma (HND)/Higher National Certificate (HNC) or equivalent; 2) Post-secondary non-tertiary: Other professional qualifications (e.g., nursing, teaching); 3) Secondary: General Certificate of Education Advanced Level (A levels)/General Certificate of Education Advanced Subsidiary Level (AS levels) or equivalent, General Certificate of Education Ordinary Level (O levels)/General Certificate of Secondary Education (GCSEs) or equivalent, Certificate of Secondary Education (CSEs) or equivalent; 4) Primary: None of the above	
Smoking status	1) Never; 2) Previous; 3) Current	
Alcohol consumption	1) ≤ 4 times per week; 2) Daily or almost daily	

BMI	The classification of BMI is utilized by the World Health Organization:[207] 1) Normal (<25 kg/m^2); 2) Overweight (≥25–<30 kg/m^2); 3) Obese (≥30 kg/m^2)	(Physical measures) height and weight
History of depression	Self-reported illness code: "depression"; ICD-9: 2962, 2963, 29682; ICD-10: F32, F33	Self-reported doctor diagnoses during verbal interview; Linked hospital inpatient records
History of anxiety and stress-related disorders	Self-reported illness code: "anxiety/panic attacks", "post-traumatic stress disorder"; ICD-9: 3000, 3002, 308, 309; ICD-10: F40, F41, F43	
History of diabetes	Self-reported illness code: "diabetes", "type 1 diabetes", "type 2 diabetes"; ICD-9: 250; ICD-10: E10, E11, E13	
History of hypertension	Self-reported illness code: "hypertension", "essential hypertension"; ICD-9: 401–405; ICD-10: I10–I15	
History of ischaemic heart disease	Self-reported illness code: "angina", "heart attack/myocardial infarction"; ICD-9: 410–414; ICD-10: I20–I25	

TDI, Townsend deprivation index; BMI, body mass index; ICD, International Classification of Diseases

Genetic variants

Genetic association estimates were drawn from the largest publicly available GWAS of European ancestry available at the time of analysis (April 2023). For neuroticism, this study used summary statistics from a meta-analysis combining data from UK Biobank (N=372,903) and the Genetics of Personality Consortium (N=17,375), totalling 390,278 participants.[70]

For dementia outcomes, well-powered GWAS are currently available only for late-onset AD. Accordingly, this study used summary statistics from the International Genomics of Alzheimer's Project, comprising 21,982 cases and 41,944 controls.[22] In contrast, the multifactorial nature of VaD and variability in diagnostic criteria have limited the availability of robust GWAS.[208] To address this limitation, WMH volume was used as a surrogate marker for vascular contributions to dementia. WMH is a well-established, objective imaging marker of cerebral small vessel disease,[209] a major contributor to VaD.[210] Previous studies have shown that WMH burden is more strongly associated with risk of VaD (73% increase) than with AD (25% increase).[211] Therefore, this study used GWAS summary statistics for WMH volume derived from 21,381 UK Biobank participants.[212]

Independent SNPs were selected as instrumental variables using standard criteria: genome-wide significance ($p<5\times10^{-8}$), minor allele frequency≥0.01, low linkage disequilibrium ($R^2<0.001$) within a 10,000 kb clumping window, and F-statistic≥10. SNPs were harmonized to align effect alleles across exposure and outcome datasets. Palindromic variants with a minor allele frequency>0.42 or missing frequency data were excluded.

Statistical analysis

Association of neuroticism with dementia and its subtypes

Cox proportional hazards regression was used to test the association between neuroticism score and incident dementia. The shape of the association was assessed using restricted cubic splines with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the neuroticism score. This knot placement balances model flexibility with the risk of overfitting.[213] Non-linearity was tested using a likelihood ratio test comparing models with and without spline terms. As no evidence of non-linearity was observed, the standardized neuroticism score (z-score) was used as the primary exposure in subsequent analyses. Models were adjusted for preselected baseline covariates, with follow-up time as the underlying timescale. Participants were followed from the date of attending baseline assessment until a record of dementia diagnosis, death, or the censoring date of hospital inpatient records (31 October 2022 for England, 31 August 2022 for Scotland, 31 May 2022 for Wales), whichever occurred first. Violation of the proportional hazards assumption was visually assessed using Schoenfeld's residuals.

Two sensitivity analyses were performed: 1) multiple imputation by chained equations was used to impute missing neuroticism score and covariates. The imputation model included the 12 EPQ-RS items, all preselected covariates, the Nelson-Aalen estimate of cumulative baseline hazard, and dementia status.[214] The imputed item scores were then added and standardized to form a z-score.[215] Cox proportional hazards regression analyses

were conducted to assess the associations of neuroticism z-score with incident dementia and its subtypes in five imputed datasets, and the results from each of the five imputed datasets were combined using Rubin's rules.[216] 2) all UK Biobank participants without dementia were included in the analysis with no restrictions on baseline age.

Subgroup analyses were conducted across all baseline covariates. For each subgroup, Cox models with the same adjustment set were fitted, and heterogeneity was assessed using Wald tests of interaction by introducing cross-product terms between neuroticism and each covariate.

To investigate potential reverse causation due to preclinical dementia affecting exposure status prior to a dementia diagnosis, the main analyses were repeated restricting to three separate follow-up periods: ≤5 years, >5–≤10 years, and >10 years.

Effect modification by genetic risk factors

Genetic risk was measured using *APOE* genotypes and a non-*APOE* PRS for AD (hereafter referred to as "non-*APOE* PRS"). *APOE* genotypes were estimated from two SNPs, rs7412 and rs429358. Participants with at least one copy of *APOE* ε2 were considered *APOE* ε2 carriers, those with at least one copy of *APOE* ε4 were considered *APOE* ε4 carriers, and *APOE* ε3/ε3 was used as the reference group. Ambiguous genotypes, *APOE* ε1/ε3 and *APOE* ε2/ε4, were excluded.

Dementia non-*APOE* PRS was calculated based on a 39-SNP PRS developed by Ebenau et al,[217] which predicted AD dementia independently of *APOE* ε4. Ebenau et al selected those SNPs from GWAS for late-onset AD, and derived variant-specific weights from International Genomics of Alzheimer's Project studies. For this analysis, quality controls were performed by excluding one SNP that had minor allele frequency <0.005, leaving 38 SNPs for PRS calculation. The PRS was then divided into quintiles, and participants were categorized into three genetic risk groups: low (lowest PRS quintile), intermediate (PRS quintiles 2 to 4), and high (highest PRS quintile).

This study incorporated a two-way interaction term between neuroticism z-score and the genetic risk factors and examined significant interaction effects using the likelihood ratio test. The analyses were then stratified by *APOE* genotypes (carrier of *APOE* ε2, *APOE* ε3/ε3, or carrier of *APOE* ε4) and non-*APOE* PRS status (quintile groups). Analyses stratified by *APOE* genotypes were restricted to individuals who self-reported as White, and the same restriction was applied to non-*APOE* PRS analyses to align with the ancestry of the GWAS reference data.

Mediation analysis

This analysis estimated the extent to which the association between neuroticism z-score (exposure, denoted as "A") and incident dementia risk (outcome, denoted as "Y") was mediated by the history of the following diseases (potential mediators, denoted as "M"): depression, anxiety and stress-related disorders, IHD, hypertension, and diabetes.

A marginal structural model approach within the counterfactual framework was used.[174] This approach decomposes the total effect of neuroticism on dementia into natural direct effects and natural indirect effects. Let $Y_{a,m}$ denote the outcome value when A and M are set to A=a and M=m, respectively. The natural direct effect is defined as $Y_{a,M(a^*)}-Y_{a^*,M(a^*)}$, where $a \neq a^*$, i.e., the difference between the outcome value under exposure A=a and the outcome value if the same individual were instead exposed to A=a* with the mediator fixed at the level it would take under exposure level a*. The natural indirect effect is defined as $Y_{a,M(a)}-Y_{a,M(a^*)}$, reflecting the change in the outcome value when the exposure is fixed at level A=a, and the mediator is changed to its level under exposure A=a*. At the population level, the natural direct effect represents the effect of neuroticism on dementia through pathways unrelated to the specific disease's history, while the natural indirect effects represent the mediating effect of the association between neuroticism and dementia through the disease. The proportion mediated via the disease was calculated by dividing the natural indirect effects by the total effect.

Marginal structural models were implemented through the following steps:

1. Fitting logistic regression models to estimate the association between each potential mediator (history of a specific disease) and neuroticism z-score, conditioned on baseline covariates.
2. Constructing a new dataset by repeating each observation in the original data five times and replacing A* for subject i by randomly drawn exposures through resampling from the observed exposures.

3. Calculating the weight for each observation in the new dataset using the fitted models from step 1.

$$W_i^C = \frac{P(M = M_i | A = A_i^*, C = C_i)}{P(M = M_i | A = A_i, C = C_i)}$$

4. Fitting a weighted Cox model to estimate the HR for the direct and indirect effects, while controlling for baseline covariates. To account for the correlation between repeated observations, robust standard errors were calculated.

5. Calculating the proportion of the total effect that is explained by each individual mediator as $HR_{\text{indirect effect}}/HR_{\text{total effect}}$.

Association between neuroticism and cognitive function

The association of the neuroticism z-score (measured at the imaging assessment) with cognitive function was tested using linear regression. Covariates such as sex, ethnicity, and TDI measured at baseline were included, and for other covariates (age, education, smoking status, alcohol consumption, and BMI), measurements at the imaging assessment were used.

Mendelian randomisation

Two-sample MR was used to examine bidirectional causal associations between neuroticism and both AD and WMH volume. The primary analysis used the inverse-variance weighted (IVW) method. To assess robustness and account for potential bias from horizontal pleiotropy, sensitivity analyses were performed using MR-Egger regression[218] and the weighted median estimator.[219] For exposure–outcome pairs with overlapping GWAS samples (e.g., both including UK Biobank participants), MRlap was used to adjust for bias

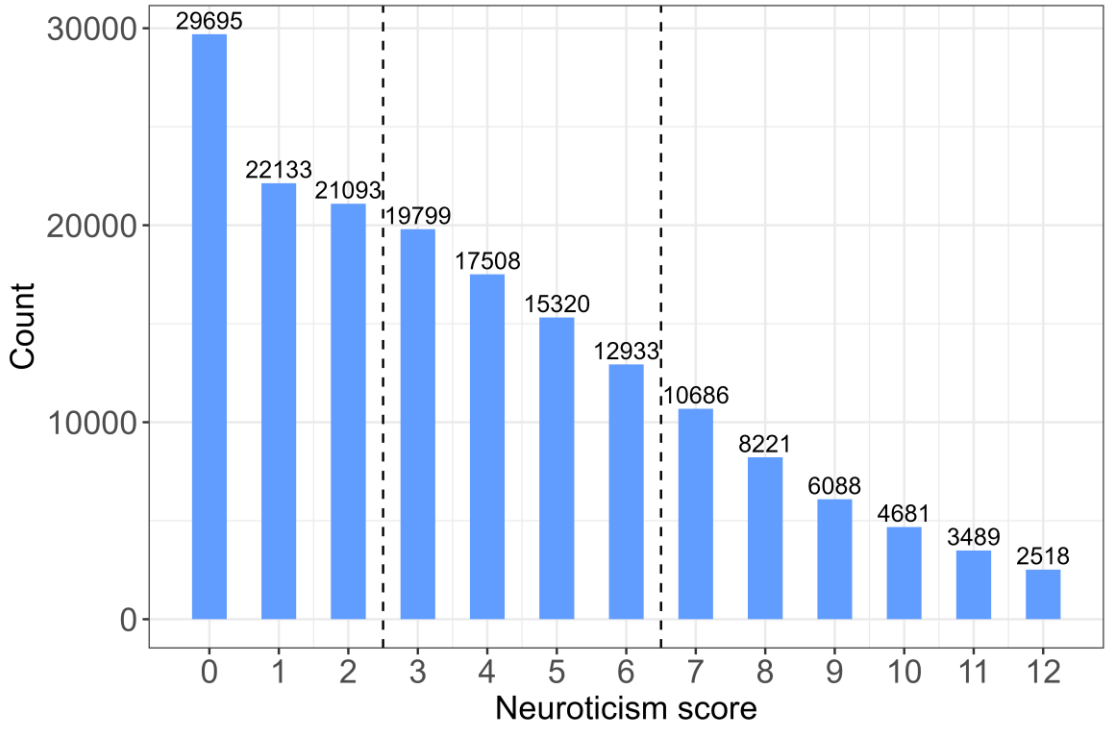
from partial sample overlap, as well as for weak instrument bias and winner's curse.[220] Heterogeneity was evaluated using Cochran's Q-statistic. Directional pleiotropy was assessed via the Egger intercept. Steiger directionality test was applied to confirm that genetic variants explain more variance in the exposure than the outcome.[221] All analyses were conducted in R (version 4.2.2) using the TwoSampleMR[221,222] and MRlap[220] packages.

3.4 RESULTS

Sample characteristics

Among the final sample of 174,164 participants, neuroticism scores were right-skewed, with a large proportion scoring 0, and only one-third of participants scoring above 6 (**Figure 3.2**). Compared with those with lower neuroticism scores, individuals with higher neuroticism scores were more likely to be female, have lower socioeconomic status, be current or previous smokers, and have a history of depression, anxiety, CVD, and diabetes (**Table 3.4**). Levels of neuroticism were comparable across *APOE* genotypes and non-*APOE* PRS levels.

Figure 3.2: Distribution of neuroticism score



Dashed lines divide the histogram into tertiles.

Table 3.4: Baseline characteristics of participants

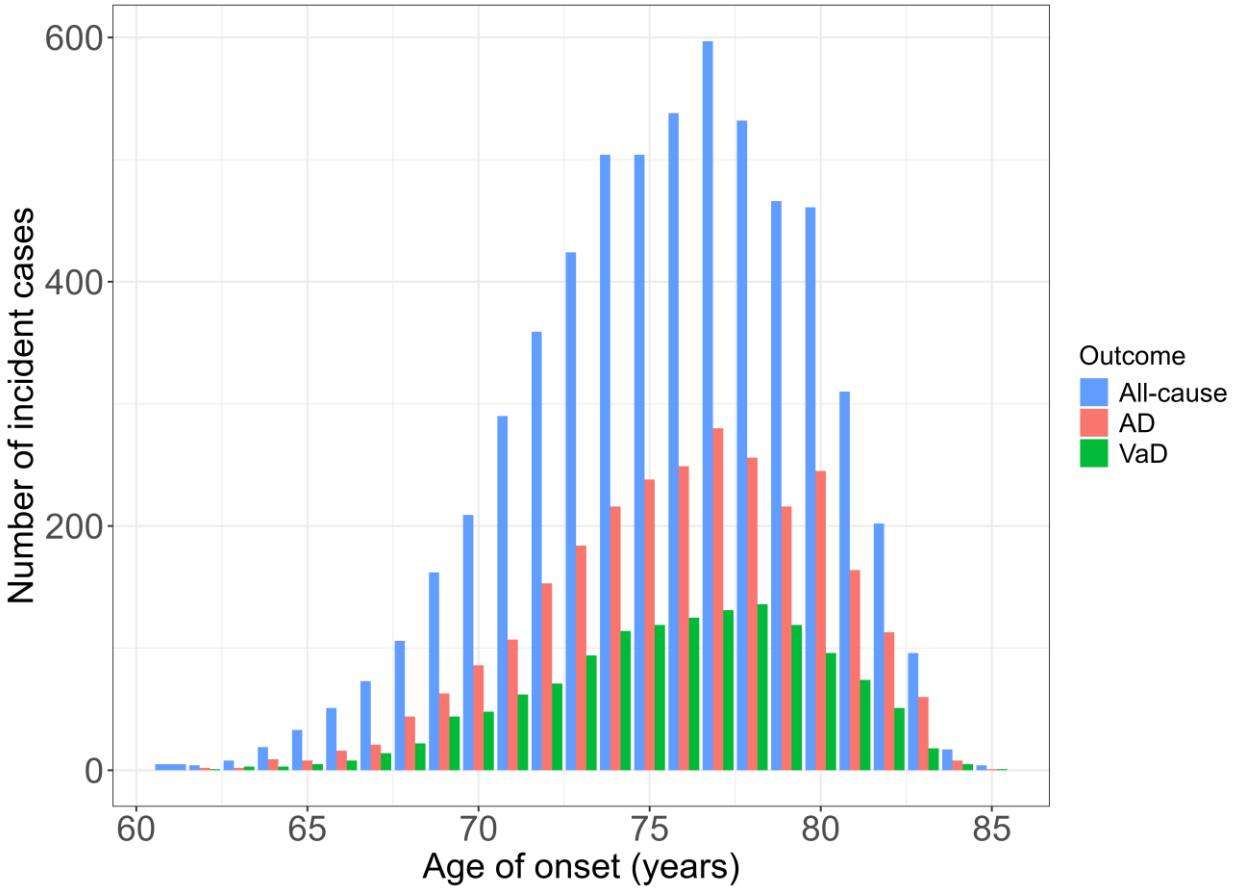
Characteristic	Overall	Neuroticism score tertile		
		1 (score 0–2)	2 (score 3–6)	3 (score 7–12)
N	174164	72921	52627	48616
Age (mean (SD))	64.36 (2.96)	64.49 (2.97)	64.37 (2.97)	64.14 (2.94)
Female (%)	83849 (48.1)	31566 (43.3)	29278 (55.6)	29471 (60.6)
Townsend deprivation index quintile				
1 (Least deprived)	38198 (21.9)	16834 (23.1)	11634 (22.1)	9730 (20.0)
2	38197 (21.9)	16423 (22.5)	11639 (22.1)	10135 (20.8)
3	36256 (20.8)	15391 (21.1)	11041 (21.0)	9824 (20.2)
4	32841 (18.9)	13351 (18.3)	10014 (19.0)	9476 (19.5)
5 (Most deprived)	28672 (16.5)	10922 (15.0)	8299 (15.8)	9451 (19.4)
Education (%)				
Primary	44741 (25.7)	16084 (22.1)	13581 (25.8)	15076 (31.0)
Secondary	36128 (20.7)	14309 (19.6)	11116 (21.1)	10703 (22.0)
Post-secondary non-tertiary	24329 (14.0)	10633 (14.6)	7617 (14.5)	6079 (12.5)
Tertiary	68966 (39.6)	31895 (43.7)	20313 (38.6)	16758 (34.5)
Ethnic group - White (%)	170011 (97.6)	71060 (97.4)	51492 (97.8)	47459 (97.6)
BMI (%)				
Normal (<25 kg/m^2)	51858 (29.8)	20757 (28.5)	16190 (30.8)	14911 (30.7)
Overweight (≥25–<30 kg/m^2)	78883 (45.3)	34182 (46.9)	23591 (44.8)	21110 (43.4)
Obese (≥30 kg/m^2)	43423 (24.9)	17982 (24.7)	12846 (24.4)	12595 (25.9)
Drinking ≤4 times weekly (%)	132224 (75.9)	54444 (74.7)	39994 (76.0)	37786 (77.7)
Smoking status (%)				
Never	86655 (49.8)	37843 (51.9)	26062 (49.5)	22750 (46.8)
Previous	73118 (42.0)	29416 (40.3)	22329 (42.4)	21373 (44.0)
Current	14391 (8.3)	5662 (7.8)	4236 (8.0)	4493 (9.2)
APOE genotypes (%)				
APOE ε2 carriers	22236 (12.8)	9282 (12.7)	6723 (12.8)	6231 (12.8)
APOE ε3/ε3 carriers	100368 (57.6)	41985 (57.6)	30402 (57.8)	27981 (57.6)
APOE ε4 carriers	43683 (25.1)	18449 (25.3)	13094 (24.9)	12140 (25.0)
Missing/Ambiguous genotypes[a]	7877 (4.5)	3205 (4.4)	2408 (4.6)	2264 (4.7)
Non-*APOE* PRS (%)				
Low (lowest quintile)	27996 (16.1)	12221 (16.8)	8522 (16.2)	7816 (16.1)
Intermediate (quintiles 2 to 4)	84795 (48.7)	35505 (48.7)	25561 (48.6)	23729 (48.8)
High (highest quintile)	28559 (16.4)	11640 (16.0)	8608 (16.4)	7748 (15.9)
Missing	32814 (18.8)	13555 (18.6)	9936 (18.9)	9323 (19.2)
Medical history (%)				
Depression	8744 (5.0)	938 (1.3)	1893 (3.6)	5913 (12.2)
Anxiety and stress disorder	2800 (1.6)	365 (0.5)	593 (1.1)	1842 (3.8)
Hypertension	64338 (36.9)	25419 (34.9)	19510 (37.1)	19409 (39.9)
Ischaemic heart disease	15176 (8.7)	5792 (7.9)	4553 (8.7)	4831 (9.9)
Diabetes	12083 (6.9)	5009 (6.9)	3525 (6.7)	3549 (7.3)

N, number of participants; SD, standard deviation; BMI, body mass index; PRS, polygenic risk score.
[a] *APOE* ε1/ε3 and *APOE* ε2/ε4 genotypes.

Association of neuroticism with dementia and its subtypes

During a median follow-up of 13.5 years, 5,974 participants developed incident all-cause dementia, of which 2,741 consisted of AD and 1,364 consisted of VaD. The age of incident dementia diagnoses was mostly concentrated between 70 and 80 years (**Figure 3.3**).

Figure 3.3: Distribution of incident dementia diagnoses by age of onset

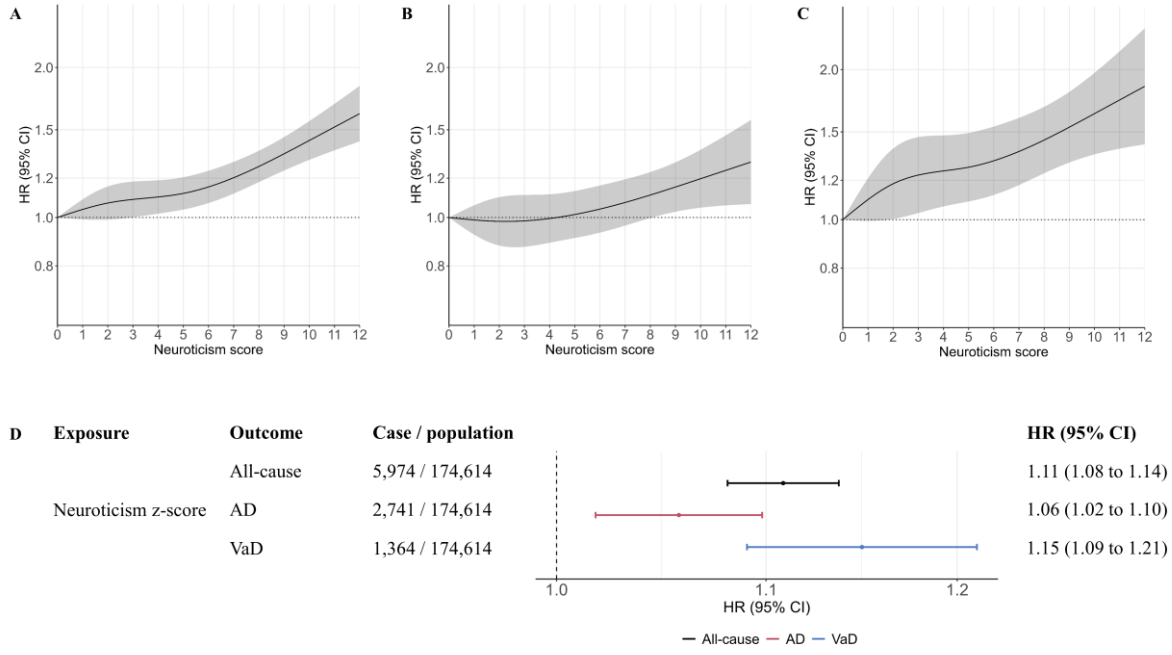


AD, Alzheimer's disease; VaD, vascular dementia.

Individuals who developed dementia had lower educational attainment, were less likely to be female, and were more likely to be current smokers but less likely to drink frequently, compared with those who did not (**Appendix 3.2**). Hypertension, ischaemic heart disease, diabetes, depression, and anxiety were also more common among dementia cases. They had a higher proportion of *APOE* ε4 carriers and higher non-*APOE* polygenic risk scores.

There was a dose-response association between neuroticism score and risk of incident all-cause dementia (p for non-linearity=0.08), AD (p=0.27), and VaD (p=0.57) (**Figure 3.4**). A 1-unit increase in neuroticism z-score was associated with an 11% (HR 1.11, 95% CI [1.08 to 1.14]), 6% (1.06, [1.02 to 1.10]), and 15% (1.15, [1.09 to 1.21]) higher risk of incident all-cause dementia, AD, and VaD, respectively. The sensitivity analyses using multiple imputation and removing baseline age restrictions produced similar results to the main findings (**Appendix 3.3**).

Figure 3.4: Associations between neuroticism score (original values and z-score) and incident dementia



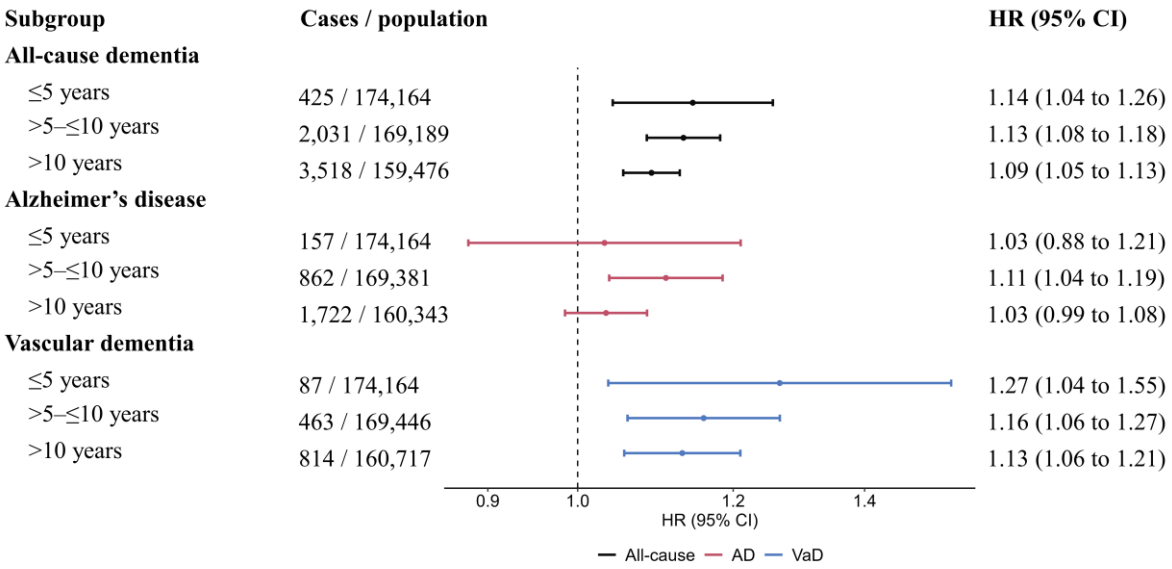
HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia; Panels A–C show associations between neuroticism score and risk of all-cause dementia (A), AD (B), and VaD (C). Panel D shows hazard ratios (HRs) per 1-SD increase in neuroticism score for each outcome. Estimates are adjusted for age, sex, ethnicity, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index. In panels A–C, solid lines represent adjusted HRs with shaded areas indicating 95% confidence intervals, derived from restricted cubic spline regressions with four knots. The dashed line marks the reference HR of 1.0. The reference point for neuroticism score is 0, indicating the lowest level of neuroticism.

The positive association between neuroticism and dementia risk was consistent across subgroups defined by sex, socioeconomic status, and lifestyle factors (**Appendix 3.4**), with no evidence of heterogeneity in effect estimates (all p for interaction>0.05).

The association with all-cause dementia remained similar for participants with <5 years (1.14, [1.04 to 1.26]) and >5–≤10 years of follow-up (1.13, [1.08 to 1.18]) and was attenuated, but still significant, for those with >10 years of follow-up (1.09, [1.05 to 1.13]) (**Figure 3.5**). The association with VaD followed a similar trend to that observed for all-

cause dementia, whereas for AD, the association was significant only in those with >5–≤10 years of follow-up.

Figure 3.5: Associations between neuroticism z-score and incident dementia by different follow-up periods

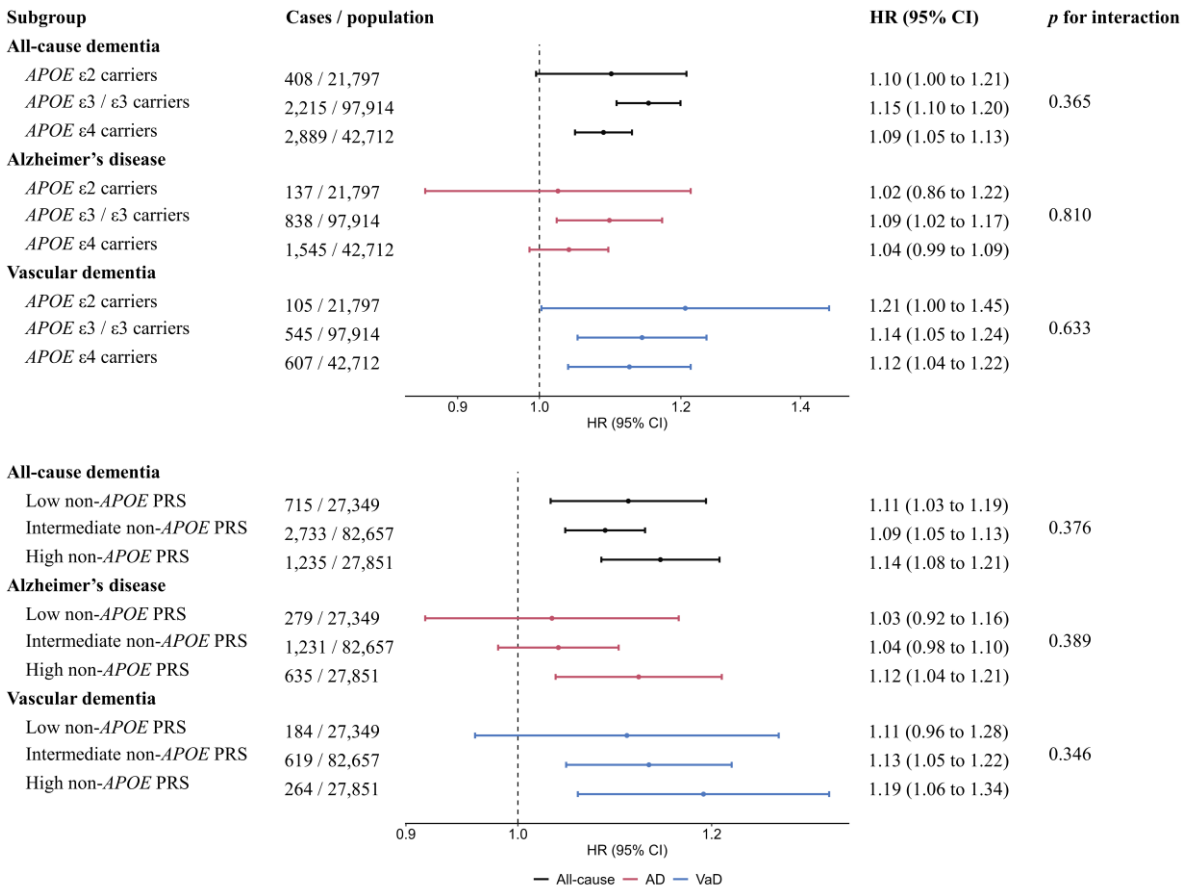


Estimates are adjusted for age, sex, ethnicity, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index. HR, hazard ratio. CI, confidence interval. Estimates represent adjusted hazard ratios per 1-SD increase in neuroticism score. Models were adjusted for age, sex, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index, with follow-up time as the underlying timescale. The dashed vertical line marks the reference HR of 1.0.

Effect modification by genetic risk factors

There were no statistically significant interactions between neuroticism z-score and *APOE* genotypes or non-*APOE* PRS (p for interaction >0.05) (**Figure 3.6**). The associations between neuroticism z-score and the risk of incident dementia and its subtypes remained consistent across all genetic subgroups.

Figure 3.6: Associations between neuroticism z-score and incident dementia by *APOE* genotype and non-*APOE* polygenic risk scores



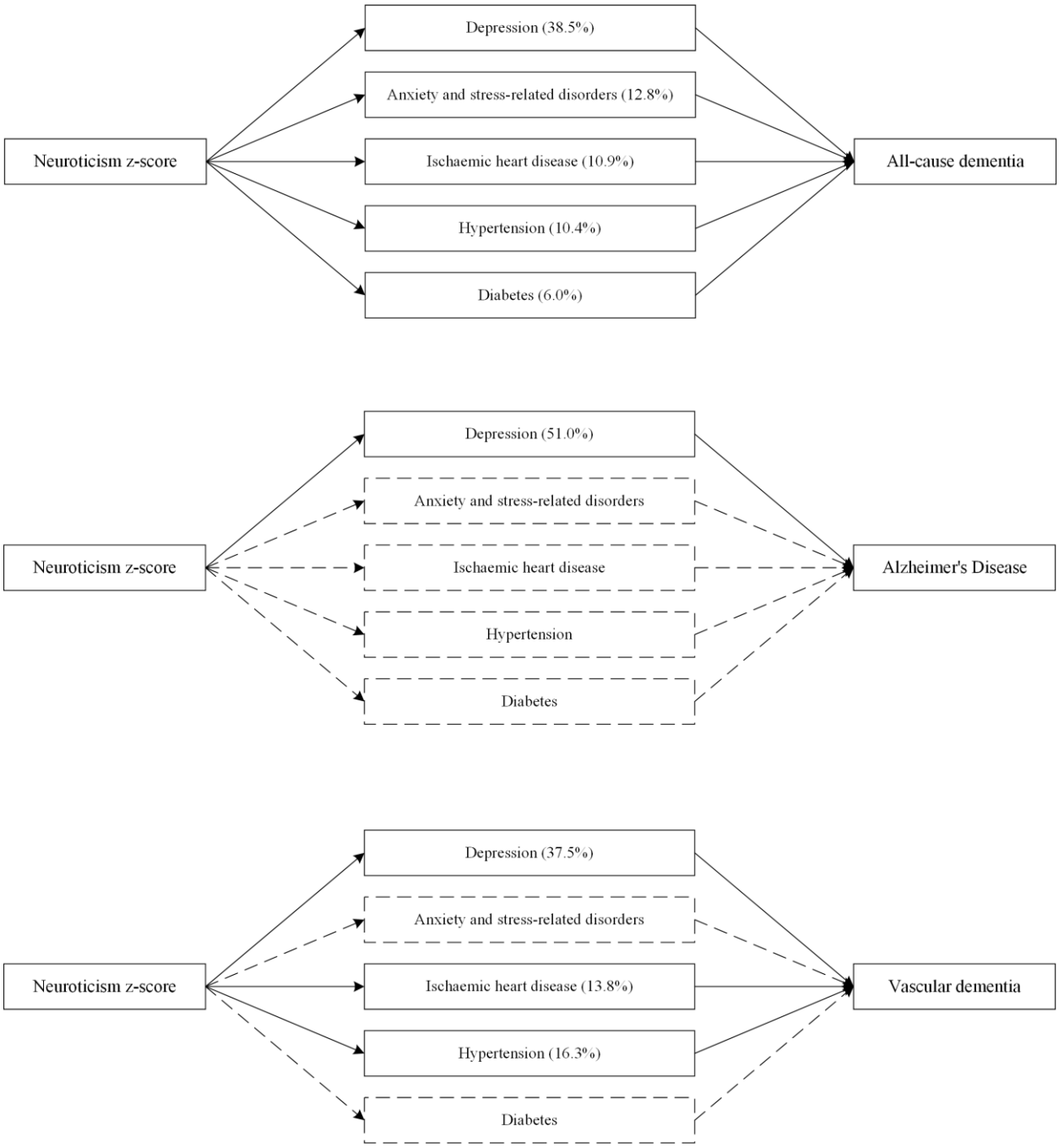
Estimates are adjusted for age, sex, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index. HR, hazard ratio. CI, confidence interval. PRS, polygenic risk score. Estimates represent adjusted hazard ratios per 1-SD increase in neuroticism score. Models were adjusted for age, sex, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index, with follow-up time as the underlying timescale. P-values correspond to Wald tests of interaction examining whether associations between neuroticism and dementia differed across genetic risk groups. The dashed vertical line marks the reference HR of 1.0.

Mediation analysis

A history of depression, anxiety and stress-related disorders, IHD, hypertension, and diabetes explained 38.5%, 12.8%, 10.9%, 10.4%, and 6.0% of the association between neuroticism z-score and all-cause dementia, respectively (**Figure 3.7**, **Appendix 3.5**). Similar mediated proportions by depression were observed for VaD (37.5%), with IHD and

hypertension mediating a larger proportion compared to the association with all-cause dementia (13.8% and 16.3% vs 10.9% and 10.4%). Depression mediated a larger proportion of the association with AD than all-cause dementia (51.0% vs 38.5%), while no mediation by IHD or hypertension was observed. There was no evidence of anxiety or diabetes mediating the association for both AD and VaD.

Figure 3.7: Associations between neuroticism z-score and dementia mediated by history of diseases at baseline



Estimates are adjusted for age, sex, ethnicity, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index. The percentage values within brackets represent the proportion by which each mediator mediated the association between neuroticism z-score and the dementia outcome, calculated as the natural indirect effect divided by the total effect, estimated using the counterfactual framework and marginal structural models. Mediators depicted with dashed borders and arrows indicate statistically insignificant mediation effects.

Association between neuroticism and cognitive function

The characteristics of the 39,459 non-demented individuals included in the cognitive function analyses are presented in **Appendix 3.6**. Neuroticism measured at the time of cognitive assessment was strongly correlated with baseline neuroticism (Pearson correlation coefficient r=0.77). Neuroticism z-score was associated with worse function across all cognitive domains (all p<0.001; **Table 3.5**) with similar magnitudes, ranging from β (standardized)= −0.02 for verbal declarative memory to β=−0.05 for complex processing speed.

Table 3.5: Associations between neuroticism z-score and cognitive function

Domain	Test	β (95% CI)	p
Processing speed	SDST	−0.05 (−0.06 to −0.04)	<0.001
Verbal and numerical reasoning	FI	−0.03 (−0.04 to −0.02)	<0.001
Non-verbal reasoning	MPC	−0.03 (−0.04 to −0.02)	<0.001
Working memory	BDST	−0.03 (−0.05 to −0.02)	<0.001
Verbal memory	PAL	−0.02 (−0.04 to −0.01)	<0.001
Executive function	TMT-A	−0.04 (−0.05 to −0.03)	<0.001
Executive function	TMT-B	−0.04 (−0.05 to −0.03)	<0.001

Estimates are adjusted for age, sex, ethnicity, education, Townsend deprivation index (TDI, in quintiles), smoking status, alcohol consumption, and body mass index (BMI). Sex, ethnicity, and TDI were measured at baseline, and for other covariates (age, education, smoking status, alcohol consumption, and BMI), measurements from the imaging study were used. CI, confidence interval. SDST, Symbol Digit Substitution Test; FI, Fluid Intelligence; MPC, Matrix Pattern Completion; BDST, Backward Digit Span Test; PAL, Paired Associate Learning; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B.

Mendelian randomisation

This study used 91 genetic instruments for neuroticism, 19 for AD, and 15 for WMH (**Appendix 3.7**). Genetically predicted neuroticism was not significantly associated with AD

risk across IVW, weighted median, or MR Egger methods. Similarly, reverse MR showed no evidence for AD liability causally influencing neuroticism (**Table 3.6**).

For WMH, genetically predicted higher neuroticism was associated with greater WMH burden using the IVW method (β=0.17, 95% CI [0.01 to 0.33], p=0.038). This association remained significant after adjusting for sample overlap (β=0.26, p=0.017), was marginally significant with MR-Egger (β=0.81, p=0.050), and showed a same direction in the weighted median estimate. Sensitivity analyses indicated no significant heterogeneity (p for Q=0.109) or pleiotropy (p for Egger intercept=0.112), and Steiger test confirmed that the genetic variants explained more variance in the exposure than the outcome (p<0.001) (**Appendix 3.8**). In contrast, there was no evidence that genetically predicted WMH burden influenced neuroticism in reverse MR analyses (all p>0.05).

Table 3.6: Bidirectional Mendelian randomisation analyses of neuroticism and dementia-related outcomes

Method	**Neuroticism → AD**		**AD → Neuroticism**	
	OR (95% CI)	**p**	**β (95% CI)**	**p**
Inverse-variance weighted	0.94 (0.73 to 1.21)	0.632	−0.001 (−0.010 to 0.007)	0.740
Weighted median	0.88 (0.62 to 1.24)	0.451	−0.001 (−0.007 to 0.005)	0.723
MR-Egger	0.30 (0.08 to 1.08)	0.069	0.0004 (−0.012 to 0.011)	0.952

Method	**Neuroticism → WMH**		**WMH → Neuroticism**	
	β (95% CI)	**p**	**β (95% CI)**	**p**
Inverse-variance weighted	0.17 (0.01 to 0.33)	0.038	0.001 (−0.028 to 0.030)	0.945
Weighted median	0.18 (−0.03 to 0.38)	0.099	−0.009 (−0.036 to 0.019)	0.540
MR-Egger	0.81 (0.01 to 1.62)	0.050	−0.022 (−0.102 to 0.059)	0.610
MRlap [a]	0.26 (0.05 to 0.47)	0.017	0.005 (−0.025, 0.035)	0.730

[a] MRlap was applied only to MR analyses of neuroticism and WMH, as both GWAS included UK Biobank participants. MRlap was not used for AD, since its GWAS did not include UK Biobank participants.
OR, odds ratio; CI, confidence interval; AD, Alzheimer's disease; WMH, white matter hyperintensities.

3.5 DISCUSSION

This chapter presents findings from a large population-based cohort, demonstrating that neuroticism was associated with an increased risk of all-cause dementia regardless of genetic predisposition to dementia, with a stronger association observed for VaD than for AD. The associations were largely explained by depression, anxiety, IHD, and hypertension. Higher neuroticism was also associated with worse function across multiple cognitive domains in dementia-free adults. MR analyses revealed no genetic association between neuroticism and AD, but suggested a unidirectional association between genetically predicted higher neuroticism and greater WMH burden.

Terracciano et al. conducted a similar analysis in UK Biobank, including all participants recruited at baseline (N = 401,422) without restricting baseline age, but with follow-up censored at February 2018 (maximum 12 years).[116] In contrast, this study excluded those younger than 60 years at baseline to focus on late-onset dementia, and extended follow-up to May (Wales), August (Scotland), and October 2022 (England). Because dementia incidence increases exponentially with age,[194] these additional four years of follow-up captured ~4,000 more incident dementia cases, providing greater power and more precise effect estimates. Although effect sizes observed here were slightly smaller (HR 1.11 vs 1.18 for all-cause dementia, 1.06 vs 1.13 for AD, and 1.15 vs 1.16 for VaD), the longer follow-up reduces potential bias from reverse causality. Time-stratified analyses further showed that associations persisted beyond 10 years, strengthening confidence that these associations are not solely due to reverse causality.

The similarity of associations between neuroticism and dementia risk across demographic, socioeconomic, and lifestyle subgroups suggests that the relationship is broadly robust and therefore relevant across a wide range of individuals. Only a few studies have examined interactions between neuroticism and genetic risk, with limited and inconsistent findings. One study (mean baseline age 78.6 years; 6.5 years follow-up) reported an interaction between *APOE* ε4 and neuroticism on AD (N=86), but not on non-AD dementia (N=12).[223] Another study (mean baseline age 56.5 years; 12 years follow-up) found no such interaction for AD (N=90).[121] A longitudinal study (N=912) found that *APOE* ε4 did not modify the association between neuroticism and either cognitive ability or cognitive decline.[139] In the current study, neuroticism was consistently associated with dementia and its subtypes regardless of genetic predisposition to dementia based on either *APOE* ε4 carrier status or non-*APOE* polygenic risk.

This study also found evidence that the associations were mediated by mental health conditions, specifically depression, as well as vascular conditions, including hypertension and IHD, with these mediators contributing more strongly to VaD than to AD. Compared with other conditions, the proportion mediated via diabetes was smaller for all-cause dementia, and there's no evidence that diabetes explains the association for AD and VaD, suggesting that metabolic conditions might not be the major contributors to the neuroticism-dementia association. This is expected with previous evidence that neuroticism is not linked to diabetes and supporting its role here as a 'negative control.'[91]

This study demonstrated that neuroticism was significantly associated with worse cognitive function across all, rather than specific, domains. This extends previous findings that identified the association between neuroticism and worse global cognitive outcomes,[114] and enhances the reliability of previous studies (N=7,685;[128] N=2,865[149]) that demonstrated the association between neuroticism and worse cognitive function in multiple domains (memory, executive function, verbal fluency, and visuospatial skills). Together, these findings suggest that neuroticism is broadly associated with cognitive functioning, consistent with dementia's widespread impact across multiple domains.[179] The strong correlation between baseline and follow-up neuroticism indicates stability of the trait over time, reducing the likelihood that short-term fluctuations account for its associations with cognitive outcomes.

MR analyses did not support a genetic association between neuroticism and AD, but they indicated that neuroticism contributes to greater WMH burden, with no evidence of reverse causation. These results align with the stronger observational associations observed for VaD compared with AD and support a potential vascular pathway linking neuroticism to dementia risk. Nonetheless, the lack of MR evidence for AD should not be taken as proof of absence. The true effect size may be small, AD GWAS often include cases with mixed pathology that dilute signal specificity, and binary outcomes such as AD reduce MR power relative to continuous traits like WMH.[30]

Strengths and limitations

Strengths of this study include the large sample size, number of dementia cases, long follow-up and the breadth of available genetic, clinical, and cognitive data, allowing novel analyses of effect modification, mediation, and MR approaches. However, this study has several limitations to consider. UK Biobank only achieved a 5.5% response rate, recruiting 0.5 million participants for baseline assessment out of nine million invited.[224] UK Biobank participants,[225] especially those in the imaging study,[226] are generally healthier and of higher socioeconomic status compared to the wider UK population. Dementia cases were identified through hospital records and death registry data, likely missing less severe cases diagnosed in other settings. Distinguishing between dementia subtypes using ICD codes from administrative data can be challenging, as the positive predictive value—the proportion of identified cases that are true positives—was 84.5% for all-cause dementia, 70.8% for AD, and 33.3% for VaD in UK Biobank-linked hospital inpatient and death registry data.[227] This misclassification of outcomes may have biased associations toward the null. The non-*APOE* PRS was developed based on GWAS on AD, rather than all-cause dementia or VaD. Exposure and mediator data were collected concurrently, but neuroticism is generally stable from early adulthood, and prior MR studies suggest a unidirectional link from neuroticism to these conditions rather than the reverse.[70,85,91] Cognitive tests in UK Biobank were brief and non-standard, collected through a fully automated, unsupervised touchscreen assessment. However, a small study (N=160) in a non-UK Biobank sample demonstrated moderate-to-high concurrent validity and short-term stability for the tests included in this study.[188] Finally, MR analyses were constrained by the lack of well-powered GWAS for all-cause dementia and VaD, partially due to their multifactorial nature and heterogeneous diagnostic criteria.[208]

Conclusion

The study in this chapter suggests high levels of neuroticism are associated with an elevated risk of dementia, in particular VaD, accompanied by worse cognitive function. This association remained significant regardless of genetic risk in this study cohort. Despite neuroticism being a stable personality trait, which might not be easily modifiable, evaluating neuroticism may serve as a means to identify individuals at high risk for dementia. Furthermore, this study suggests that the associations between neuroticism and dementia are largely driven by mental and vascular conditions, implying that addressing the increased burden of mental and vascular health conditions in individuals with higher neuroticism could, if causal, ultimately help prevent or delay the onset of dementia.

Chapter 4 Association of neuroticism with incident dementia and cognitive function: 26 year follow-up of EPIC-Norfolk study

4.1 CHAPTER SUMMARY

This chapter examined whether the association between neuroticism and dementia risk persists over extended follow-up and differs between midlife and later life, using the EPIC-Norfolk cohort. Neuroticism was measured using the same self-reported scale as in UK Biobank. Dementia cases were ascertained via linked hospital, death, and mental health records, and cognitive function assessed with a detailed battery. Statistical analyses, including models, covariates, and mediators, were aligned with Chapter 3.

Among 19,678 dementia-free participants aged 40–80 years (mean 60.8), higher neuroticism was associated with increased dementia risk, with each 1-SD increase corresponding to a 14% higher risk of all-cause dementia, 15% higher risk of AD, and 16% higher risk of VaD. Although attenuated over time, associations remained significant for all-cause dementia and AD after 20 years of follow-up and were consistent across mid- and later life. A significant interaction with *APOE* ε4 indicated stronger associations among carriers, and mediation analyses showed partial contributions of mental and vascular conditions. Neuroticism was linked to poorer performance across multiple cognitive domains, most notably episodic memory.

In conclusion, findings from this chapter demonstrate that high neuroticism levels in both mid- and later life are associated with long-term dementia risk and poorer cognitive function.

4.2 BACKGROUND

A growing body of evidence, including a meta-analysis of 12 longitudinal studies and two large UK Biobank investigations,[103,116] shows that higher neuroticism is associated with increased dementia risk. In the previous chapter, the association was attenuated but remained significant beyond 10 years of follow-up, suggesting that shorter follow-up periods may partly reflect early disease manifestations. Extending follow-up is therefore important to strengthen evidence that neuroticism contributes to dementia risk.

It remains unclear whether these associations vary by life stage. This is critical not only for disentangling directionality—if midlife neuroticism predicts dementia decades later, this would support a forward association—but also for informing how dementia prevention strategies could be tailored to specific age groups and psychological profiles. Most existing studies focus on mid-life samples, while only a few have examined older cohorts (mean baseline age>70) and reported positive associations.[117-120] Yet these older-age studies often had mean follow-up durations <6 years,[117,118,120] increasing the possibility of reverse causation. Because most prior studies had narrow baseline age ranges, stratified analyses across mid- and later life have rarely been feasible.

The previous chapter also showed that the neuroticism–dementia association was independent of genetic risk. However, the UK Biobank cohort has a relatively younger age of onset for dementia, a group more strongly influenced by genetic factors such as *APOE* ε4.[228] It remains unknown whether neuroticism contributes additional risk in cases of later onset, where the genetic component is typically weaker. Moreover, the previous chapter

found that mental and vascular conditions, such as depression and hypertension, partially mediated the association. These conditions are stronger predictors of dementia when present in mid-life than in later life,[17] raising the question of whether neuroticism contributes via these pathways primarily earlier in life or consistently across the life course.

Although the previous chapter examined the association between neuroticism and cognitive performance in a large sample, it relied on brief, single-task assessments with limited testing time. It is important to use more detailed, standardized cognitive batteries to determine whether the broad associations across multiple domains observed previously persist, and whether stronger associations are evident in domains more sensitive to age-related decline, such as memory,[229] while weaker or null associations are seen in domains that tend to remain stable, such as crystallized intelligence.[230]

The EPIC-Norfolk cohort is ideally suited to address these gaps, comprising over 25,000 participants aged 39–79 at recruitment (1993–1997) and followed through to 2022. This allows robust evaluation of time- and age-specific associations between neuroticism and incident dementia. This study also examined interaction with genetic factors, mediation by health conditions, and the relationship between neuroticism and domain-specific cognitive performance using a detailed battery in dementia-free individuals.

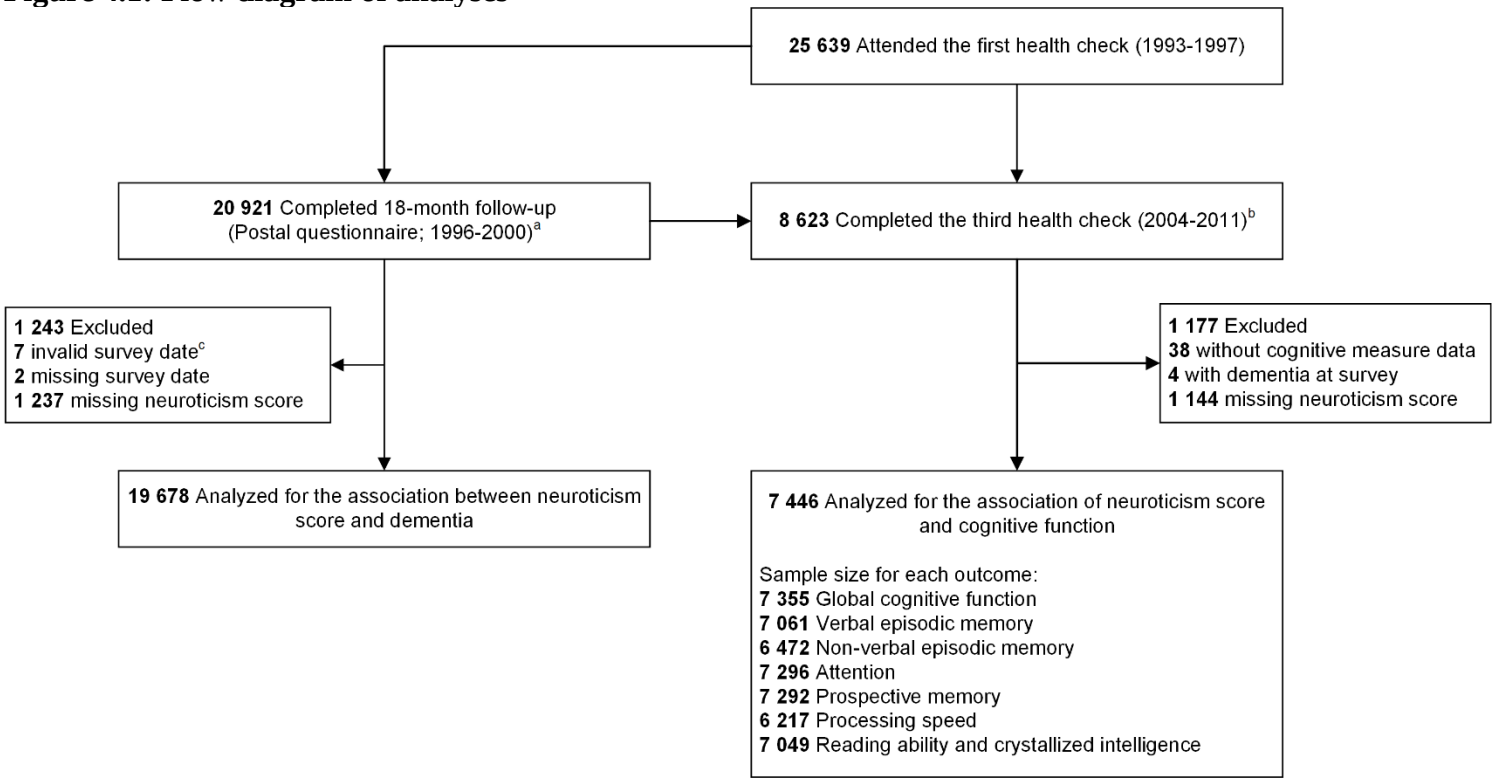
4.3 METHODS

Study population

The EPIC-Norfolk study is a large population-based prospective cohort of men and women aged 39–79 years, recruited between 1993 and 1997.[231] 25,639 participants underwent an initial assessment,[232] referred to as the first "health check," which included self-administered written questionnaires on sociodemographic, lifestyle, and medical history, as well as physical examinations and collection of biological samples. Eighteen months later, participants were invited to complete the Health and Life Experiences Questionnaire (HLEQ), a postal questionnaire which included a measure of neuroticism; 20,921 responded between 1996 and 2000 (73.2% response rate from the eligible sample of 28,582).[233] The questionnaire completion date is taken as the baseline for this study, restricted to the 20,921 HLEQ respondents, excluding those with an invalid completion date (same as date of death; n=7), missing completion date (n=2), or missing neuroticism data (n=1,237), yielding a final analytic sample of 19,678. No participants had dementia at baseline (**Figure 4.1**).

Third health checks for EPIC-Norfolk were conducted between 2004 and 2011, in 8,623 participants aged 48–92 years (46.9% response rate from the eligible sample of 18,380).[234] During this assessment, 8,585 participants completed at least one of eight validated cognitive tests assessing different domains of cognitive function, such as memory, executive function, and language. After excluding participants with prevalent dementia prior to the third health check (n=4) and those with missing neuroticism data (n=1,144), the final sample comprised 7,446 individuals.

Figure 4.1: Flow diagram of analyses



[a] The 18-month follow-up recruitment occurred between 1994 and 1999. The Health and Life Experiences Questionnaire (HLEQ), which included the neuroticism assessment, was completed between 1996 and 2000.
[b] The Third Health Check (3HC) included 8,623 participants from the original EPIC-Norfolk cohort, drawn from those who previously attended the baseline (1HC) and likely also completed the 18-month postal questionnaire.
[c] Cases where the survey date is recorded as the same day as the date of death.

The EPIC-Norfolk study received ethics approval from the Norfolk Research Ethics Committee (REC Ref: 98CN01), the East Norfolk and Waveney National Health Service Research Governance Committee (2005EC07L), and the Norwich Local Research Ethics Committee (05/Q0101/191). All participants provided written informed consent, including access to their medical records.

Assessment of neuroticism

Neuroticism was assessed using the EPQ-RS,[61] the same as in the UK Biobank study. Both the total score (range: 0–12) and a standardized z-score (mean=0, SD=1) were used as exposures.

Incident dementia outcomes

Incident all-cause dementia and its subtypes were identified by the EPIC-Norfolk team using multiple data sources. Cases were primarily identified using national death records and England hospital inpatient data, which were available for the entire cohort, with diagnoses recorded according to the ICD coding system. The ICD codes used for dementia and its subtypes were consistent with those applied in the UK Biobank study in Chapter 3.[229] Additional all-cause dementia cases were identified through primary care records and the national mental healthcare dataset. Primary care data, available for approximately 18% of participants, captured dementia diagnoses and prescriptions using Read codes.[235] The national mental healthcare dataset recorded diagnoses using ICD codes. The censoring date

for death records and England hospital inpatient data was March 31st, 2022, while for primary care and mental healthcare data, it was March 31st, 2019.

Cognitive outcomes

The test battery was researcher-led and required approximately 35 minutes to complete, which included global cognitive function (Short Form Extended Mental State Exam), verbal episodic memory (Hopkins Verbal Learning Test), non-verbal episodic memory (Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test), attention (PW Letter Cancellation Task), prospective memory (Event and Time Based Task), processing speed (Visual Sensitivity Test), and crystallized intelligence (National Adult Reading Test). The brief description and performance score for each test were summarized below.

Short Form Extended Mental State Exam required participants to complete 11 items assessing orientation, attention, and recall. The score reflected the number of correct responses, aligned with MMSE scoring.

Hopkins Verbal Learning Test required participants to memorize a 12-word list presented across three trials and recall as many words as possible after each. The total score was the sum of correctly recalled words across trials (maximum: 36).

Paired Associates Learning Test required participants to recall the locations of abstract patterns presented in boxes on a touchscreen. The score was the ‘first trial memory

score', summing correct pattern-location matches made on the first attempt across eight stages.

PW Letter Cancellation Task required participants to scan a grid of letters and identify all instances of the letters "P" and "W" within one minute. The score was the number of correct targets identified minus missed targets and errors.

Event- and Time-Based Prospective Memory Task required participants to remember and execute future instructions (e.g., sealing and initialing an envelope later in the session without a prompt). Performance was recorded as success (≥1 action completed unprompted) or fail.

Visual Sensitivity Test required participants to detect a triangle under two conditions—simple (on a blank screen) and complex (among moving dots)—and press a response key as quickly as possible. Reaction times were recorded in milliseconds; higher values indicated slower responses.

National Adult Reading Test required participants to pronounce 50 irregularly spelled English words aloud. The score was the number of pronunciation errors, with higher scores reflecting poorer performance. A shortened version was used, with full scores derived algorithmically.

Most test scores were non-normally distributed (**Appendix 4.1**); therefore, following the EPIC-Norfolk team's approach, poor cognitive performance was defined as scoring below the 10th percentile of the population distribution for each cognitive measure, except for the prospective memory test, where poor performance was defined as failing the task (a dichotomous outcome).[230] The composite outcome was categorized into three groups based on the number of cognitive tests with poor performance: 1) 1 poor performance test, 2) 2–3 poor performance tests, and 3) 4–8 poor performance tests. Participants with no poor performance tests served as the reference group. This categorization follows a previous study using EPIC-Norfolk data, which demonstrated a steep linear increase in dementia risk across these categories.[229]

Covariates and mediators

To ensure comparability with the study in Chapter 3, covariates and mediators in this study were selected to align with those used in Chapter 3.

Socioeconomic covariates included the TDI (quintiles) derived from the 1991 census, and educational status, categorized into four groups based on the highest qualification attained: degree, A-level (educational attainment at age 17), O-level (educational attainment at age 15), and less than O-level or no qualifications. Lifestyle covariates included smoking status (never, former, current), alcohol consumption (never, former, ≤14 units per week, and >14 units per week), and BMI (derived from physical measurements at assessment, categorized as normal [<25 kg/m²], overweight [≥25–<30 kg/m^2], and obese [≥30 kg/m²]). Participants with missing data were assigned to a distinct category for each covariate.

Potential mediating conditions included depression, anxiety and stress-related disorders, hypertension, and IHD. Diabetes was selected as a negative control mediator. All conditions were identified based on self-reported doctor-diagnosed history at baseline.

Statistical analysis

Association of neuroticism with dementia and its subtypes

Cox proportional hazards regression was used to examine the association between neuroticism scores and the risk of incident dementia. Given the wide baseline age range in EPIC-Norfolk, age was used as the underlying timescale, with models adjusted for sex and preselected socioeconomic and lifestyle covariates. The proportional hazards assumption in the Cox model was checked by visually examining the distribution of scaled Schoenfeld residuals. The relationship shape was assessed using restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentiles of the neuroticism score. Non-linearity was tested using a likelihood ratio test comparing models with and without cubic spline terms. Based on these results, the neuroticism z-score was used as the primary exposure in subsequent analyses. The association between neuroticism z-score and incident dementia risk was then assessed. Sensitivity analyses included: (1) multiple imputation for missing exposure and covariate data, conducted using chained equations as described in Chapter 3; (2) adjustment for the competing risk of non-dementia death using the Fine-Gray subdistribution hazard model, given the older baseline age and long follow-up in EPIC-Norfolk.

To investigate the potential role of reverse causality, follow-up time was divided into three intervals (<15, 15–19, and ≥20 years), with participants contributing to longer follow-up groups until incident dementia, death, or the last follow-up date (March 31st, 2022). If the observed association between neuroticism and dementia weakens or disappears over longer follow-up periods, it suggests that the association is at least partially driven by changes in neuroticism as an early symptom of dementia.

Effect modification and mediation

To examine associations across different age stages, analyses were stratified by baseline age (<60, 60–69, and ≥70 years). Additionally, to assess whether similar genetic modification patterns seen in UK Biobank (Chapter 3) extend to the older EPIC-Norfolk cohort, analyses were stratified by *APOE* ε4 status (non-carrier, carrier). The multiplicative interaction was tested using the Wald test by adding interaction terms into multivariable models. Analyses involving the *APOE* gene were restricted to participants of White ethnicity. While *APOE* genotype information was available in EPIC-Norfolk, the dataset did not contain the additional genome-wide SNP data needed to construct the dementia non-*APOE* PRS used in the UK Biobank analyses. Therefore, effect modification by PRS was not assessed in this cohort.

Mediation analyses were conducted using the counterfactual framework, consistent with the approach detailed in Chapter 3.

Association between neuroticism and cognitive function

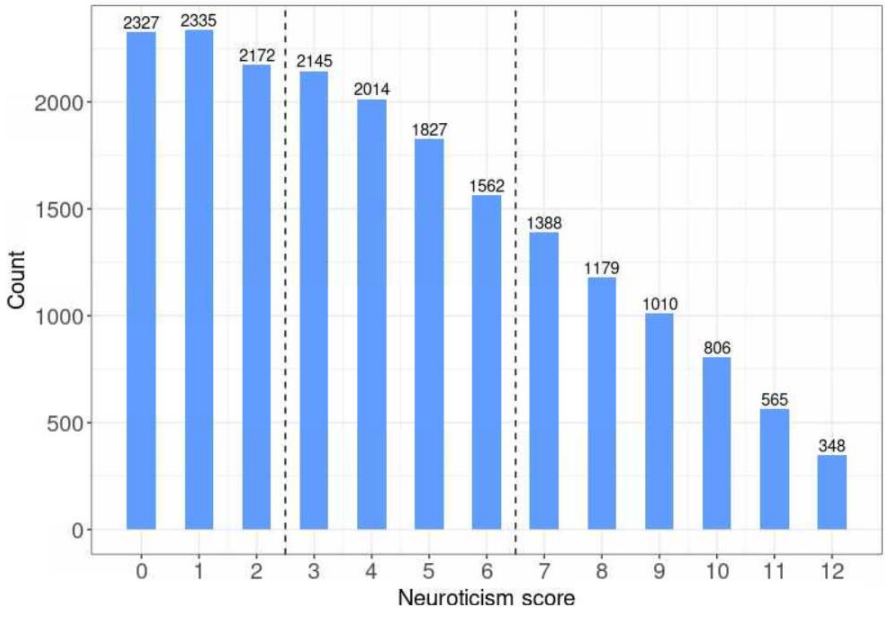
The association between neuroticism z-score and poor cognitive performance on each test was assessed using logistic regression, while the association with composite cognitive function outcomes was examined using multinomial logistic regression, both adjusted for age at the third health check, sex, and the same preselected socioeconomic and lifestyle covariates as in the dementia models. Neuroticism and all covariates used in this analysis were based on measurements taken at the third health check.

4.4 RESULTS

Sample characteristics

Among the 19,678 participants in EPIC-Norfolk, neuroticism scores showed a similar distribution to that observed in the UK Biobank—right-skewed, with tertile cut-offs at 2 (lower third) and 6 (upper third) (**Figure 4.2**). The mean age of participants was 60.8 years (SD=9.3), and 55.8% were female (**Table 4.1**). Those with higher neuroticism tended to be younger, female, have lower socioeconomic status, consume less alcohol, and be current smokers. The proportion of *APOE* ε4 carriers was similar across neuroticism levels. Additionally, histories of depression, anxiety, and hypertension were more common among participants with higher neuroticism, while histories of IHD and diabetes were similar across neuroticism score tertiles.

Figure 4.2: Distribution of neuroticism score



Dashed lines divide the histogram into tertiles.

Table 4.1: Baseline characteristics of participants

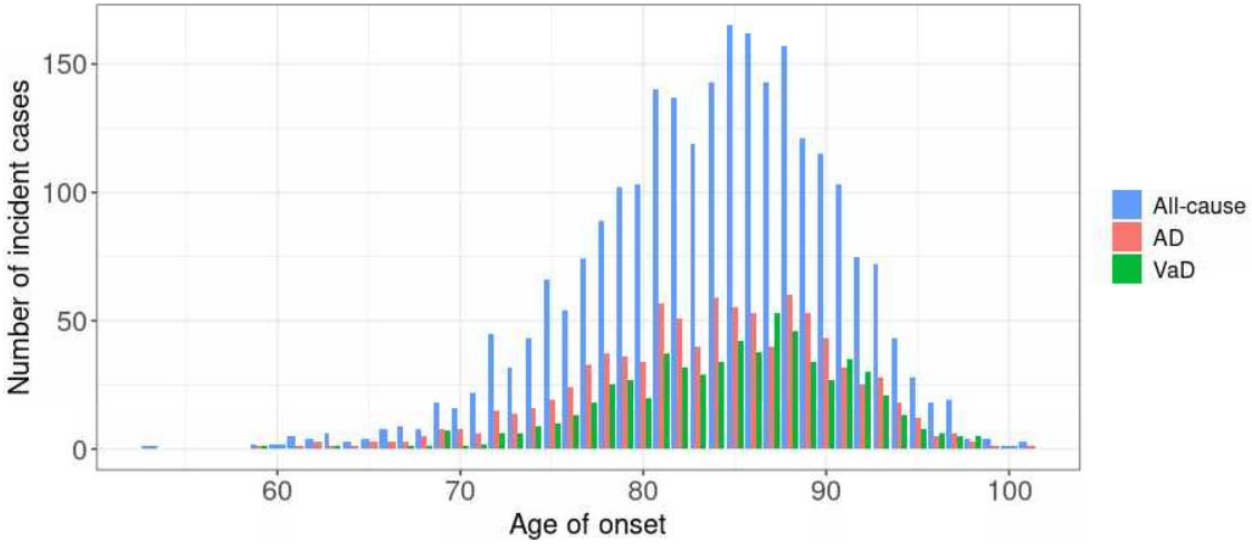
Characteristic	Overall	Neuroticism score tertile		
		1 (score 0–2)	2 (score 3–6)	3 (score 7–12)
N	19678	6834	7548	5296
Age (mean [SD])	60.82 (9.26)	62.07 (9.14)	60.64 (9.24)	59.44 (9.23)
Female (%)	10973 (55.8)	3049 (44.6)	4423 (58.6)	3501 (66.1)
Townsend deprivation index quintile (%)				
1 (Least deprived)	4052 (20.6)	1407 (20.6)	1576 (20.9)	1069 (20.2)
2	4021 (20.4)	1410 (20.6)	1546 (20.5)	1065 (20.1)
3	3953 (20.1)	1438 (21.0)	1480 (19.6)	1035 (19.5)
4	3911 (19.9)	1382 (20.2)	1511 (20.0)	1018 (19.2)
5 (Most deprived)	3667 (18.6)	1176 (17.2)	1406 (18.6)	1085 (20.5)
Missing	74 (0.4)	21 (0.3)	29 (0.4)	24 (0.5)
Education (%)				
Less than O-level	7129 (36.2)	2337 (34.2)	2722 (36.1)	2070 (39.1)
O-level	2088 (10.6)	654 (9.6)	843 (11.2)	591 (11.2)
A-level	7885 (40.1)	2876 (42.1)	2982 (39.5)	2027 (38.3)
Degree	2567 (13.0)	963 (14.1)	998 (13.2)	606 (11.4)
Missing	9 (0.0)	4 (0.1)	3 (0.0)	2 (0.0)
Body mass index category (%)				
Normal (<25 kg/m^2)	6804 (34.6)	2211 (32.4)	2672 (35.4)	1921 (36.3)
Overweight (≥25–<30 kg/m^2)	7874 (40.0)	2935 (42.9)	2967 (39.3)	1972 (37.2)
Obese (≥30 kg/m^2)	2518 (12.8)	878 (12.8)	962 (12.7)	678 (12.8)
Missing	2482 (12.6)	810 (11.9)	947 (12.5)	725 (13.7)
Alcohol intake (%)				
Never	1005 (5.1)	367 (5.4)	373 (4.9)	265 (5.0)
Previous	1899 (9.7)	589 (8.6)	715 (9.5)	595 (11.2)
Current (≤14 units/week)	13772 (70.0)	4733 (69.3)	5317 (70.4)	3722 (70.3)
Current (>14 units/week)	2819 (14.3)	1093 (16.0)	1073 (14.2)	653 (12.3)
Missing	183 (0.9)	52 (0.8)	70 (0.9)	61 (1.2)
Smoking (%)				
Never	9276 (47.1)	3226 (47.2)	3599 (47.7)	2451 (46.3)
Previous	8126 (41.3)	2889 (42.3)	3126 (41.4)	2111 (39.9)
Current	2126 (10.8)	665 (9.7)	768 (10.2)	693 (13.1)
Missing	150 (0.8)	54 (0.8)	55 (0.7)	41 (0.8)
APOE ε4 Carrier (%)	3795 (26.5)	1353 (26.5)	1449 (26.5)	993 (26.5)
Depression (%)	2705 (13.8)	323 (4.7)	837 (11.1)	1545 (29.2)
Anxiety and stress related disorders (%)	582 (3.0)	79 (1.2)	182 (2.4)	321 (6.1)
Ischaemic heart disease (%)	1199 (6.1)	429 (6.3)	453 (6.0)	317 (6.0)
Hypertension (%)	2810 (14.3)	937 (13.7)	1090 (14.5)	783 (14.8)
Diabetes (%)	437 (2.2)	152 (2.2)	169 (2.2)	116 (2.2)

N, number of participants; SD, Standard deviation

Association of neuroticism with dementia and its subtypes

Over a median follow-up of 22.7 years, 2,488 participants developed incident all-cause dementia, of which 913 consisted of AD and 643 consisted of VaD. **Figure 4.3** showed the distribution of incident dementia diagnoses by age of onset, with most clinical onsets occurring between ages 80 and 90.

Figure 4.3: Distribution of incident dementia diagnoses by age of onset

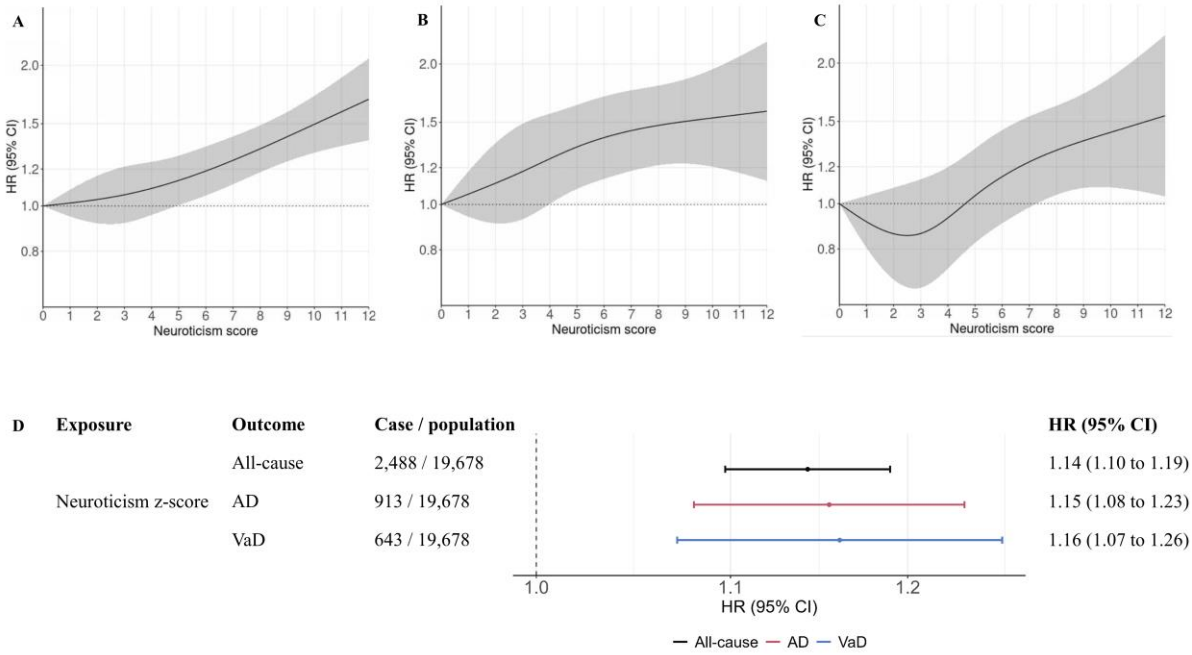


AD, Alzheimer's disease; VaD, vascular dementia.

After adjustment for covariates, the risk of incident dementia and its subtypes increased in a dose-response manner for all-cause dementia (p for non-linearity=0.34), AD (p=0.69), and VaD (p=0.10) (**Figure 4.4**). A 1-unit increase in neuroticism z-score was associated with a 14% (HR 1.14, 95% CI, [1.10 to 1.19]), 15% (1.15, [1.08 to 1.23]), and 16% (1.16, [1.07 to 1.26]) higher risk of incident all-cause dementia, AD, and VaD, respectively. Sensitivity analyses using multiple imputation produced similar results, though

in competing risk models accounting for non-dementia mortality, the associations were attenuated yet remained statistically significant (**Appendix 4.2**).

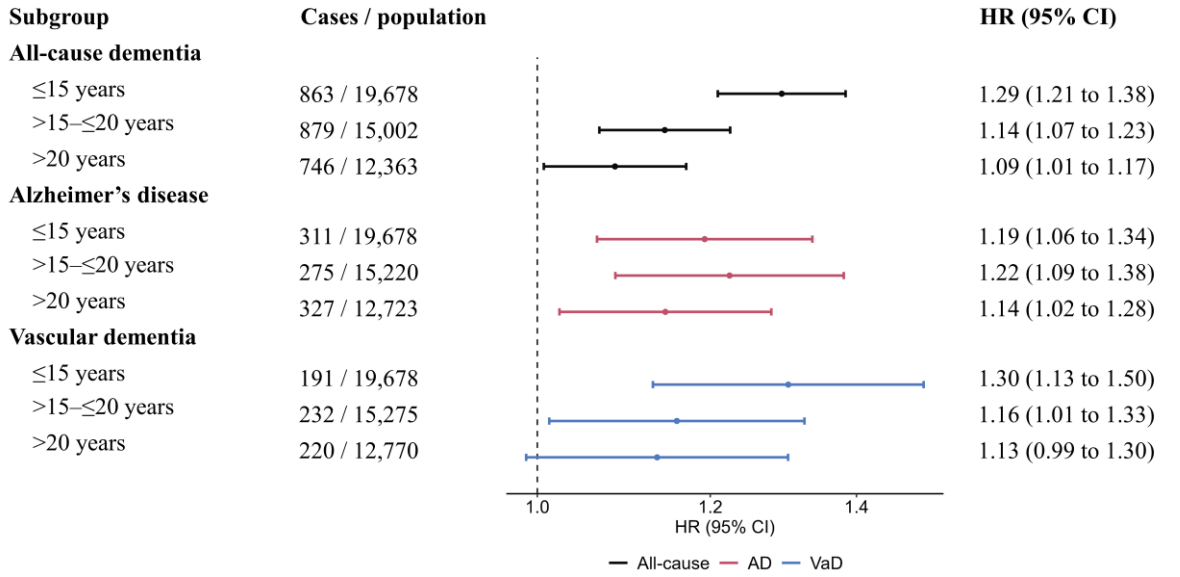
Figure 4.4: Associations between neuroticism score (original values and z-score) and incident dementia



HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia; Panels A–C show associations between neuroticism score and risk of all-cause dementia (A), AD (B), and VaD (C). Panel D shows hazard ratios (HRs) per 1-SD increase in neuroticism score for each outcome. Estimates are adjusted for age, sex, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index. In panels A–C, solid lines represent adjusted HRs with shaded areas indicating 95% confidence intervals, derived from restricted cubic spline regressions with four knots. The dashed line marks the reference HR of 1.0. The reference point for neuroticism score is 0, indicating the lowest level of neuroticism.

For all-cause dementia, the risk was highest in the first 15 years of follow-up (1.29, [1.21 to 1.38]), gradually decreasing but remaining modestly elevated even after 20 years (1.09, [1.01 to 1.17]) (**Figure 4.5**). A similar attenuating trend was observed for subtypes, with VaD ultimately attenuating to null after 20 years.

Figure 4.5: Associations between neuroticism z-score and incident dementia stratified by follow-up period

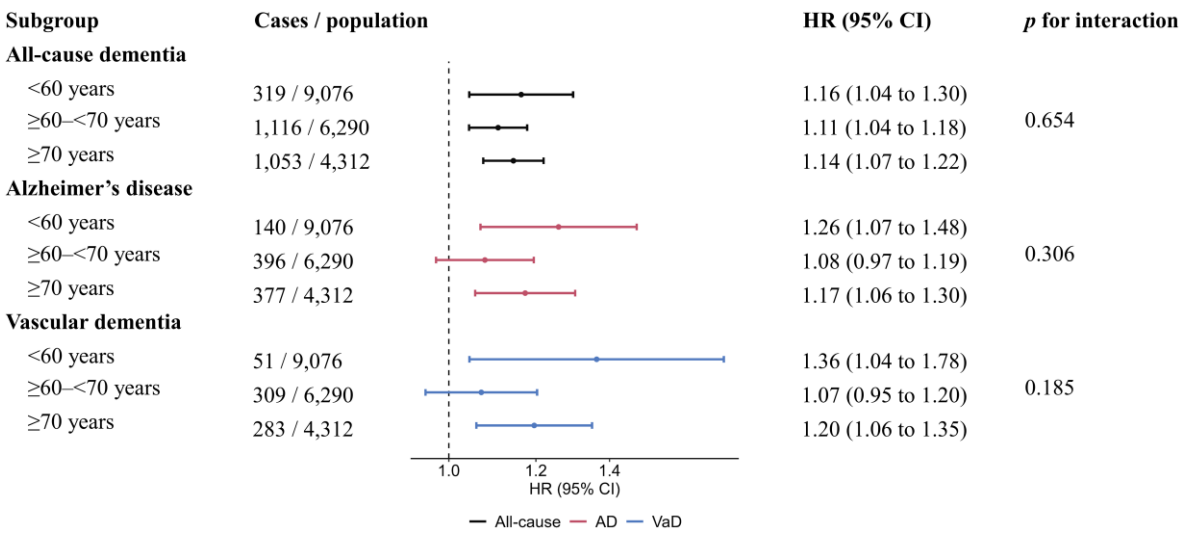


HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia. Cox proportional hazards models were fitted using age as the underlying timescale and adjusted for sex, education, socioeconomic status, smoking status, alcohol consumption, and body mass index. The dashed vertical line marks the reference HR of 1.0.

Effect modification and mediation

In age-specific analyses, neuroticism was significantly associated with a similarly increased risk of all-cause dementia across baseline age groups (p for interaction=0.654): early midlife (<60 years) (1.16, [1.04 to 1.30]), late midlife (≥60–<70 years) (1.11, [1.04 to 1.18]), and later life (≥70 years) (1.14, [1.07 to 1.22]) (**Figure 4.6**). For dementia subtypes, significant associations were observed only in the <60 and ≥70 age groups, although there was no statistical evidence of interaction with age (all p>0.05).

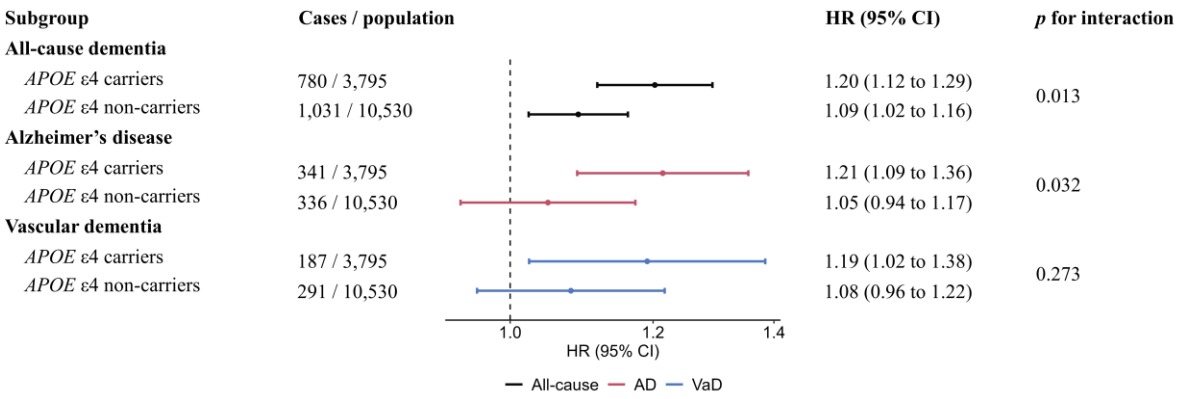
Figure 4.6: Associations between neuroticism z-score and incident dementia stratified by baseline age



HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia. Cox proportional hazards models were fitted using age as the underlying timescale and adjusted for sex, education, socioeconomic status, smoking status, alcohol consumption, and body mass index. The dashed vertical line marks the reference HR of 1.0.

Additionally, the association was stronger among *APOE* ε4 carriers than non-carriers for all-cause dementia (1.20, [1.12 to 1.29] vs 1.09, [1.02 to 1.16], p for interaction=0.013), and AD (1.21, [1.09 to 1.36] vs 1.05, [0.94 to 1.17], p for interaction=0.032), but not for VaD (**Figure 4.7**).

Figure 4.7: Associations between neuroticism z-score and incident dementia stratified by *APOE* ε4 carrier status



HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia. Cox proportional hazards models were fitted using age as the underlying timescale and adjusted for sex, education, socioeconomic status, smoking status, alcohol consumption, and body mass index. The dashed vertical line marks the reference HR of 1.0.

A significant indirect (mediating) effect of selected conditions was observed in the association between neuroticism z-score and all-cause dementia (**Table 4.2**). The highest proportion was explained by depression (13.9%), followed by vascular conditions, including hypertension (8.8%) and IHD (8.6%), with diabetes contributing similarly (8.4%). No significant mediating effects were detected for AD or VaD.

Table 4.2: Mediation analyses for the associations between neuroticism z-score, baseline disease history, and incident dementia

Outcome	Mediator	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)	Proportion mediated (%)
All-cause	Depression	1.16 (1.11 to 1.21)	1.13 (1.09 to 1.19)	1.02 (1.00 to 1.04)	13.9
	Anxiety	1.15 (1.10 to 1.20)	1.14 (1.09 to 1.19)	1.01 (0.99 to 1.03)	-
	Hypertension	1.15 (1.10 to 1.20)	1.14 (1.09 to 1.19)	1.01 (1.00 to 1.03)	8.8
	IHD	1.15 (1.10 to 1.20)	1.14 (1.09 to 1.19)	1.01 (1.00 to 1.03)	8.6
	Diabetes	1.15 (1.10 to 1.20)	1.14 (1.09 to 1.19)	1.01 (1.00 to 1.03)	8.4
AD	Depression	1.17 (1.09 to 1.25)	1.17 (1.09 to 1.25)	1.00 (0.97 to 1.03)	-
	Anxiety	1.16 (1.08 to 1.24)	1.16 (1.08 to 1.23)	1.00 (0.98 to 1.03)	-
	Hypertension	1.16 (1.08 to 1.24)	1.15 (1.08 to 1.23)	1.01 (0.98 to 1.03)	-
	IHD	1.16 (1.08 to 1.24)	1.15 (1.08 to 1.23)	1.01 (0.98 to 1.03)	-
	Diabetes	1.16 (1.09 to 1.24)	1.15 (1.08 to 1.23)	1.01 (0.98 to 1.03)	-
VaD	Depression	1.19 (1.09 to 1.29)	1.16 (1.06 to 1.27)	1.02 (0.98 to 1.07)	-
	Anxiety	1.16 (1.07 to 1.27)	1.16 (1.07 to 1.26)	1.00 (0.97 to 1.03)	-
	Hypertension	1.16 (1.07 to 1.26)	1.15 (1.06 to 1.25)	1.01 (0.98 to 1.04)	-
	IHD	1.17 (1.07 to 1.27)	1.16 (1.07 to 1.26)	1.01 (0.98 to 1.04)	-
	Diabetes	1.17 (1.07 to 1.27)	1.16 (1.07 to 1.26)	1.01 (0.98 to 1.04)	-

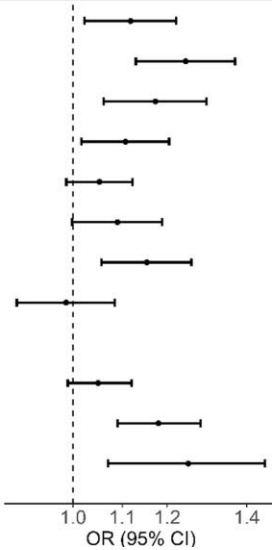
CI, confidence interval; IHD, ischaemic heart disease; AD, Alzheimer's disease; VaD, vascular dementia; Estimates are adjusted for age, sex, ethnicity, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index. Total, direct, and indirect effects represent hazard ratios per 1-SD increase in neuroticism, estimated using the counterfactual framework and marginal structural models. The proportion mediated was calculated as the natural indirect effect divided by the total effect. "-" indicate insignificant indirect (mediating) effect.

Association between neuroticism and cognitive function

The analyses of cognitive outcomes included 7,446 participants, with a mean age of 68.2 years (SD=8.1), of whom 55.2% were female (**Appendix 4.3**). Compared to baseline participants, these individuals had a higher socioeconomic status and were less likely to be current alcohol consumers or current smokers. The distribution of characteristics by neuroticism level followed a similar pattern to that observed in the baseline participants. Neuroticism at cognitive assessment correlated strongly with baseline levels (Pearson correlation coefficient r=0.73). Neuroticism was positively associated with poor performance across several cognitive domains (**Figure 4.8**). The strongest associations were observed for poor performance in verbal episodic memory (OR 1.29, 95% CI [1.17 to 1.42]) and non-verbal episodic memory (1.16 [1.04, 1.28]). Whilst higher neuroticism was associated with poor performance in prospective memory and simple processing speed, these trends were not statistically significant. Neuroticism showed no clear trend with crystallized intelligence. A dose-response association was observed between neuroticism and the composite cognitive outcome, with neuroticism linked to a higher likelihood of poor performance across multiple cognitive domains compared to those with no poor performance.

Figure 4.8: Associations between neuroticism z-score and cognitive function

Domain	Test	Poor/Complete Data (N)	OR (95% CI)
Global cognitive function	SF-EMSE	587/7355	1.13 (1.03 to 1.24)
Verbal episodic memory	HVLT	508/7061	1.29 (1.17 to 1.42)
Non-verbal episodic memory	CANTAB-PAL	463/6472	1.16 (1.04 to 1.28)
Attention	PW Letter Cancellation Task	647/7296	1.12 (1.03 to 1.22)
Prospective memory	Event and Time Based Task	1317/7292	1.05 (0.99 to 1.12)
Processing speed (simple)	VST (simple)	611/6217	1.08 (0.99 to 1.18)
Processing speed (complex)	VST (complex)	599/6217	1.14 (1.05 to 1.25)
Reading ability and crystallized intelligence	NART	554/7049	1.01 (0.92 to 1.12)
Composite outcome			
1 poor performance test		1747/6887	1.06 (0.99 to 1.12)
2-3 poor performance test		828/6887	1.18 (1.09 to 1.29)
4-8 poor performance test		204/6887	1.28 (1.10 to 1.50)



OR, odds ratio; CI, confidence interval; SF-EMSE, Short form-Extended Mental State Exam; HVLT, Hopkins Verbal Learning Test; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test; VST, Visual Sensitivity Test; NART, National Adult Reading Test. Cross-sectional associations between the neuroticism z-score and cognitive performance were assessed using logistic regression, adjusting for age, sex, socioeconomic deprivation, education, smoking status, alcohol consumption, and body mass index. Poor cognitive performance was defined as scoring below the 10th percentile for each cognitive test, except for the prospective memory test, where poor performance was defined as failing the task (a dichotomous outcome). The composite outcome was categorized into three groups based on the number of tests with poor performance, with those having none as the reference. Multinomial logistic regression was used to assess the association between neuroticism and the composite outcome.

4.5 DISCUSSION

In this population-based study of nearly 20,000 individuals aged 40–80 years followed for up to 26 years, higher neuroticism was associated with an increased risk of dementia, with each 1-SD increase in neuroticism score linked to a 14% higher risk for all-cause dementia, with comparable risk estimates for AD (15% higher) and VaD (16% higher). The association was stronger in the short term but remained significant even when the lag time between neuroticism measurement and dementia onset exceeded 20 years. A similarly increased risk was observed across age groups, including early midlife (<60 years), late midlife (≥60–<70 years), and later life (≥70 years). Among mid- to later-life adults without dementia, higher neuroticism was associated with poorer performance across multiple cognitive domains. Additionally, this study found interactions between neuroticism and *APOE* ε4 genotype, and mediation by mental and vascular conditions.

The previous chapter, based on UK Biobank, showed a stronger association with VaD than with AD, whereas in EPIC-Norfolk the risks for AD and VaD were comparable. This difference may reflect regional variations in diagnostic practices and underlying population risk profiles. EPIC-Norfolk includes more oldest-old participants (>85 years), where mixed dementia and VaD are more common and pure AD is less dominant,[236] while UK Biobank participants were generally younger, with AD remaining the predominant subtype. In UK Biobank, VaD diagnoses may represent a subgroup with more pronounced vascular risk profiles, which aligns with neuroticism's known links to vascular factors such as hypertension and IHD, explaining the stronger observed association with VaD.

The association between neuroticism and dementia remained significant when neuroticism was measured before age 60 or more than 20 years prior to diagnosis, supporting its role as a long-term risk factor rather than a psychological change emerging in the early stages of the disease. Two previous studies with follow-ups exceeding 20 years both reported significant associations, though with varying magnitudes. One study (N=800, baseline age 38–54, maximum follow-up 38 years) found each 1-SD higher baseline neuroticism score was associated with a 4% increased risk of AD.[127] This estimate is lower than that observed in this study and may be influenced by survival bias, as previous studies suggest that individuals with higher neuroticism are at increased risk of earlier mortality and may die before developing dementia.[237,238] This interpretation is supported by the Fine-Gray model results, which indicated that the association was further attenuated after accounting for competing risks of non-dementia mortality. Another study (N=1,671, median baseline age 56.5, maximum follow-up 22 years) found a 37% increased risk of AD,[121] though this estimate may be inflated by residual confounding due to limited adjustment (age, sex, ethnicity, and education only). Additionally, a study that assessed personality-related characteristics in adolescence (mean age 15.8) found each 1-SD higher level of "calm"—an indicator of low neuroticism—was associated with a 5% lower risk of dementia after 54 years of follow-up.[239] Together, these findings reinforce neuroticism as a potential risk factor for dementia and highlight the importance of early identification and intervention, as neuroticism typically stabilizes in late adolescence.[51]

In this study, the association between neuroticism and dementia risk was similar for those whose baseline in the study was in mid- or later- life. This suggests that neuroticism may help identify individuals at elevated risk of dementia even in later life. While earlier exposure to high neuroticism could allow more time for cumulative damage (e.g., cerebrovascular injury), this study did not observe a stronger association in younger age groups (e.g., baseline age <60). This may reflect survival bias, where younger individuals with high neuroticism are less likely to survive to dementia onset.[240]

The direct association between neuroticism and dementia is further supported by its link to poor cognitive function. This study used a validated, detailed cognitive battery shown to predict future dementia.[229] A previous cross-sectional study (N=2,865) used a similarly detailed multi-domain cognitive battery (five domains) and reported comparable associations across domains.[149] However, its older population (mean age=76) makes the findings more susceptible to reverse causation, as some participants may already have been in preclinical dementia stages. In contrast, participants in the present analysis were a healthier, younger (mean age=68), dementia-free subgroup of EPIC-Norfolk, making the findings less prone to such bias. The association with poor global cognition and the observed dose-response relationship for the composite cognitive outcome suggest that neuroticism is linked to poor cognitive function across a broad range of domains, an important early indicator of cognitive decline.[241] The strongest association was found for verbal episodic memory, the strongest predictor of dementia among all cognitive tests in EPIC-Norfolk.[229] In contrast, the lack of association with crystallized intelligence may reflect its relative stability with age compared to other cognitive domains.[230] This strong correlation between baseline and cognitive-

assessment neuroticism is consistent with findings from UK Biobank (Chapter 3), reinforcing neuroticism as a stable marker linked to poorer cognitive performance.

In this study, a significant interaction between neuroticism and *APOE* ε4 was observed, with stronger associations in *APOE* ε4 carriers. This finding is consistent with a previous study (mean baseline age 78.6; 6.5 years follow-up)[140] in which most dementia cases occurred in the mid-80s, similar to the present analysis and more representative of the general population.[242] By contrast, the UK Biobank study in the previous chapter and another study (mean baseline age 56.5 years; 12 years follow-up),[121] where dementia onset occurred earlier (mid-70s), found no significant interaction. Together, these findings suggest that neuroticism may confer additional risk for late-onset dementia among genetically vulnerable individuals.

Our mediation analyses were consistent with findings from the previous chapter, showing that depression accounted for the largest proportion of the association, followed by vascular conditions, with diabetes contributing the least. The mediation proportions for depression (13.9%), hypertension (8.8%), and IHD (8.6%) were smaller than those reported previously (38.5%, 10.4%, and 10.9%, respectively). These differences may reflect variation in cohort characteristics. Importantly, these factors still explained a significant part of the association, indicating that neuroticism is linked to dementia risk partly through modifiable pathways even in older age.

Strengths and limitations

This study has several strengths, including a large population with a wide baseline age range and long follow-up, allowing us to examine whether the association between neuroticism and dementia remained stable across different age groups and time periods, helping to clarify the direction and timing of the association. Additionally, the use of well-established cognitive tests for global and domain-specific function, which are sensitive to early cognitive changes preceding dementia symptoms, further strengthens these findings. However, EPIC-Norfolk was geographically restricted to Norwich and surrounding areas and served by a single District General Hospital,[231] which may limit generalisability to more diverse populations. As in the UK Biobank, healthier individuals with higher socioeconomic status were more likely to participate at baseline and follow-up,[234] potentially introducing healthy volunteer bias. In addition, reliance on hospital inpatient and mortality records for dementia identification likely resulted in under-ascertainment and potential misclassification, particularly for dementia subtypes such as AD and VaD.[227]

Conclusion

Findings from this chapter extend the significant association between neuroticism and incident dementia risk—previously observed with follow-up periods of up to 16 years in Chapter 3—to more than 20 years, strengthening the evidence supporting neuroticism as a risk factor. Additionally, this chapter provides new insights by demonstrating that the association remains significant regardless of whether neuroticism is assessed in mid- or later life. Furthermore, neuroticism was associated with poorer cognitive performance across

multiple domains before dementia onset. Together, the two large-scale population-based cohort studies in Chapters 3 and 4 provide robust, consistent evidence that higher neuroticism is associated with an increased risk of dementia. Both chapters also suggest that vascular pathways may underlie this association.

Chapter 5 Neuroticism, omega-3 fatty acids, and risk of incident dementia

5.1 CHAPTER SUMMARY

Neuroticism has been linked to dementia risk, but the biological pathways remain unclear. Given the role of metabolites in both neuroticism and dementia, this study analysed 215,624 UK Biobank participants with nuclear magnetic resonance (NMR)-based metabolomics data. Linear regression identified metabolites associated with neuroticism, and those reaching Bonferroni significance were tested for associations with incident dementia using Cox proportional hazards regression. Robustness of significant observational relationships was evaluated through two-sample MR.

Neuroticism was significantly associated with 119 of 249 metabolites (Bonferroni-adjusted $p<0.05$). Five metabolites involved in fatty acid metabolism showed consistent directional associations with both neuroticism and dementia. Higher levels of docosahexaenoic acid (DHA), DHA% of total fatty acids, omega-3% of total fatty acids, and degree of unsaturation were associated with lower neuroticism levels and a decreased risk of dementia, whereas the omega-6/omega-3 ratio was positively associated with both neuroticism and dementia risk. Associations were stronger for VaD than for AD. MR analyses suggested that high levels of neuroticism reduce DHA levels, which, in turn, contribute to white matter pathology, a hallmark of VaD.

In conclusion, neuroticism is associated with lower levels of omega-3 fatty acids, particularly DHA, which may increase dementia risk, primarily via cerebrovascular pathways.

5.2 BACKGROUND

Findings from previous chapters consistently suggest that neuroticism is associated with an increased risk of dementia. Since neuroticism is established early in life and remains relatively stable throughout the life course, it is not easily modifiable. However, it may indirectly increase dementia risk through other modifiable factors, which could serve as promising candidates for targeted interventions. Evidence highlighted in earlier chapters points to cerebrovascular health as a key pathway: neuroticism has been robustly associated with VaD and WMH, a marker of cerebrovascular damage;[116,170] vascular conditions such as hypertension and IHD have been identified as mediators of this association. Further exploration with molecular data may provide additional clues about the biological pathways and offer insights for precision prevention strategies.

To better understand the underlying pathways, studying metabolites may be a promising approach. Metabolites are the final downstream products of metabolic processes, capturing both genetic and environmental influences on metabolism.[44] They may play a crucial role in the association between neuroticism and dementia. First, neuroticism is associated with factors influencing metabolic processes,[243] including lifestyle changes (e.g., diet),[100] chronic inflammation,[244] and disrupted gut microbiota.[245] Second, dysregulated metabolism is a major contributor to vascular damage; abnormal levels of metabolites like high LDL cholesterol,[246] high hemoglobin A1c,[247] and low omega-3 fatty acids,[248] are well-established risk factors for CVD. Third, evidence supports a metabolic basis for dementia, with associations found between high LDL cholesterol,[17] diabetes,[17] metabolic syndrome,[249] and increased dementia risk.

Previous research on neuroticism's association with metabolites has focused only on high-density lipoprotein (HDL) cholesterol, triglycerides, fatty acids, and glucose, with inconsistent results.[250-258] The recent availability of reproducible high-throughput, large-scale metabolomics data now enables studies to explore neuroticism's association with a broader range of metabolites, including lipids, lipoproteins, fatty acids, amino acids, ketone bodies, and those involved in glycolysis and energy metabolism. Metabolomics also provides more granular measurements, such as specific subfractions (e.g., concentrations of triglycerides, phospholipids, and total cholesterol) and the sizes of lipoproteins. To date, no studies have systematically examined the association between neuroticism and the metabolome or investigated whether the identified metabolites are further linked to dementia risk.

Leveraging the large-scale metabolomics platform of the UK Biobank, the study in this chapter first conducted a hypothesis-free analysis to examine the relationship between neuroticism and 249 plasma metabolites. For the metabolites identified as related to neuroticism, this study further explored their associations with the incident risk of all-cause dementia and key dementia subtypes. Additionally, MR was applied to reduce confounding and enhance the robustness of the significant observational associations.

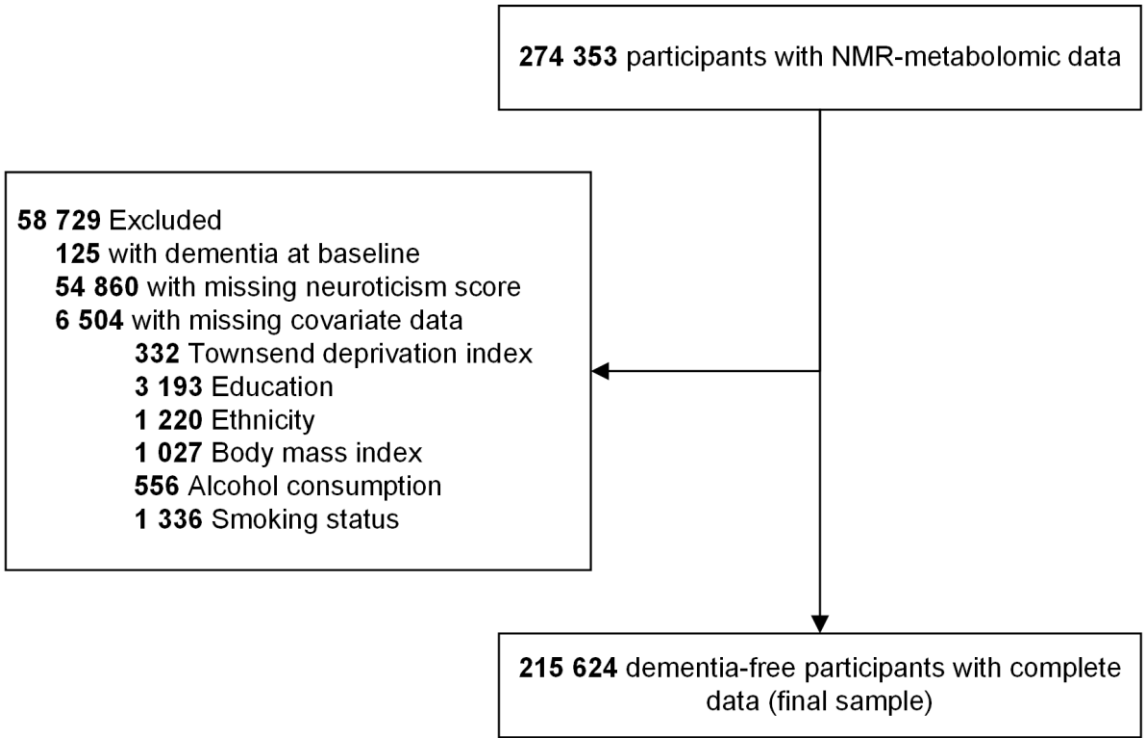
5.3 METHODS

Study population

The study in this chapter used data from the UK Biobank, with details previously described in Chapter 3 and elsewhere.[186] Blood samples were collected at recruitment from 2007 to 2010. Plasma metabolite profiling was conducted by Nightingale Health Plc using a high-throughput NMR spectroscopy platform. The July 2023 release of UK Biobank metabolomics data (the latest available at the time of analysis) covered ~275,000 participants' baseline plasma samples, consisting of ~118,000 samples measured between 2019 and 2020 and an additional ~157,000 samples measured between 2020 and 2022.[259]

For the study examining the association between neuroticism and metabolites, participants had a prior history of dementia, based on either hospital inpatient diagnoses or self-reported dementia or cognitive impairment at the verbal interview (n=125) were excluded, as were those with missing neuroticism scores (n=54,860) and covariates (n=6,504) (**Figure 5.1**). We did not exclude participants with prevalent mental or vascular conditions, as these conditions are part of the pathway linking neuroticism to dementia, as shown in previous chapters. Excluding such individuals would truncate key causal pathways, induce selection bias by restricting the sample to a healthier subset, and reduce the generalisability of the findings.

Figure 5.1: Flow diagram of analyses



NMR, nuclear magnetic resonance

Metabolomics

Handling and storage protocols for blood samples have been previously described.[260] Briefly, blood samples were collected using standardized vacutainer tubes containing various preservatives and anti-coagulants, then minimally processed at assessment centres before being transported under controlled temperatures to a central laboratory. There, samples were aliquoted and stored either at −80°C or in the vapour phase of liquid nitrogen to preserve long-term stability. Samples from each participant were split between two geographically separated archives to mitigate risks and prevent degradation from freeze–thaw cycles. Each processing step was highly automated and quality-controlled.

Metabolites were quantified from ethylenediaminetetraacetic acid plasma using six 500 MHz NMR spectrometers, with each sample generating two spectra to capture both macromolecules and low-molecular-weight metabolites. Sample preparation and measurement followed EN ISO 13485-certified protocols, with strict temperature control and automation to ensure consistency. Quality control included the use of internal standards, blind duplicates, and detailed monitoring of variation across instruments and batches.[261]

The NMR platform quantified 249 metabolites, consisting of 168 absolute and 81 ratio measurements. Most of the absolute measurements are concentrations, including those of lipoproteins—very-low-density (VLDL), low-density (LDL), intermediate-density (IDL), and high-density lipoproteins (HDL)—of various sizes, as well as their lipid components, such as triglycerides, total cholesterol, cholesteryl esters, free cholesterol, phospholipids, and total lipids. Concentrations of fatty acids, amino acids, ketones, and glycolysis metabolites

were also measured. Other absolute measurements included lipoprotein particle diameters and the degree of unsaturation (the total number of pi bonds and rings within a molecule). **Appendix 5.1** presents the complete list of 249 metabolites.

Measurements of metabolites outside four interquartile ranges from the median,[261] and those flagged as quality control concerns by Nightingale Health Plc were treated as missing data. Measurements were adjusted for the specific NMR spectrometer used by applying a linear regression model with log1p-transformed metabolite data as the outcome and the spectrometer as the predictor. The resulting residuals were then standardized.

Assessment of neuroticism

As detailed in Chapter 3, UK Biobank measured neuroticism using the EPQ-RS.[61] Total scores (range: 0–12) were standardized to z-scores with a mean of 0 and an SD of 1.

Incident dementia outcomes

Dementia diagnoses were identified through the UK Biobank's linkage with hospital inpatient records and the death registry, based on the ICD codes for all-cause dementia and its subtypes as defined by the UK Biobank Outcome Adjudication Group.[193] Details of these data sources and codes are provided in Chapter 3. Incident dementia was defined as the earliest recorded instance of a dementia ICD code from either source.

Covariates

To ensure comparability with the studies in Chapters 3 and 4, covariates in this study were selected to align with those used in Chapters 3 and 4. These include baseline measures of sex, age (continuous), assessment centre, ethnicity (White and non-White), quintiles of the TDI, education (primary, secondary, post-secondary non-tertiary, and tertiary), smoking status (never, previous, and current smoker), alcohol consumption (≤4 times/week, daily or almost daily), BMI (normal [<25 kg/m^2], overweight [≥25–<30 kg/m^2], and obese [≥30 kg/m^2]). Detailed definitions and the corresponding UK Biobank variables for these covariates are provided in Chapter 3. Additionally, this study adjusted for common medications that may influence metabolic processes,[262] including antihypertensives, antidiabetes, lipid-lowering drugs, gastrointestinal-related drugs, corticosteroids, and psychiatric medication. Current medication use was self-reported during the baseline verbal interview.

Genetic variants

Genetic association estimates were drawn from the largest publicly available GWAS of European ancestry available at the time of analysis (July 2023). The GWAS sources for neuroticism,[70] AD,[22] and WMH[212] were the same as those used in Chapter 3. As justified in Chapter 3, WMH volume was used as a proxy for VaD due to the lack of well-powered GWAS for VaD. For metabolites, summary statistics were obtained from a GWAS of 114,999 UK Biobank participants with metabolomics data.[263]

Genetic instruments were selected using standard criteria for genome-wide significance, allele frequency, linkage disequilibrium, and F-statistic, as detailed in Chapter 3.

Statistical analysis

Observational analyses

Associations between neuroticism z-scores and 249 log1p-transformed standardized metabolites were analysed using linear regression, adjusted for all covariates. Significance was determined by a Bonferroni-adjusted threshold of $p<0.05/249=2.0\times10^{-4}$ for each metabolite. This approach is conservative given the substantial correlation among metabolites. Metabolites significantly associated with neuroticism were further analysed for their relationship with incident all-cause dementia using Cox proportional hazards regression, with follow-up time as the timescale. For metabolites with consistent directional associations with both neuroticism and dementia, their links to dementia subtypes (AD and VaD) were further explored. Participants were followed from baseline until dementia diagnosis, death, or the censoring date of hospital records (31 October 2022 for England, 31 August 2022 for Scotland, and 31 May 2022 for Wales), whichever came first.

Assessing potential causal relationships with Mendelian randomisation

Two-sample MR analyses were performed to explore potential causal relationships between neuroticism and metabolites with consistent directional links to neuroticism and dementia, as well as between these metabolites and AD and WMH. Primary analyses used

the IVW method, with sensitivity analyses conducted to assess robustness and potential pleiotropy, including MR-Egger, weighted median, MRlap, the Steiger directionality test, and tests for Cochran's Q-statistic and Egger intercept. Associations that were significant in the IVW analysis and supported by sensitivity tests were further examined using leave-one-out analysis to assess whether the results were driven by any single variant. Further methodological details are provided in Chapter 3.

5.4 RESULTS

Sample characteristics

The final sample for metabolomics profiling of neuroticism included 215,624 participants (mean age [SD], 56.9 [8.1] years; 53.3% female). Participants with higher neuroticism scores were younger, more likely to be female, lived in deprived areas, had lower educational levels, and were more prone to obesity and smoking. They also tended to take more corticosteroids, gastrointestinal-related drugs, antihypertensives, and psychiatric medications (**Table 5.1**). Over a median follow-up of 13.7 years, 3,844 participants developed all-cause dementia, including 1,699 with AD and 863 with VaD.

Metabolome-wide association analysis of neuroticism with 249 metabolites

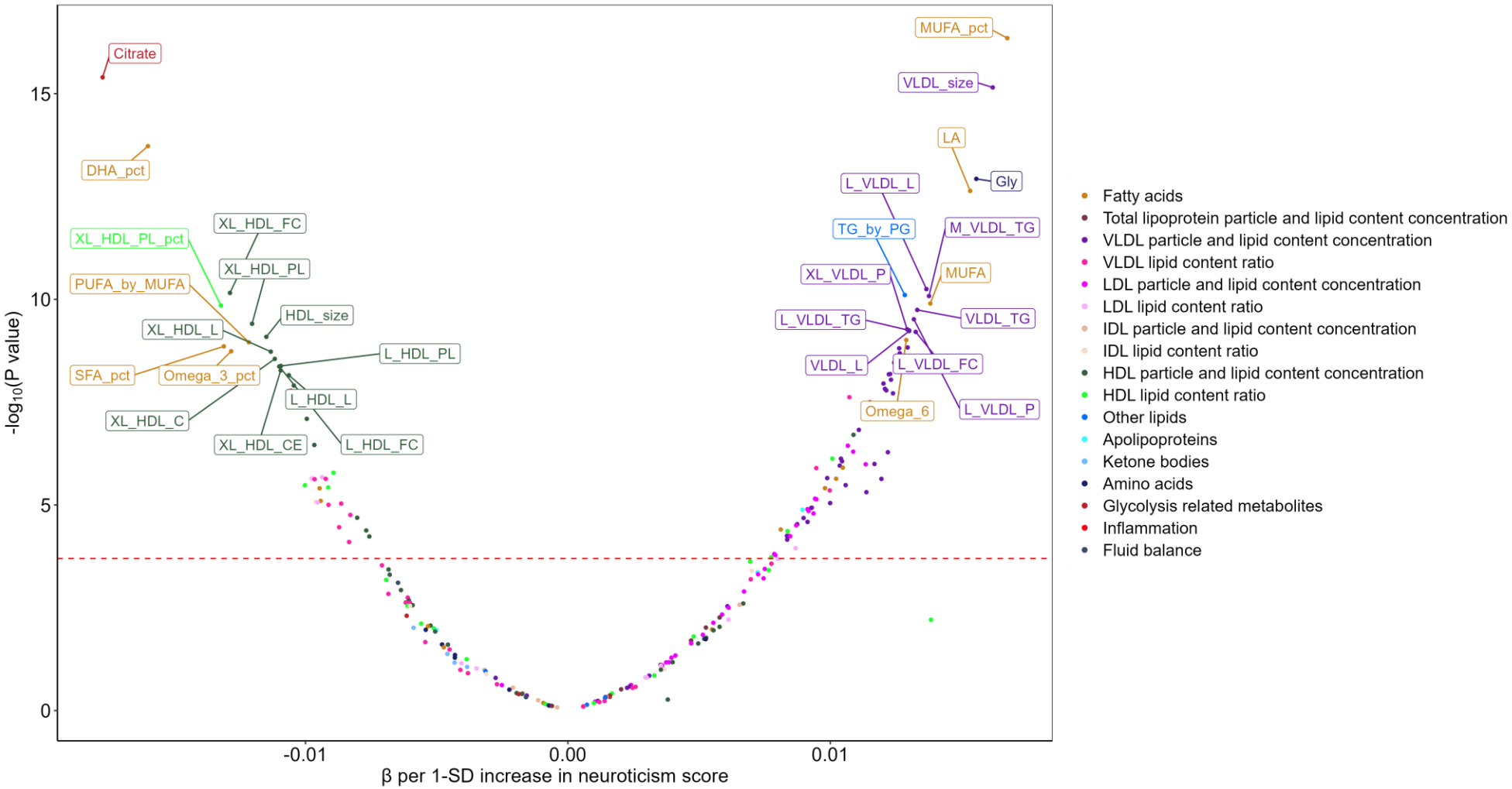
Neuroticism was associated with 119 of 249 metabolites at a Bonferroni-adjusted p-value<0.05. The most significant associations were observed for concentrations of fatty acids and lipoproteins and their lipid components. Neuroticism z-score was inversely associated with polyunsaturated to monounsaturated fatty acid (PUFA to MUFA) ratio, omega-3 fatty acids (especially DHA), and large-sized HDL and its lipid components (especially cholesterol, phospholipids, and total lipid). Conversely, neuroticism was positively associated with MUFA, omega-6 fatty acids, very-low-density lipoproteins (VLDL), and triglycerides (**Figure 5.2**, effect size for all metabolites in **Appendix 5.1**).

Table 5.1: Baseline characteristics of participants

Characteristic	Overall	Neuroticism score tertile		
		1 (score 0–2)	2 (score 3–5)	3 (score 6–12)
N	215624	82244	64348	69032
Age (mean (SD))	56.93 (8.06)	57.72 (7.97)	57.02 (8.05)	55.89 (8.05)
Female (%)	114875 (53.3)	36363 (44.2)	36237 (56.3)	42275 (61.2)
Townsend deprivation index quintile (%)				
1 (Least deprived)	45632 (21.2)	18471 (22.5)	13827 (21.5)	13334 (19.3)
2	44922 (20.8)	17911 (21.8)	13581 (21.1)	13430 (19.5)
3	43699 (20.3)	16955 (20.6)	13206 (20.5)	13538 (19.6)
4	42005 (19.5)	15609 (19.0)	12589 (19.6)	13807 (20.0)
5 (Most deprived)	39366 (18.3)	13298 (16.2)	11145 (17.3)	14923 (21.6)
Education (%)				
Primary	35376 (16.4)	11928 (14.5)	10419 (16.2)	13029 (18.9)
Secondary	48233 (22.4)	16942 (20.6)	14557 (22.6)	16734 (24.2)
Post-secondary non-tertiary	26651 (12.4)	10622 (12.9)	8202 (12.7)	7827 (11.3)
Tertiary	105364 (48.9)	42752 (52.0)	31170 (48.4)	31442 (45.5)
Ethnic group - White (%)	207203 (96.1)	78853 (95.9)	61965 (96.3)	66385 (96.2)
BMI (%)				
Normal (<25 kg/m^2)	70759 (32.8)	25779 (31.3)	21631 (33.6)	23349 (33.8)
Overweight (≥25–<30 kg/m^2)	92454 (42.9)	37000 (45.0)	27390 (42.6)	28064 (40.7)
Obese (≥30 kg/m^2)	52411 (24.3)	19465 (23.7)	15327 (23.8)	17619 (25.5)
Drinking daily or almost daily (%)	44766 (20.8)	17850 (21.7)	13401 (20.8)	13515 (19.6)
Smoking status (%)				
Never	117780 (54.6)	46774 (56.9)	35227 (54.7)	35779 (51.8)
Previous	75479 (35.0)	27987 (34.0)	22750 (35.4)	24742 (35.8)
Current	22365 (10.4)	7483 (9.1)	6371 (9.9)	8511 (12.3)
Medications (%)				
Corticosteroids	11334 (5.3)	3745 (4.6)	3309 (5.1)	4280 (6.2)
GI-related drugs	24965 (11.6)	7354 (8.9)	7355 (11.4)	10256 (14.9)
Lipid-lowering drugs	38860 (18.0)	15031 (18.3)	11254 (17.5)	12575 (18.2)
Antidiabetes	7781 (3.6)	3009 (3.7)	2158 (3.4)	2614 (3.8)
Antihypertensives	49086 (22.8)	18352 (22.3)	14420 (22.4)	16314 (23.6)
Psychiatric medication	17252 (8.0)	2169 (2.6)	3813 (5.9)	11270 (16.3)
Depression (%)	13163 (6.1)	1137 (1.4)	2504 (3.9)	9522 (13.8)
Ischaemic heart disease (%)	11476 (5.3)	4051 (4.9)	3354 (5.2)	4071 (5.9)
Hypertension (%)	58134 (27.0)	21120 (25.7)	17193 (26.7)	19821 (28.7)
Diabetes (%)	10809 (5.0)	4146 (5.0)	3033 (4.7)	3630 (5.3)

N, number of participants; SD, standard deviation; BMI, body mass index; GI, gastrointestinal.

Figure 5.2: Associations between neuroticism and 249 metabolites



The top 15 most significant metabolites with the strongest negative and positive associations with neuroticism were labelled. Models were adjusted for sex, age, assessment centre, ethnicity, Townsend deprivation index, education, smoking, alcohol consumption, body mass index, and medication use. Bonferroni p-value threshold is shown by the red dashed line. DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; SFA, saturated fatty acids; LA, linoleic acid; Gly, glycine; TG, triglycerides; PG, phosphoglycerides; Prefixes 'XL_', 'L_', 'M_' indicate particle sizes. Suffixes '_FC', '_PL', '_L', '_C', '_CE', '_TG' denote specific lipid types: free cholesterol, phospholipids, total lipids, cholesterol, cholesteryl esters, and triglycerides, respectively. Suffix '_pct' indicates lipid-to-total lipid ratio or fatty acid-to-total fatty acid ratio.

Associations of neuroticism-related metabolites with dementia and WMH

Of the 119 neuroticism-related metabolites, 74 were significantly linked to incident all-cause dementia (**Appendix 5.2**), with only five showing consistent directional associations with both neuroticism and all-cause dementia. Four of these reflected omega-3 fatty acid levels and were negatively associated with both neuroticism and dementia: DHA (HR for 1-SD increase 0.94, 95% CI 0.91 to 0.97), DHA% of total fatty acids (0.95, [0.92 to 0.98]), omega-3% of total fatty acids (0.91, [0.88 to 0.94]), and degree of unsaturation (0.95, [0.92 to 0.98]) (**Table 5.2**). Conversely, omega-6/omega-3 ratio, positively associated with neuroticism, was also linked to an increased risk of dementia (1.09, [1.05 to 1.13]). Among the remaining 69 metabolites with inconsistent directions, most were related to lipoproteins (HDL and VLDL) and their lipid components (**Appendix 5.3**). Neuroticism was negatively associated with large-sized HDL, which was positively linked to dementia risk; and positively associated with VLDL, triglyceride-to-cholesterol ratio in lipoproteins, and total triglycerides, which were inversely associated with dementia risk.

When looking at the association of metabolites with dementia subtypes, associations of omega-3% of total fatty acids and the omega-6/omega-3 ratio were stronger with VaD compared to AD (omega-3% of total fatty acids: 0.90 [0.84 to 0.97] vs 0.95 [0.90 to 1.00]; omega-6/omega-3 ratio: 1.08 [1.00 to 1.16] vs 1.06 [1.01 to 1.12]) (**Table 5.3**).

Table 5.2: Consistent directional associations of metabolites with neuroticism and incident all-cause dementia

Metabolites	Linear regression (neuroticism → metabolites)		Cox regression (metabolites → all-cause dementia)	
	β (95% CI)	p[a]	HR (95% CI)	p
DHA	−0.009 (−0.014 to −0.005)	0.002	0.94 (0.91 to 0.97)	4.0×10^{-4}
DHA% of total fatty acids	−0.016 (−0.020 to −0.012)	4.7×10^{-12}	0.95 (0.92 to 0.98)	0.004
Omega-3% of total fatty acids	−0.013 (−0.017 to −0.009)	4.6×10^{-7}	0.91 (0.88 to 0.94)	1.9×10^{-8}
Omega-6/omega-3 ratio	0.010 (0.006 to 0.015)	3.1×10^{-4}	1.09 (1.05 to 1.13)	8.8×10^{-7}
Degree of unsaturation	−0.009 (−0.013 to −0.005)	9.8×10^{-4}	0.95 (0.92 to 0.98)	0.001

HR, hazard ratio; CI, confidence interval; DHA, docosahexaenoic acid. Linear regression coefficients represent associations between neuroticism z-scores and metabolite levels, adjusted for sex, age, assessment centre, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, body mass index, and baseline medication use. Cox models estimate the hazard ratio for incident all-cause dementia per 1-SD increase in each metabolite, adjusted for the same covariates.
[a]Bonferroni-adjusted p values.

Table 5.3: Associations between omega-3 fatty acids and dementia subtypes

Metabolites	AD		VaD	
	HR (95% CI)	p	HR (95% CI)	p
DHA	0.98 (0.93 to 1.03)	0.497	0.97 (0.90 to 1.05)	0.455
DHA% of total fatty acids	0.98 (0.94 to 1.04)	0.546	0.94 (0.88 to 1.01)	0.114
Omega-3% of total fatty acids	0.95 (0.90 to 1.00)	0.037	0.90 (0.84 to 0.97)	0.008
Omega-6/omega-3 ratio	1.06 (1.01 to 1.12)	0.024	1.08 (1.00 to 1.16)	0.049
Degree of unsaturation	0.99 (0.94 to 1.04)	0.572	0.95 (0.88 to 1.01)	0.112

AD, Alzheimer's disease; VaD, vascular dementia; HR, hazard ratio; CI, confidence interval; DHA, docosahexaenoic acid. Cox models estimate the hazard ratio for incident Alzheimer's disease and vascular dementia per 1-SD increase in each metabolite, adjusted for sex, age, assessment centre, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, body mass index, and baseline medication use.

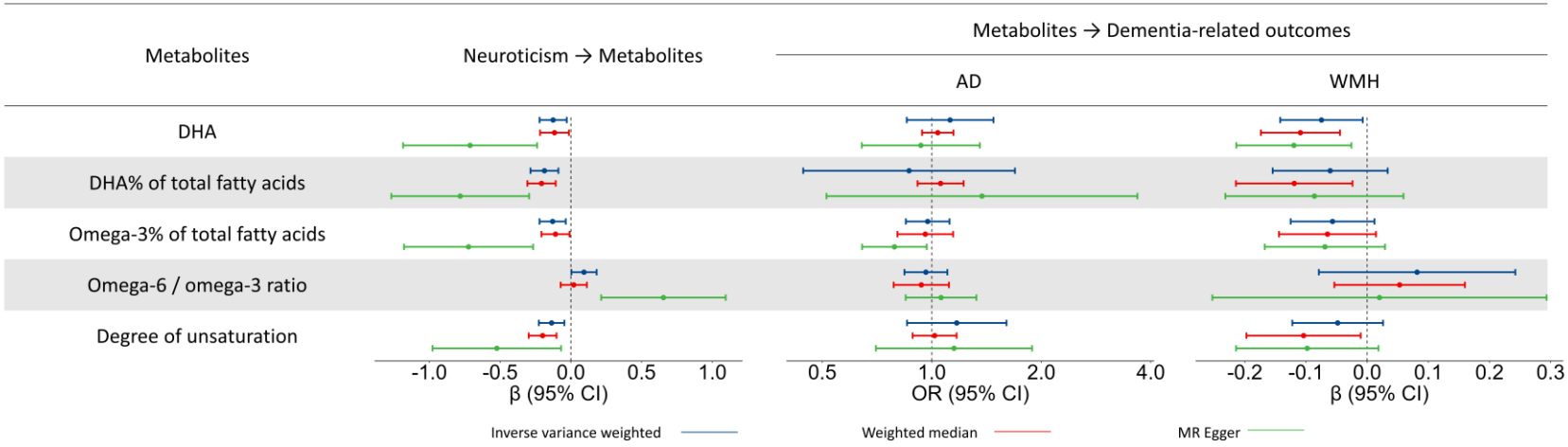
Mendelian randomisation

Genetic instruments for neuroticism, AD and WMH were the same as those used in Chapter 3, and each metabolite was instrumented using 28–45 independent SNPs (**Appendix 5.4**). Genetically predicted higher neuroticism was significantly associated with lower levels of DHA (IVW β=−0.125, p=0.011), DHA% of total fatty acids (β=−0.187, p<0.001), omega-3% of total fatty acids (β=−0.129, p=0.007), and degree of unsaturation (β=−0.136, p=0.003) (**Figure 5.3**; estimates are presented in **Appendix 5.5**). While there was evidence of heterogeneity (all p for Q<0.05) and pleiotropy (all p for Egger intercept<0.05 except for degree of unsaturation) (**Appendix 5.6**), the associations remained consistent across sensitivity analyses that accounted for pleiotropy and sample overlap. Genetically predicted neuroticism was also positively associated with omega-6/omega-3 fatty acids ratio (β=0.093, p=0.042), with the association remaining significant in the MR-Egger (β=0.654, p=0.005). Steiger test indicated stronger instrument-exposure than instrument-outcome correlations in all cases (all p<0.001). Leave-one-out analyses indicated that these associations were not driven by any single SNP (**Appendix 5.7**).

There was no evidence that genetically predicted lower omega-3 fatty acid levels increased risk of AD. Genetically predicted higher DHA levels were associated with lower WMH burden (β=–0.075, p=0.030). Leave-one-out analyses showed that this association was largely driven by rs174547; removing this variant attenuated the association to null (**Appendix 5.7**). Other metabolites showed consistent directional associations with WMH volume and neuroticism, although these associations were not statistically significant.

Bonferroni adjustment was not applied to these five preselected metabolites in the MR analyses; therefore, the reported associations should be interpreted as nominal.

Figure 5.3: Mendelian randomisation analyses of neuroticism, omega-3 fatty acids, and dementia outcomes



OR, odds ratio; CI, confidence interval; DHA, docosahexaenoic acid; WMH, white matter hyperintensities; AD, Alzheimer's disease; VaD, vascular dementia.

5.5 DISCUSSION

In this large-scale metabolomics study of 215,624 individuals, omega-3 fatty acids, including DHA and the degree of unsaturation were inversely associated with both neuroticism and dementia risk, while the omega-6/omega-3 ratio was positively associated with both. Omega-3 fatty acids were more strongly associated with VaD than with AD. MR analyses supported a link between genetically predicted neuroticism and both omega-3 fatty acids and the omega-6/omega-3 ratio, as well as between genetically predicted DHA and WMH. These findings suggest that omega-3 fatty acids and their balance with omega-6 fatty acids may play a crucial role in linking neuroticism to dementia, potentially through vascular pathways.

The association between neuroticism and fatty acids has previously been examined in only two small studies of middle-aged populations (N=116, mean age 45[257]; N=2,912, mean age 41.9[258]). Both studies found neuroticism to be negatively associated with DHA, while one also reported a positive association with arachidonic acid (AA), a key omega-6 fatty acid, and the AA/DHA ratio.[257] Importantly, that study used gas chromatography/mass spectrometry (GC/MS),[257] the gold standard for metabolite quantification,[264] which strengthens the validity of the NMR-based findings. The current study extended these associations to an older and larger population and also reported a negative association between neuroticism and the degree of unsaturation, which is higher in omega-3 fatty acids than in omega-6. The relationship between circulating omega-3 fatty acids and reduced dementia risk has been previously observed in small cohort studies using GC/MS,[265,266]

including one with over 17 years of follow-up.[265] Additionally, a positive association between the omega-6/omega-3 ratio and increased dementia risk was identified, reinforcing findings from a previous small study (N=1,214; 4 years follow-up) that linked the GC/MS-measured omega-6/omega-3 ratio to increased dementia risk.[267]

Omega-3 fatty acids and its balance with omega-6 fatty acids may primarily act through vascular rather than neurodegenerative pathways in linking neuroticism to dementia. Stronger associations between omega-3 fatty acids and the omega-6/omega-3 ratio with VaD compared to AD were observed, further supported by MR results showing a link between omega-3 fatty acids and reduced WMH volume, but not with AD. This aligns with findings in previous chapters that neuroticism is consistently associated with VaD and that its link with dementia is partially mediated by vascular conditions. Furthermore, omega-3 fatty acids have consistently been associated with markers of improved cerebrovascular health, including blood-brain barrier integrity,[268,269] enhanced cerebral perfusion,[270] and lower WMH volume;[271] However, studies have generally not found associations with key AD pathology markers, such as Aβ and tau accumulation[272] and hippocampal atrophy.[271] This is biologically plausible, as Omega-3 fatty acids exhibit vasodilatory, anti-aggregatory, and anti-inflammatory effects, all closely linked to circulatory benefits. Their balance with omega-6 fatty acids is also important because omega-6 and omega-3 fatty acids compete for the same enzymes involved in their elongation and desaturation. In contrast to omega-3, omega-6 fatty acid derivatives promote vasoconstriction, platelet activation, and inflammatory cytokine production, potentially harming circulatory function. Therefore, the

circulatory benefits of omega-3 fatty acids may be diminished by high levels of omega-6 fatty acids.[273]

A deeper inspection using leave-one-out analyses showed that the DHA-WMH association was largely driven by a single influential variant, rs174547, located in the *FADS1* gene. This variant is in strong linkage disequilibrium with rs174528 (D'=1, R^2=0.84 in Europeans from the 1000 Genomes Project),[274] which has previously been identified as an influential SNP linking genetically predicted linoleic acid (an omega-6 fatty acid) to higher WMH, and DHA% and omega-3% to lower WMH.[49] Prior work also showed that linoleic acid and WMH colocalise, and that genetically predicted linoleic acid partially mediates the association between blood *FADS1* expression and WMH.[49] The *FADS* gene cluster plays a central role in the desaturation of PUFAs, including the conversion of alpha-linolenic acid to DHA.[275] *FADS1* is expressed widely across human tissues, including the brain.[276] Other studies have reported colocalisation between DHA and psychiatric traits at the *FADS* locus,[277,278] and variants in this region have been associated with multiple brain imaging phenotypes.[279,280] Taken together, these findings suggest that associations between omega-3 fatty acids and WMH may reflect both peripheral and brain-specific pathways.

The identification of omega-3 and omega-6 fatty acids as critical factors suggests that the neuroticism-dementia association may be driven by poor dietary behaviours. Humans have limited capacity to synthesize these fatty acids endogenously, so their levels depend on dietary intake.[273] Thus, the underlying dietary issue may involve both low omega-3 intake and an imbalance between omega-6 and omega-3 consumption, where even high omega-3

intake may be counteracted by excessive omega-6 intake.[281] Omega-3 is largely sourced from oily fish, while omega-6 is abundant in vegetable oils.[273] Previous research indicates that higher neuroticism is linked to unhealthy dietary patterns,[100] including reduced fish consumption.[101,102] A meta-analysis of 48 prospective studies highlighted that dietary intake or nutritional supplementation of omega-3, particularly DHA, is associated with improved cognition and decreased dementia risk.[282] A higher omega-6/omega-3 ratio, as estimated through dietary questionnaires, has been associated with an increased risk of cognitive decline.[283]

Metabolites showing opposite associations with neuroticism and dementia mainly include: (1) large and very large HDL and their lipid components, (2) VLDL and its lipid components, and (3) the proportion of triglycerides in lipoproteins. Neuroticism was negatively associated with large-sized HDL, yet both this study and previous research have linked larger HDL to an increased risk of dementia.[284] One possible explanation is that larger HDL particles may be less efficient at delivering apoA-I,[285,286] which inhibits Aβ aggregation,[287] to the brain; whereas small HDL is the only lipoprotein capable of crossing the blood-brain barrier and may exert direct protective effects on cerebrovascular health.[288] Although this study did not focus on small HDL due to its insignificant association with neuroticism, other studies have linked it to lower dementia risk.[289,290] In contrast, neuroticism was positively associated with VLDL and triglycerides, which were inversely related to dementia risk,[249,284] possibly due to: (1) reverse causation, where metabolic and dietary disturbances in the prodromal phase of dementia lead to lower serum lipid levels, particularly triglycerides, and BMI;[291,292] or (2) individuals with elevated VLDL and triglycerides, which

are linked to higher CVD risk,[293,294] may not survive long enough to develop dementia, as they experience earlier mortality from CVD-related conditions.

Strengths and limitations

The main strengths of this study include its large sample size and the availability of 249 metabolites, enabling a comprehensive investigation of underlying metabolic pathways. The use of both observational and MR analyses strengthened the findings, while the inclusion of dementia subtypes and intermediate traits such as WMH—a marker of cerebrovascular damage—offered valuable insights into potential differences in pathogenesis.

This study has several limitations. The Nightingale metabolomics platform assesses a limited range of metabolites and is primarily focused on lipoproteins. A GC/MS-based platform like Metabolon would offer broader insights.[295] Medication use lies downstream of underlying mental and vascular conditions, which previous chapters have shown to be part of the biological pathways linking neuroticism to dementia. Adjusting for medication may therefore attenuate the associations of interest, both between neuroticism and metabolites and between those metabolites and dementia outcomes. Residual confounding may also remain despite adjustment. Given the observational nature of these analyses, consistent directional patterns should not be taken as evidence of causality.

In the MR analyses of neuroticism and metabolites, Cochran's Q identified heterogeneity in the SNP-specific estimates, suggesting differences in instrument strength or horizontal pleiotropy. The MR-Egger intercept was also significantly different from zero,

suggesting the presence of directional pleiotropy. However, the pleiotropy-robust estimators—including the MR-Egger slope and weighted median—produced effect estimates consistent with the primary IVW results, and associations remained significant after accounting for sample overlap.

The *APOE* locus, which strongly influences lipid metabolism and is the major genetic risk factor for AD, could in principle introduce horizontal pleiotropy by directly altering metabolite levels independent of neuroticism or by affecting AD risk irrespective of circulating metabolites. Nevertheless, Chapter 3 and 4 showed comparable neuroticism levels across *APOE* genotypes, and the metabolite-AD MR analyses were null, leaving limited scope for bias from *APOE*-driven type I error.

The genetic instruments for omega-3 fatty acids include variants at the *FADS* locus, such as rs174547, which strongly influence fatty acid metabolism and also drive the observed associations with WMH. Although biologically plausible as instruments, these variants may introduce pleiotropy. Future work using colocalisation and expression quantitative trait loci (eQTL) analyses is needed to clarify whether omega-3 fatty acid metabolism forms the pathway linking *FADS*-related genetic variation to WMH.

While mediation could, in principle, be assessed using two-step MR,[296] which involves estimating the association between genetically predicted neuroticism and metabolites and then using separate, independent genetic instruments for metabolites to estimate their association with WMH in a multivariable MR framework, this approach was

not undertaken. The genetic instruments explain only a small proportion of neuroticism variance, and in multivariable MR they must additionally predict neuroticism conditional on metabolite levels, resulting in small conditional F-statistics and a high risk of weak-instrument bias.[297] Two-step MR also requires no interaction between neuroticism and metabolites and a linear relationship between them,[297] which are unlikely to be fully satisfied.

Overall, the MR findings should be interpreted as supportive but not conclusive evidence of causality.

Conclusion

In summary, this study identified metabolites associated with neuroticism, highlighting the role of omega-3 fatty acid levels, particularly DHA, and the omega-6/omega-3 ratio in the association between neuroticism and dementia. Strong associations with VaD and WMH suggest these metabolites may contribute to vascular pathology. For individuals with high neuroticism, maintaining a healthy fatty acid profile through dietary interventions or supplements could, if causal relationships are confirmed, potentially reduce the dementia risk.

Chapter 6 Association between neuroticism and brain-wide structural outcomes: mediation by vascular and mental conditions

6.1 CHAPTER SUMMARY

Neuroticism has been linked to dementia and poorer cognition, but its relationship with brain structure is unclear. This study examined brain-wide associations between neuroticism and 1,747 structural brain outcomes derived from T1-, T2-weighted, and diffusion MRI (dMRI) in 36,901 UK Biobank participants. Associations were tested using multiple linear regression adjusted for sociodemographic, lifestyle, and imaging confounders. Bonferroni-significant findings were followed by mediation analyses of pathways identified in Chapters 3 and 4 for neuroticism and dementia, and bidirectional MR to assess directionality.

Higher neuroticism was found to be associated with reduced grey matter volumes in the frontal and limbic regions, as well as widespread differences in white matter microstructure, particularly in thalamic radiations. Hypertension mediated the associations between neuroticism and both grey and white matter measures, while depression and anxiety primarily mediated associations with white matter microstructure. Contributions from IHD and diabetes were minimal. MR analyses supported a potential link between genetically predicted neuroticism and increased diffusivity in the thalamic radiations.

In conclusion, neuroticism is linked to differences relevant to cognitive impairment and dementia, partly mediated by vascular and mental conditions.

6.2 BACKGROUND

Previous studies, including those presented in this thesis (Chapters 3 and 4), have demonstrated significant associations of higher levels of neuroticism with poorer cognitive function and an increased risk of dementia.[103,116,298] However, the neural pathways underlying this link remain unclear. Previous studies have identified associations of neuroticism with reduced global grey matter volume and increased WMH,[115,170] suggesting broad neurodegenerative and cerebrovascular burden. These findings are consistent with Chapters 3 and 4, which showed neuroticism linked to higher risk of both AD and VaD. To further clarify these pathways, it is essential to examine neuroticism in relation to specific brain structures, such as regional grey matter volumes and the microstructure of individual white matter tracts. Identifying such early, subtle structural differences, particularly before clinical cognitive decline, may inform targeted strategies for early dementia prevention.

Evidence linking neuroticism to specific brain structures remains limited. Prior research has largely focused on grey matter volume. A recent meta-analysis of 17 whole-brain studies (mean age 34 years; most with sample sizes under 100) found no significant associations between neuroticism and regional cortical or subcortical volumes,[115] despite some individual studies reporting smaller frontal lobe volumes.[158,161,299-301] Even less evidence exists for white matter microstructure, which can be assessed using dMRI and serves as an early and sensitive indicator of vascular-related brain changes.[210,302] dMRI studies in adolescent cohorts reported null associations,[303,304] but three adult studies (N=51, mean age 30 years;[171] N=668, mean age 73 years;[172] and N=265, mean age 50 years[160])

consistently found neuroticism-related reductions in FA and increases in mean diffusivity (MD) across multiple white matter tracts.

These initial findings have several key limitations. First, most studies have been underpowered, with sample sizes below 100. A minimum sample size of 1,000 has been recommended to reliably detect associations between brain structure and psychological traits, including personality.[180,305] Second, most samples were composed of younger adults, making examination of age- or dementia-related structural differences impossible. Third, previous research has neglected other neuroimaging modalities. For example, neurite orientation dispersion and density imaging (NODDI) offers greater specificity for features such as axonal density and fibre orientation and thus biological insights,[306] yet its association with neuroticism remains unexamined. Additionally, neuroticism has rarely been explored in relation to other emerging preclinical markers of dementia, such as ventricular enlargement[307] and reduced cerebellar volume.[308]

A crucial unanswered question is whether neuroticism leads to structural brain changes, or conversely, whether brain structure influences neuroticism tendencies. Cross-sectional observational studies conducted to date have been unable to distinguish between these two possibilities. However, as introduced in the previous chapters, MR analysis offers a powerful method to establish the directionality of the relationship between neuroticism and brain structure. Previous chapters also suggest that the link between neuroticism and dementia risk is likely driven by mental and vascular conditions. However, their role in neuroticism–brain structure associations remain unexplored.

To address these gaps, this study performed the largest brain-wide analysis of neuroticism, integrating multiple neuroimaging modalities, in a large sample of dementia-free older adults. This study examined a comprehensive range of imaging metrics, including global measures, regional cortical and subcortical volumes, surface area, thickness, signal intensity, white matter microstructure (traditional and NODDI-derived), and ventricular and brainstem volumes. This study further assessed whether associations were mediated by modifiable health conditions linked to neuroticism or dementia (depression, anxiety and stress-related disorders, IHD, hypertension, and diabetes). Additionally, this study applied the bidirectional two-sample MR to evaluate potential causal relationships between neuroticism and brain structure.

6.3 METHODS

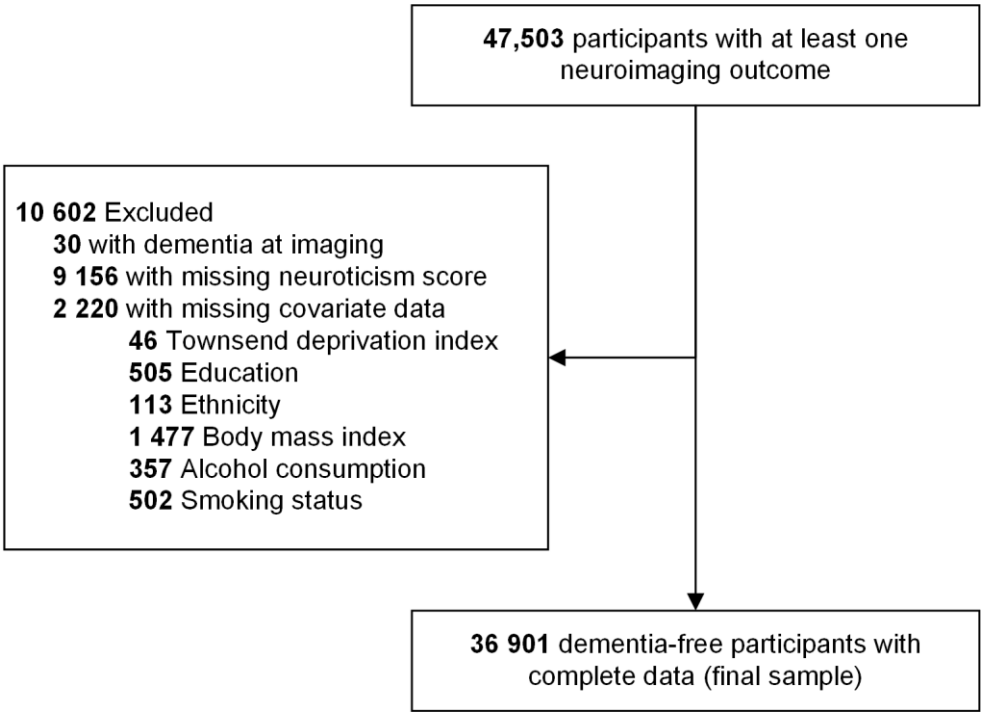
Study population

This study used data from the UK Biobank, with details previously described in Chapter 3 and elsewhere.[186] As mentioned in Chapter 3, UK Biobank launched its imaging study in 2014, inviting participants to undergo multimodal brain MRI.[187] The scans were performed at three centres (Newcastle upon Tyne, Stockport, and Reading) using 3 Tesla Siemens Skyra scanners (Siemens Healthineers) equipped with VD13 software and 32-channel head coils, following standardized operating procedures.[309]

During the imaging visit, participants also provided comprehensive demographic, socioeconomic, lifestyle, and health-related information through self-administered touchscreen questionnaires and verbal interviews conducted by trained nurses.

This study included participants with valid measurements for at least one neuroimaging outcome of interest as of June 30, 2024 (n=47,503). Participants were excluded if they self-reported a diagnosis of dementia/cognitive impairment or had a dementia diagnosis in inpatient records (n=30), or had missing data for neuroticism (n=9,156). Due to the low proportion of missing covariate data (2.9% for BMI and <1% for other covariates), this study also excluded participants with missing covariate data (n=2,220) (**Figure 6.1**).

Figure 6.1: Flow diagram of analyses



Assessment of neuroticism

This study used the neuroticism scores obtained during the UK Biobank imaging visit, using the same EPQ-RS instrument as at baseline.[61] Further details were provided in Chapter 3. Neuroticism scores were standardized to a mean of 0 and an SD of 1.

IDP selection

Brain structure measurements were obtained from three imaging modalities: T1-weighted MRI, T2-weighted fluid-attenuated inversion recovery (FLAIR), and dMRI. The

imaging data from these modalities were processed, quality-controlled, and released as imaging-derived phenotypes (IDPs) by the UK Biobank team.[309]

T1-weighted imaging allows precise volumetric measurements of cortical and subcortical regions. Using T1-weighted data, FMRIB's Automated Segmentation Tool (FAST)[310] segmented brain tissue into CSF, grey matter, and white matter. 139 cortical ROIs were defined using the MNI152 template, combining parcellations from Harvard-Oxford cortical and subcortical atlases and the Diedrichsen cerebellar atlas. Grey matter volumes in these ROIs were summed to create 139 IDPs representing cortical grey matter volume. 15 subcortical structures' shapes and volumes were modelled using FMRIB's Integrated Registration and Segmentation Tool (FIRST).[311] The T1 images were also processed with FreeSurfer based on different brain atlases (e.g., a2009s, BA exvivo, desikan white, and DKT).

T2-FLAIR identified WMH. dMRI reflects white matter microstructure by measuring how water molecules move within tissue. Water molecules show greater directional coherence and reduced diffusion when fibres are densely packed, with undamaged myelin and cell membranes. dMRI generates three diffusivity parameters ($\lambda1$, $\lambda2$, and $\lambda3$). Axial diffusivity ($\lambda ax=\lambda1$) reflects diffusion along the axonal fibres. In contrast, radial diffusivity ($\lambda rad=(\lambda2+\lambda3)/2$) represents the average diffusion perpendicular to the fibres. FA measures the directional coherence of water diffusion along axonal fibres, while MD provides an average of all diffusion directions. dMRI data was also fed into NODDI modelling,[312] which provides estimates of neurite density (intracellular volume fraction, ICVF), extracellular

water diffusion (isotropic volume fraction, ISOVF), and tract complexity/fanning (orientation dispersion, OD).

This study focused on structural IDPs, including measures of global and regional cortical volumes, surface area, thickness, and intensity; CSF volumes; subcortical structure volumes and intensity; white matter hypo- and hyperintensities; and white matter microstructure. Among the available IDPs, those that had been pre-adjusted for head size by the UK Biobank were excluded, as this study applied its own adjustments for imaging confounds. Additionally, new IDPs for radial diffusivity in white matter tracts were generated by averaging the diffusivity parameters (λ2 and λ3), with the original λ2 and λ3 IDPs removed. Ultimately, 1,747 IDPs were included for analysis. The complete list of IDPs is included in **Appendix 6.1**.

To enhance the robustness of association estimates, a rank-based inverse Gaussian transformation (quantile normalization) was applied to all IDPs.[309] A total of seven image-related confounds were adjusted in the analysis, including head size (based on the volumetric scaling from the T1 head image to standard atlas), head motion (mean absolute head motion from dMRI calculated by Eddy), head position (X, Y, Z brain centre of gravity, and table position), and imaging centre.[313] These image-related confounds were included as predictors in a linear regression model with IDPs as the dependent variables. The residuals from these models were then standardized for use in further analyses.

Covariates and mediators

Models were adjusted for the same covariates as in Chapters 3–5 to ensure comparability across analyses, including sex, age (continuous), polynomial terms for age (age^2 and age^3) to account for nonlinear age effects across outcomes,[313] age×sex to capture sex-specific patterns,[313] self-reported ethnicity (White and non-White; using the first non-missing value across all assessments), quintiles of the TDI (computed from national census data preceding baseline and assigned based on the participant's postcode), education (primary, secondary, post-secondary non-tertiary, and tertiary), smoking status (never, previous, current), drinking (≤ 4 times per week, daily or almost daily), and BMI (normal [<25 kg/m^2], overweight [≥25–<30 kg/m^2], and obese [≥30 kg/m^2]). All covariates, except ethnicity and TDI, were measured at the imaging visit. Detailed definitions and the corresponding UK Biobank variables for these covariates are provided in Chapter 3.

The rationale for selecting mediators in this study has been detailed in Chapter 3. Briefly, to ensure the correct temporal sequence with neuroticism preceding the mediators, mental health conditions (depression, anxiety and stress-related disorders) and vascular conditions (IHD and hypertension) were selected, given evidence that neuroticism increases the risk of these conditions without strong evidence for reverse causation.[70,85,91] Additionally, diabetes was included as a negative control mediator due to its established association with poor brain health but limited evidence of an association with neuroticism.[91,204] These conditions were ascertained through verbal interview and linked hospital inpatient records preceding the imaging visit, with diagnostic codes detailed in Chapter 3.

Genetic variants

Genetic associations with neuroticism and IDPs were obtained from the largest publicly available GWAS of European ancestry available at the time of analysis (December 2024). The GWAS for neuroticism included 240,000 individuals of European ancestry from the Million Veteran Program cohort, with summary statistics meta-analysed with data from the UK Biobank and Genetics of Personality Consortium, resulting in a total sample size of 623,482.[71] The GWAS for IDPs was based on 39,691 UK Biobank participants.[212] For fibre radial diffusivity IDPs, instrumental variables were selected from the GWAS of the corresponding fibre's λ2 IDPs. Genetic instruments for neuroticism and IDPs were selected and harmonized using standard criteria, as detailed in Chapters 3.

Statistical analysis

Observational analyses

Linear regression was used to examine the association between the neuroticism z-score and each of the 1,747 IDPs, adjusting for all preselected covariates. To account for multiple testing, Bonferroni corrections were applied, and IDPs meeting the adjusted significance threshold ($p<2.86\times10^{-5}$) were considered for further analyses.

Causal mediation analyses[314] were performed to evaluate whether the observed associations were mediated by preselected health conditions. This approach decomposed the total effect of neuroticism on IDPs into two components: (1) the average causal mediation effect (ACME), which quantifies how much the IDP changes due to the health condition,

while keeping neuroticism constant. Formally, ACME=E[$Y_{a,M(a)} - Y_{a,M(a^*)}$]), where $a \neq a^*$, and $Y_{a,m}$ represents the expected outcome if a participant had a neuroticism level a and a disease history status m (existence or absence of the disease). (2) the average direct effect (ADE), which measures how much the IDP changes directly due to neuroticism, holding the health condition status constant. expressed as ADE=E[$Y_{a,M(a^*)} - Y_{a^*,M(a^*)}$]).

These estimates were derived from a logistic regression model, where each health condition was regressed on neuroticism and preselected covariates, and a linear regression model, where each IDP was regressed on neuroticism, the health condition, and the same covariates. 95% CIs for the ACME were derived using a quasi-Bayesian Monte Carlo approach with 1000 simulations. To account for multiple testing, Bonferroni adjustment was applied to the significance level of the ACME. For ACME that were statistically significant after Bonferroni correction, the proportion mediated was calculated as the ratio of the ACME to the total effect.

Mendelian randomisation

Two-sample MR was conducted to investigate bidirectional causal relationships between neuroticism and IDPs that showed significant observational associations with neuroticism. The primary MR analysis used the IVW method. Sensitivity analyses for significant IVW associations (uncorrected $p<0.05$) followed the same procedures as in Chapters 3 and 5, including MR-Egger, weighted median, MRlap, Steiger directionality test, Cochran's Q-statistic for heterogeneity, and Egger intercept for pleiotropy. All statistical

analyses were conducted in the R software (version 4.2.2) using the TwoSampleMR,[221,222] MRlap,[220] and mediation[315] packages.

6.4 RESULTS

Sample characteristics

The mean age of the 36,901 participants was 64.4 years (SD=7.7), and 51.4% were female (**Table 6.1**). Those with higher levels of neuroticism tended to be younger, female, have lower socioeconomic status, consume less alcohol, and be current smokers. Additionally, histories of depression, anxiety, and hypertension were more common among participants with higher neuroticism, while histories of IHD and diabetes were similar across different levels of neuroticism.

Observational associations with brain structure

Associations between neuroticism scores and brain structure were examined in a brain-wide study across multiple neuroimaging modalities. Among 1,747 IDPs, 40 showed significant associations with neuroticism after Bonferroni correction ($p<2.86\times10^{-5}$) (**Figure 6.2**, **Appendix 6.1**), with the strongest associations observed for regional cortical volume and surface area, subcortical volumes, and white matter macro- and microstructure.

Table 6.1: Characteristics of participants

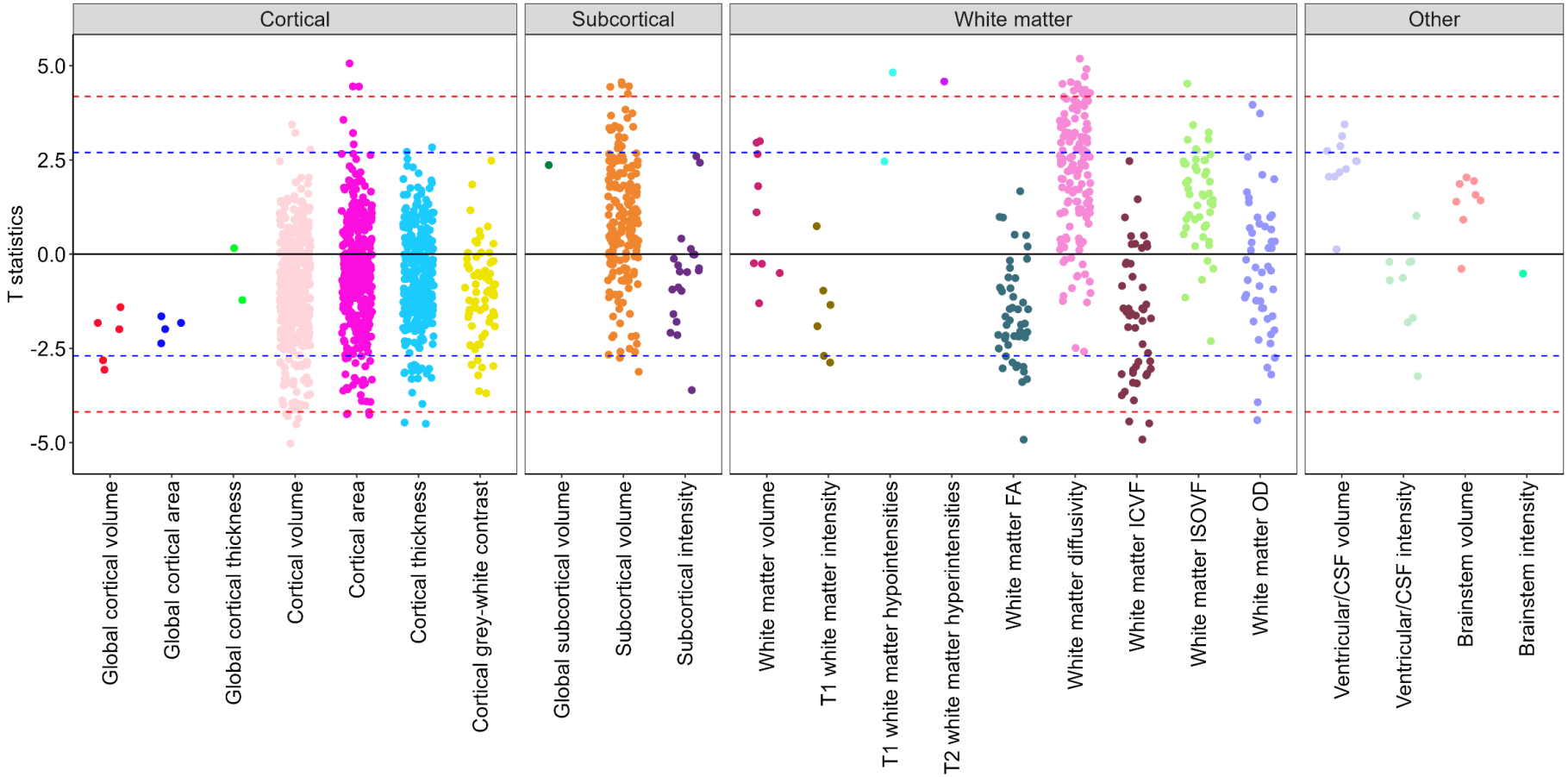
Characteristics [a]	Overall	Neuroticism score tertile		
		1 (score 0–1)	2 (score 2–4)	3 (score 5–12)
n	36901	13341	11829	11731
Age (mean (SD))	64.44 (7.71)	65.47 (7.58)	64.67 (7.64)	63.03 (7.72)
Sex (%)				
Female	18971 (51.4)	5546 (41.6)	6366 (53.8)	7059 (60.2)
Male	17930 (48.6)	7795 (58.4)	5463 (46.2)	4672 (39.8)
Townsend deprivation index quintile (%)				
1 (Least deprived)	8915 (24.2)	3319 (24.9)	2933 (24.8)	2663 (22.7)
2	8491 (23.0)	3096 (23.2)	2779 (23.5)	2616 (22.3)
3	7680 (20.8)	2805 (21.0)	2422 (20.5)	2453 (20.9)
4	6879 (18.6)	2409 (18.1)	2163 (18.3)	2307 (19.7)
5 (Most deprived)	4936 (13.4)	1712 (12.8)	1532 (13.0)	1692 (14.4)
Education (%)				
Primary	2195 (5.9)	769 (5.8)	673 (5.7)	753 (6.4)
Secondary	7001 (19.0)	2239 (16.8)	2194 (18.5)	2568 (21.9)
Post-secondary non-tertiary	4121 (11.2)	1481 (11.1)	1403 (11.9)	1237 (10.5)
Tertiary	23584 (63.9)	8852 (66.4)	7559 (63.9)	7173 (61.1)
Ethnicity (%)				
Non-White	1025 (2.8)	427 (3.2)	306 (2.6)	292 (2.5)
White	35876 (97.2)	12914 (96.8)	11523 (97.4)	11439 (97.5)
Body mass index category (%)				
Normal (<25 kg/m^2)	14839 (40.2)	5172 (38.8)	4940 (41.8)	4727 (40.3)
Overweight (≥25–<30 kg/m^2)	15255 (41.3)	5789 (43.4)	4810 (40.7)	4656 (39.7)
Obese (≥30 kg/m^2)	6807 (18.4)	2380 (17.8)	2079 (17.6)	2348 (20.0)
Alcohol intake (%)				
Less than 4 times per week	30588 (82.9)	10970 (82.2)	9830 (83.1)	9788 (83.4)
Drinking alcohol daily or almost daily	6313 (17.1)	2371 (17.8)	1999 (16.9)	1943 (16.6)
Smoking (%)				
Never	23221 (62.9)	8586 (64.4)	7494 (63.4)	7141 (60.9)
Previous	12436 (33.7)	4343 (32.6)	3944 (33.3)	4149 (35.4)
Current	1244 (3.4)	412 (3.1)	391 (3.3)	441 (3.8)
Disease history (%)[b]				
Depression	3611 (9.8)	441 (3.3)	857 (7.2)	2313 (19.7)
Anxiety and stress disorders	1761 (4.8)	206 (1.5)	403 (3.4)	1152 (9.8)
Ischaemic heart disease	2150 (5.8)	790 (5.9)	701 (5.9)	659 (5.6)
Hypertension	10719 (29.0)	3746 (28.1)	3454 (29.2)	3519 (30.0)
Diabetes	1882 (5.1)	715 (5.4)	549 (4.6)	618 (5.3)

N, number of participants; SD, standard deviation

[a] Townsend deprivation index and ethnicity were measured at baseline, other characteristics were measured at the imaging visit.

[b] These conditions were ascertained through verbal interview and linked hospital inpatient records preceding the imaging visit, with diagnostic codes detailed in Chapter 3.

Figure 6.2: Brain-wide associations between neuroticism and imaging-derived phenotypes by structural group



T statistics for the linear regression between neuroticism and brain-wide IDPs. Red dashed line indicates the Bonferroni threshold (1747 tests, $p=2.86\times10^{-5}$, T statistics=±4.18) and blue dashed line indicated the False Discovery rate threshold (1747 tests, p=0.007, T statistics=±2.70). Each point represents the estimated t-statistic from a linear regression model examining the association between neuroticism (z-score) and each of the 1,747 IDPs. Models were adjusted for all preselected covariates (sex, age, age², age³, age×sex, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, and body mass index). The solid horizontal line denotes t=0 (no association). See **Appendix 6.1** for regression coefficients and 95% confidence intervals. FA, fractional anisotropy; ICVF, intracellular volume fraction; ISOVF, isotropic volume fraction; OD, orientation dispersion; CSF, cerebrospinal fluid.

For cortical volume, higher neuroticism was most strongly associated with reduced volume in the frontal lobe (left frontal medial cortex, left subcallosal cortex, and left medial orbitofrontal cortex) and the bilateral anterior cingulate cortex in the limbic lobe (**Table 6.2**). Neuroticism was also associated with increased surface area in the left parahippocampal gyrus (temporal lobe), and reduced area in the left pericalcarine cortex and calcarine sulcus (occipital lobe). Conversely, neuroticism showed a negative association with cortical thickness in the left parahippocampal gyrus. These associations were consistent across IDPs derived from different segmentation pipelines and were observed bilaterally, though generally stronger in the left hemisphere (**Appendix 6.1**).

In subcortical regions, neuroticism was associated with larger volumes of the bilateral caudate, putamen, and ventral striatum (**Table 6.2**).

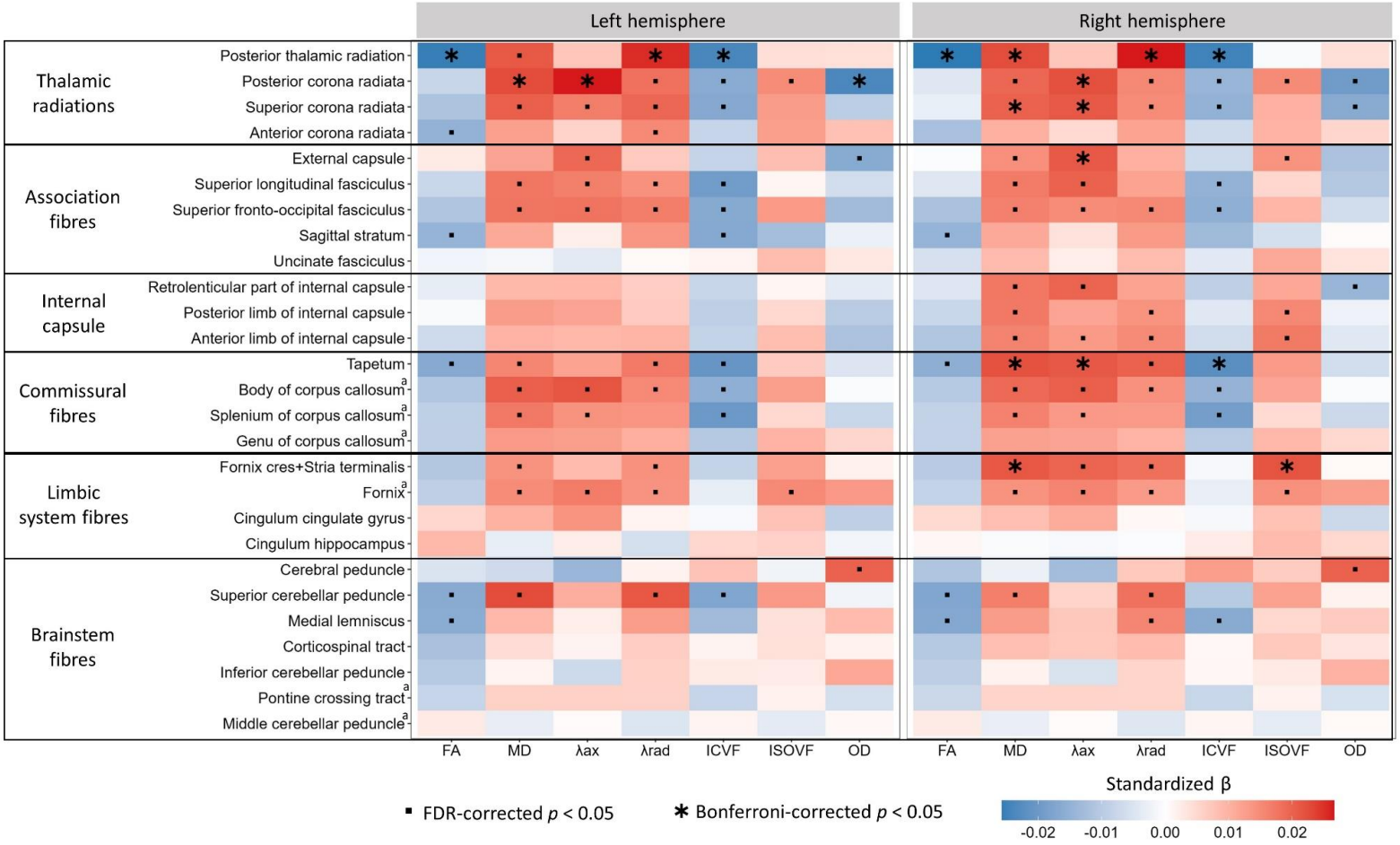
Neuroticism was also associated with markers of poorer white matter macrostructure, including higher T1 hypointensities and T2 hyperintensities, both of which reached Bonferroni-corrected significance (**Figure 6.2**). White matter microstructural metrics showed the strongest associations with neuroticism across all imaging modalities. Neuroticism was consistently associated with lower FA, higher diffusivity (MD, λax, λrad), lower ICVF and, to a lesser extent, higher ISOVF across multiple tracts (**Figure 6.2** and **Figure 6.3**), all reflecting a pattern of poorer white matter microstructure. No consistent trend was observed for OD across tracts.

Table 6.2: Summary of associations between neuroticism and cortical/subcortical structures after Bonferroni correction ($p<2.9\times10^{-5}$)

Region	Structure	Hemisphere	Structural measures	Brain segmentation tools	Standardised β	SE	p
			Cortical structure				
Temporal	Parahippocampal gyrus	Left	Area	Freesurfer DKT	0.028	0.005	4.2×10^{-7}
Frontal	Frontal medial cortex	Left	Volume	FAST	−0.027	0.005	5.1×10^{-7}
Frontal	Subcallosal cortex	Left	Volume	FAST	−0.024	0.005	6.3×10^{-6}
Temporal	Parahippocampal gyrus	Left	Thickness	Freesurfer desikan white	−0.025	0.005	6.8×10^{-6}
Temporal	Parahippocampal gyrus	Left	Thickness	Freesurfer DKT	−0.025	0.005	8.0×10^{-6}
Temporal	Parahippocampal gyrus	Left	Area	Freesurfer desikan pial	0.024	0.005	8.6×10^{-6}
Temporal	Parahippocampal gyrus	Left	Area	Freesurfer desikan white	0.024	0.005	8.8×10^{-6}
Limbic	Cingulate gyrus, caudal anterior	Left	Volume	Freesurfer DKT	−0.024	0.005	1.3×10^{-5}
Limbic	Cingulate cortex, anterior	Right	Volume	Freesurfer a2009s	−0.023	0.005	1.7×10^{-5}
Occipital	Pericalcarine cortex	Left	Area	Freesurfer desikan white	−0.024	0.006	2.1×10^{-5}
Occipital	Calcarine sulcus	Left	Area	Freesurfer a2009s	−0.023	0.006	2.2×10^{-5}
Frontal	Medial orbitofrontal cortex	Left	Volume	Freesurfer DKT	−0.023	0.005	2.3×10^{-5}
Occipital	Pericalcarine cortex	Left	Area	Freesurfer desikan pial	−0.023	0.006	2.3×10^{-5}
Occipital	Pericalcarine cortex	Left	Area	Freesurfer DKT	−0.023	0.006	2.8×10^{-5}
			Subcortical structure				
Striatum	Caudate	Left	Volume	FAST	0.025	0.005	5.0×10^{-6}
Striatum	Putamen	Right	Volume	FAST	0.024	0.005	7.0×10^{-6}
Striatum	Putamen	Left	Volume	FAST	0.024	0.005	8.4×10^{-6}
Striatum	Caudate	Right	Volume	FAST	0.024	0.005	9.1×10^{-6}
Striatum	Ventral striatum	Left	Volume	FAST	0.021	0.005	2.1×10^{-5}

Significant associations between neuroticism and cortical/subcortical structures after Bonferroni correction (1747 tests; $p<2.9\times10^{-5}$), adjusted for sex, age, age², age³, age×sex, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, and body mass index. Results were ranked by uncorrected p-values. See **Appendix 6.1** for regression coefficients and 95% confidence intervals. FAST, FMRIB's Automated Segmentation Tool; SE, standard error

Figure 6.3: Associations between neuroticism and white matter microstructure indices across white matter tract regions



[a] Structures with only a global measure (left and right hemisphere estimates are duplicated). Asterisks indicate Bonferroni-adjusted significant associations ($p<2.86\times10^{-5}$); squares indicate FDR-significant associations ($p<0.007$). Linear regression models were adjusted for all preselected covariates (sex, age, age^2, age^3, age×sex, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, and body mass index). FA, fractional anisotropy; λax, axial diffusivity; λrad, radial diffusivity; MD, mean diffusivity; ICVF, intracellular volume fraction; ISOVF, isotropic volume fraction; OD, orientation dispersion.

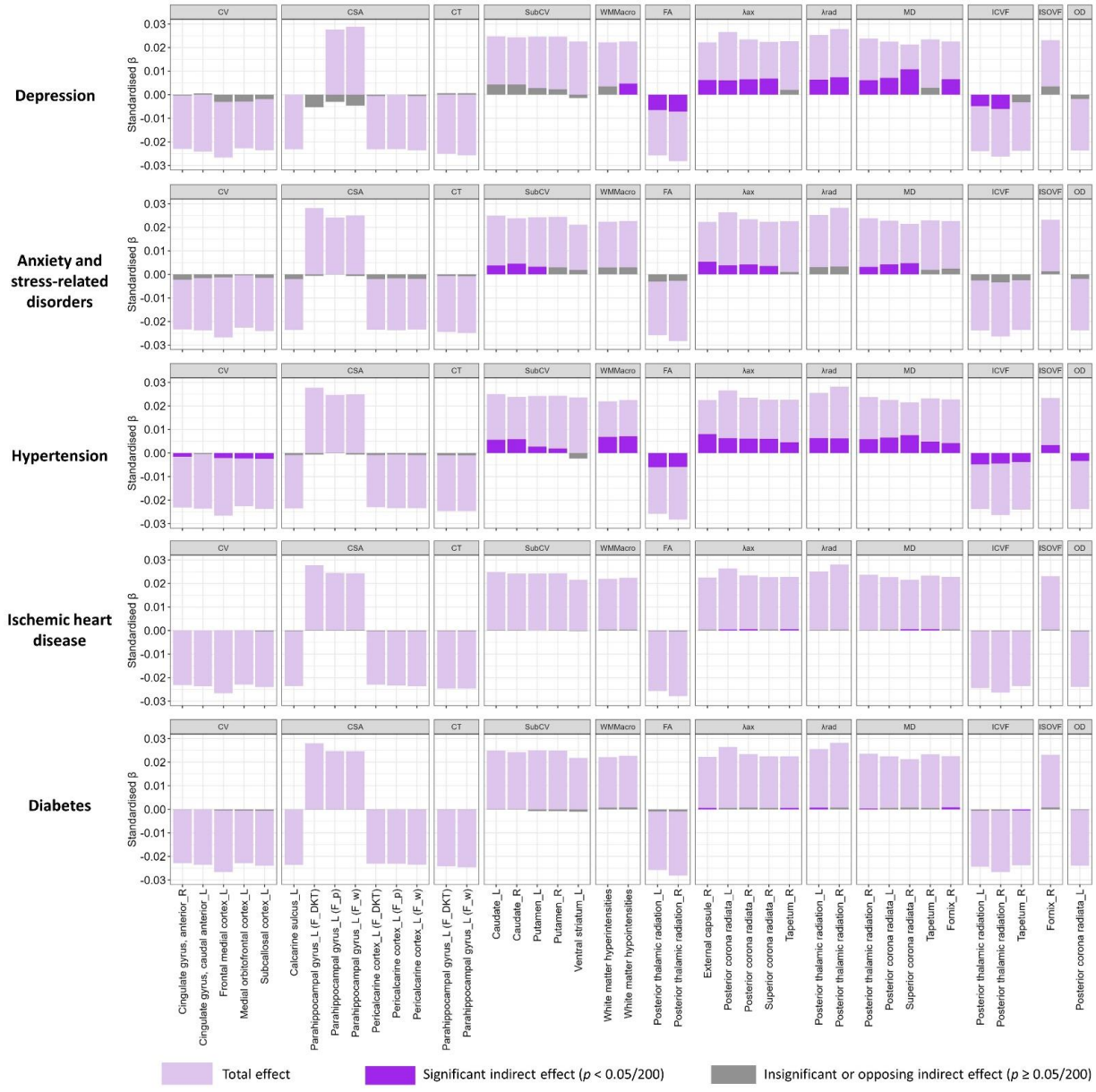
The most robust findings were localized to the thalamic radiations, with poorer microstructure in the bilateral posterior thalamic radiation, posterior corona radiata, and superior corona radiata reaching Bonferroni-corrected significance (**Figure 6.3**). Additional Bonferroni-corrected significant associations included increased diffusivity and decreased ICVF in the right tapetum (commissural fibers), increased diffusivity and ISOVF in the fornix cres/stria terminalis (limbic system fibers), and increased diffusivity in the external capsule (association fibers). Patterns were generally similar across hemispheres but tended to be stronger on the right (**Appendix 6.1**).

No Bonferroni-significant associations were observed for ventricular volume, brainstem volume, or brainstem intensity (**Figure 6.2**).

Mediation by health conditions

Overall, the examined conditions explained a substantial proportion of the associations with white matter macro- and microstructure, smaller proportions for cortical and subcortical volumes, and no mediation for cortical surface area or thickness (**Figure 6.4**).

Figure 6.4: Total effects of neuroticism on significant imaging-derived phenotypes and indirect effects mediated by preselected health conditions



Indirect effects were estimated using causal mediation analysis, with each health condition modelled as a mediator and each imaging phenotype as the outcome. Models were adjusted for all preselected covariates, including sex, age (and polynomial age terms), age×sex, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, and body mass index. Confidence intervals were derived via quasi-Bayesian Monte Carlo approach with 1000 simulations. Light purple bars represent the total effect, dark purple bars indicate (Bonferroni-adjusted) significant indirect (mediating) effects (ACME), and grey bars denote (Bonferroni-adjusted) insignificant or directionally inconsistent indirect (mediating) effects. See **Appendix 6.2** for regression coefficients and mediation proportions. CV, cortical volume; CSA, cortical surface area; CT, cortical thickness; subCV, subcortical volume; G/W, Grey-white matter contrast; FA, fractional anisotropy; λax, axial diffusivity; λrad, radial diffusivity; MD, mean diffusivity; ICVF, intracellular volume fraction; ISOVF, isotropic volume fraction; OD, orientation dispersion.

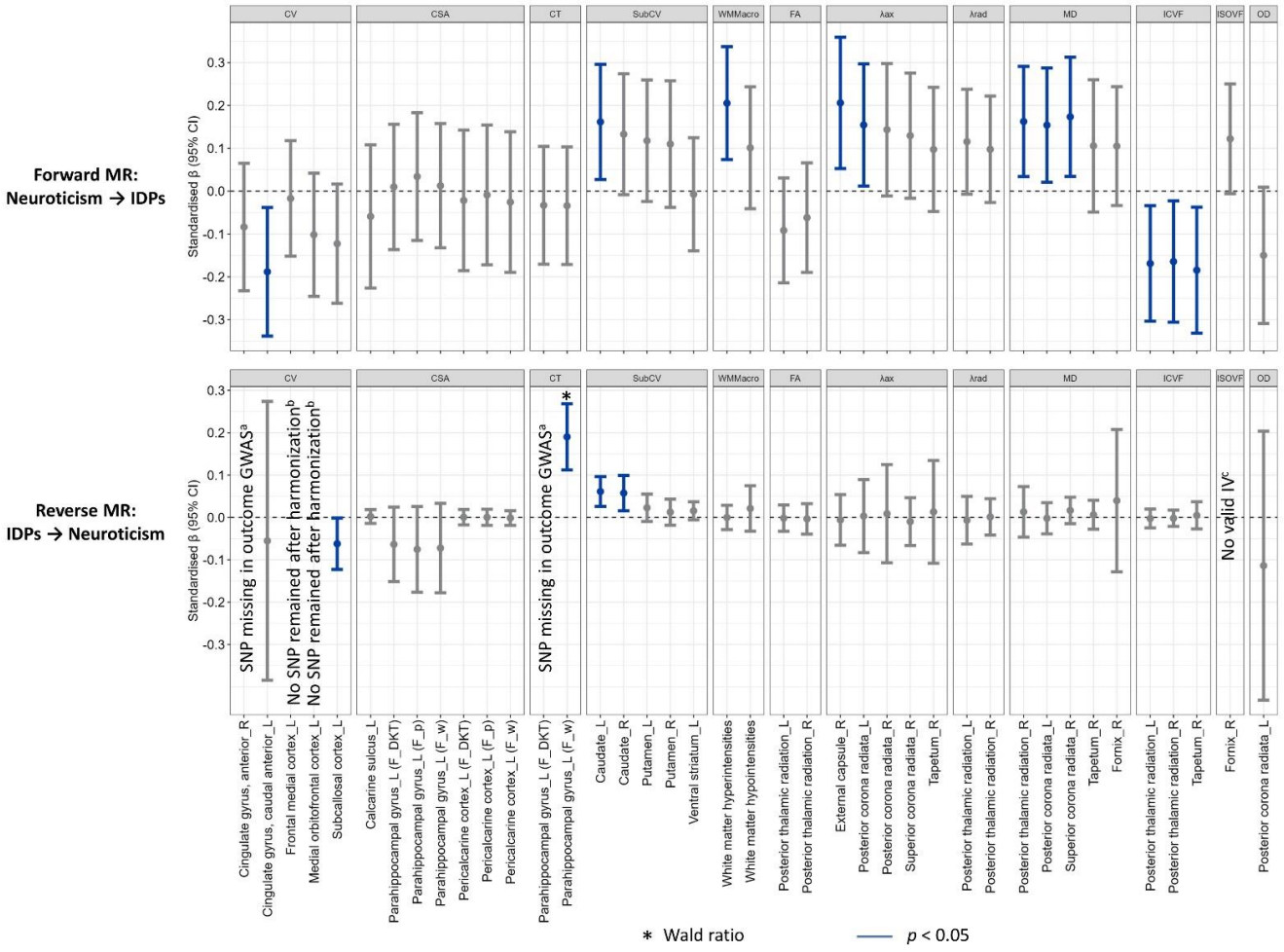
Among the examined conditions, hypertension showed the most consistent mediating effects across structures. The largest ACME was observed for the λax in the right external capsule (ACME=0.008, 95% CI [0.007, 0.010]; proportion mediated=36%; **Appendix 6.2**). Other regions with mediation proportions >30% included the MD in the right superior corona radiata (35%), T1 hypointensities (31%), and T2 hyperintensities (31%). Mediation proportions for associations with other white matter structures were ≥15%, while for the right and left caudate volume, they were 25% and 22%, respectively. For other cortical/subcortical volumes, mediation proportions were mostly <10%.

Depression did not mediate cortical/subcortical volume but strongly mediated white matter microstructure, with proportions generally >20%. Notably, it mediated 51% of the association with MD in the right superior corona radiata (ACME=0.011, 95% CI [0.008, 0.013]), 30% for λax in the same region, and 32% for MD in the left posterior corona radiata. Anxiety mediated fewer white matter tracts and with smaller proportions (9% to 24%); it also mediated associations with caudate volume (15% for the left and 19% for the right). IHD and diabetes mediated only a few associations with white matter microstructure, with smaller proportions (2% to 4%).

Genetic associations with brain structure

This study used 132 genetic instruments for neuroticism and between 1 and 24 instruments for each IDP (**Appendix 6.3**). From the 40 IDPs that showed Bonferroni-corrected significant associations with neuroticism in the observational analysis, 11 had significant genetic associations in forward MR (**Figure 6.5**).

Figure 6.5: Inverse-variance weighted estimates for the bidirectional Mendelian randomisation



[a] Only one genome-wide significant and independent SNP identified, but it was not available in the outcome GWAS;
[b] No SNP remained after harmonization due to all being palindromic with minor allele frequency>0.42 or unknown;
[c] No genome-wide significant and independent SNPs identified for use as IVs.
IV, instrumental variable; SNP, single nucleotide polymorphism; GWAS, genome-wide association studies; F_DKT, derived from FreeSurfer DKT atlas; F_w, derived from FreeSurfer Desikan white atlas; F_pial, derived from FreeSurfer Desikan pial atlas. See **Appendix 6.4** and **Appendix 6.7** for regression coefficients and 95% confidence intervals.

Genetically predicted higher neuroticism was associated with a larger volume of the left caudate (IVW β=0.16, p=0.018; **Appendix 6.4**), as well as with microstructural differences in several white matter tracts, including higher λax in the right external capsule (β=0.21, p=0.008), and both higher λax (β=0.15, p=0.034) and MD (β=0.15, p=0.024) in the left posterior corona radiata. These associations were robust across sensitivity analyses accounting for pleiotropy and sample overlap (**Appendix 6.5**). Additionally, significant IVW associations were observed with lower volume of the left anterior cingulate gyrus and higher WMH. While sensitivity analyses for these associations aligned with the direction of effects estimated by IVW, potential pleiotropy was detected (all p for Egger intercept<0.05 and p for MR-Egger>0.05, **Appendix 6.6**). Steiger test indicated stronger instrument-exposure than instrument-outcome correlations in all cases, except for the λax in right external capsule and left anterior cingulate gyrus volumes, where differences were not statistically significant, thereby supporting the assumed direction of association.

In reverse MR, genetically predicted larger volume of the bilateral caudate and lower volume of the left subcallosal cortex were associated with higher neuroticism (**Appendix 6.7**). However, none of these associations remained significant in sensitivity analyses accounting for sample overlap, and all showed evidence of pleiotropy (p for Egger intercept<0.05 or p for MR-Egger>0.05, **Appendix 6.5**). Genetically predicted larger thickness of the left parahippocampal gyrus was associated with higher neuroticism (Wald ratio=0.19, $p<10^{-5}$), but this finding was based on a single instrumental SNP.

As Bonferroni adjustment was not applied to the selected IDPs in the MR analyses, the reported MR associations should be interpreted as nominal.

6.5 DISCUSSION

In this large study of mid- to older-aged adults, neuroticism was associated with a broad range of structural brain differences. The most significant associations were observed in regions implicated in cognitive impairment and dementia, including reduced volume and thickness in key cortical areas, along with indicators of cerebrovascular burden such as increased WMH and diffusivity in white matter tracts involved in cognition. White matter macro- and microstructural differences were largely mediated by depression, anxiety, and hypertension, whereas cortical and subcortical volume associations were only modestly mediated by hypertension. MR analyses suggested that these structural differences are more likely a consequence of high neuroticism rather than a pre-existing vulnerability.

The association between neuroticism and cortical structure aligns with the most consistent finding from previous studies: reduced volume in the ventromedial prefrontal cortex (vmPFC).[158,161] This region includes the structures showing the strongest negative associations in this study—the frontal medial cortex, subcallosal cortex, anterior cingulate cortex, and medial orbitofrontal cortex—as well as those reported in prior work, such as the superior and inferior orbitofrontal gyri.[161] Additionally, another study reported negative associations with the surface area of many of these vmPFC regions.[160] vmPFC is critical for higher cognition (learning, social cognition, and decision-making)[316,317] and is a neuroimaging hallmark of frontotemporal dementia.[318]

The vmPFC is closely connected with the hippocampus and parahippocampal gyrus,[319] structures whose reduced volume and thinning serve as early biomarkers for

AD.[320,321] While a previous study reported an association between neuroticism and reduced parahippocampal volume,[161] this study instead found a pattern of increased surface area but reduced thickness—consistent with evidence that age-related volume changes in this region are primarily driven by thinning rather than surface area loss.[322] The parahippocampal gyrus is located in the temporal lobe, where prior studies have reported reduced volume in association with neuroticism.[158,161] These temporal lobe findings were not replicated in this study, potentially due to differences in cortical atlases, covariate adjustment, or participant characteristics. Instead, this study identified a novel negative association between neuroticism and surface area in the calcarine and pericalcarine cortices—regions previously reported as affected in patients with AD.[323,324]

For subcortical structures, this study observed positive associations between neuroticism and volumes of the caudate and putamen (which together form the dorsal striatum) as well as the ventral striatum. These structures were not highlighted in previous whole-brain studies,[115] likely due to insufficient power. The relationship between striatal volume and brain health remains controversial. While larger striatal volumes have been linked to better cognitive performance in cross-sectional studies,[325,326] longitudinal data suggest they predict higher dementia risk,[327] potentially reflecting early compensatory changes before broader atrophy emerges.[328]

The strongest and most widespread associations were observed in white matter, which is expected given neuroticism's established links to vascular conditions such as CVD[91] and VaD.[116] Neuroticism was associated with increased WMH—markers of small vessel disease

or vascular pathology[113]—consistent with prior findings.[170] The most significant microstructural differences in this analysis were located in the thalamic radiations, consistent with previous studies reporting differences in fiber tracts connecting thalamic nuclei to the frontal lobes,[160,171] while adding greater anatomical specificity. Additional associations with the external capsule, tapetum, and fornix cres/stria terminalis appear novel. These tracts were vulnerable to vascular brain aging[329] and degenerate early in the progression of AD.[330-337] To the best of current knowledge, this is the first study to extend beyond conventional dMRI measures to examine NODDI metrics, which suggest that these diffusivity changes primarily reflect axonal/dendritic loss (indicated by ICVF) rather than excess extracellular water (ISOVF) or tract disorganization (OD).[312]

Hypertension mediated both cortical and white matter abnormalities, likely through mechanisms such as vascular injury, reduced cerebral perfusion, and neuroinflammation, all of which contribute to neuronal death involving cell bodies, axons, and dendrites.[338-340] In contrast, depression and anxiety primarily mediated white matter microstructural changes, but not cortical alterations. This aligns with prior studies showing that polygenic risk for depression is associated with white matter abnormalities but not cortical structure.[341,342] A proposed mechanism involves hyperactivity of the hypothalamus–pituitary–adrenal axis in depression,[343] where glucocorticoid toxicity may preferentially affect axons/dendrites.[344] IHD showed minimal mediation (likely due to low prevalence [5.8%] in the sample of this study), while diabetes—included as 'negative control' given its lack of association with neuroticism—demonstrated no mediating effects as expected.

MR analyses provided further support for a link from neuroticism to white matter microstructural alterations, particularly increased diffusivity and reduced ICVF in the thalamic radiations. This study also observed bidirectional associations between neuroticism and caudate volume, though reverse MR analyses suggested potential horizontal pleiotropy, where genetic variants may influence neuroticism through pathways independent of caudate volume. For other genetically predicted IDPs, associations with neuroticism were generally null. However, it may be premature to establish a definitive unidirectional relationship from neuroticism to brain structures. This is primarily due to the small number of genome-wide significant instruments currently available for neuroimaging traits, which reduces power to detect true associations.[341]

Strengths and limitations

At the time of writing, this study is the largest and most comprehensive investigation of neuroticism's associations with brain structure, using multimodal neuroimaging metrics and a hypothesis-free approach. By applying causal mediation analyses and MR, this study provides the first evidence of potential mediators and directionality, offering new insights into neuroticism's biological underpinnings and clinical management. However, while neuroticism is generally stable across adulthood, the cross-sectional nature of neuroticism and MRI measurements precludes firm conclusions about temporal sequence, and residual confounding in observational analyses remains likely. Though this study employed MR to address these issues, however, the analysis is vulnerable to weak instrument bias: the neuroticism instruments explain only ~1–2% of trait variance, and many IDPs had very few genetic instruments. This problem may be exacerbated by sample overlap between the

neuroticism and IDP GWAS, although the proportion of overlap is relatively small given the much smaller IDP GWAS sample sizes, and MRlap was applied to mitigate this. Moreover, the sensitivity analyses indicated heterogeneous SNP-specific estimates and evidence of directional pleiotropy. Although pleiotropy-robust methods (MR-Egger, weighted median) were used, these approaches have limited power when instruments are weak.

Conclusion

In conclusion, neuroticism is associated with a broad profile of structural brain differences indicative of poorer brain health. The most prominent and widespread differences were observed in white matter macro- and microstructure, which is particularly vulnerable to vascular injury. This supports the vascular pathways identified in Chapters 3–5 linking neuroticism to dementia, and extends them to earlier brain structural changes. Additional findings include reduced frontal volumes and cortical thinning in memory-related regions, and striatal enlargement. These findings highlight shared biological pathways linking neuroticism, cognitive function, and dementia risk.

Chapter 7 Concluding remarks

7.1 SUMMARY OF MAIN FINDINGS

The overall aim of the work presented in this DPhil thesis was to advance understanding of the association between neuroticism and the risk of developing dementia. To achieve this, evidence was combined from a systematic literature search, two large-scale prospective observational analyses, in-depth investigations of potential underlying pathways using metabolomics data, and hypothesis-free analyses of multidomain cognitive performance and brain-wide structural outcomes.

In Chapter 2, findings were presented from a systematic search of the literature on the associations between neuroticism and incident dementia, cognitive function, and structural brain outcomes. The literatures indicated that while neuroticism was consistently associated with an increased risk of dementia, evidence on how this association varies by age or follow-up duration and on potential underlying pathways remains scarce. For cognitive function and brain structure, most studies were constrained by small sample sizes and lacked multi-domain cognitive assessments or brain-wide imaging, limiting hypothesis-free exploration of specific regions and functions involved. These gaps informed the direction of the subsequent analyses in this thesis.

In Chapter 3, the relationship between neuroticism and the risk of developing incident dementia was investigated using data from the UK Biobank cohort. The analysis found that higher neuroticism was associated with an increased risk of developing incident dementia, with a particularly strong association observed for VaD. These associations remained significant over long follow-up periods and were consistent regardless of genetic

predisposition to dementia. Further investigation revealed that these relationships were partially mediated by mental and vascular health conditions, and MR analyses suggested a link from neuroticism to greater WMH burden, a key marker of cerebrovascular disease.

In Chapter 4, the association between neuroticism and dementia risk was further investigated using the EPIC-Norfolk cohort, which provided a longer follow-up period (>20 years) and enabled analyses spanning both midlife and later life. Findings from these analyses supported the results from Chapter 3, demonstrating a significant relationship between higher neuroticism and increased long-term risk for all-cause dementia, AD, and VaD. This association was present for neuroticism measured in both midlife and later life. Consistent with the previous chapter, the association was partially mediated by mental and vascular conditions, and neuroticism was linked to poorer performance across multiple cognitive domains.

To further understand the biological pathways underlying the association, Chapter 5 examined the relationship between neuroticism, metabolites, and dementia risk in the UK Biobank. This analysis revealed that higher neuroticism was associated with an unfavorable metabolic profile, with fatty acid metabolism emerging as particularly relevant to dementia risk. In particular, lower levels of omega-3 fatty acids, especially DHA, were linked to both higher neuroticism and an increased risk of incident dementia, particularly VaD. MR analyses further supported an association between genetically predicted neuroticism and lower DHA levels, which in turn were related to increased WMH burden.

Chapter 6 examined associations between neuroticism and structural brain outcomes to better understand brain vulnerabilities relevant to the neuroticism-dementia association. Higher neuroticism was associated with adverse structural profiles, including smaller grey matter volumes in frontal regions and widespread differences in white matter microstructure. Consistent with findings in Chapters 3 and 4, these associations were partly explained by mental and vascular conditions previously identified as mediators of dementia risk. MR further supported a directional association from neuroticism to structural brain differences rather than the reverse.

7.2 CONTEXTUALISATION IN CURRENT KNOWLEDGE

Direct association

There is no clinical classification for neuroticism levels, instead, it is conceptualized as a continuous personality trait.[67] Consistent with this, both the UK Biobank (Chapter 3) and EPIC-Norfolk (Chapter 4) analyses found evidence of a dose-response association, whereby each increase in neuroticism score corresponded to an increasing risk of dementia, with no evidence of a threshold effect. To contextualize the findings, neuroticism scores in this thesis were expressed as SD units (z-scores), indicating how far an individual's score deviates from the population average. This approach facilitates comparisons across studies with different neuroticism measures, but presents results consistently in SD units. In a prior meta-analysis of prospective studies, each SD increase in neuroticism was associated with a 24% higher risk of dementia.[103] This effect size was larger than those observed in the UK Biobank (11% per SD) and EPIC-Norfolk (14% per SD). The difference may reflect methodological factors: the meta-analysis primarily pooled risk estimates from models adjusted only for age, sex, education, and race/ethnicity, whereas the models in this thesis additionally adjusted for lifestyle factors. Moreover, most studies in the meta-analysis had follow-up periods shorter than 10 years, increasing the likelihood that part of the association captured early disease manifestations.

Directionality and timing

Changes in behaviours characteristic of certain personality traits preceding a dementia diagnosis have been reported. Two studies that integrated data from multiple

cohorts used latent growth curve modelling to examine intra-individual trajectories of personality in people who later developed dementia versus those who remained dementia-free.[345,346] These analyses showed that neuroticism tended to increase in the years preceding a dementia diagnosis, whereas personality remained stable in those without dementia; however, these studies only covered up to 10 years before diagnosis. In contrast, a study of 2,046 older adults, with personality measured repeatedly every 1–4 years from the 1980s through 2016, found no evidence of neuroticism change prior to the onset of dementia.[347] Together, these findings suggest that disease-related changes in personality are more likely to emerge closer to diagnosis, and that longer follow-up is crucial to better distinguish long-standing personality traits from early disease manifestations.

This thesis was the first to examine the associations separately over short-term and long-term follow-up. In UK Biobank, the HR for follow-up <5 years was 1.14 and for 5–10 years was 1.13, both lower than the 24% higher dementia risk reported in the prior meta-analysis, which was based mostly on studies with mean follow-up <10 years.[103] This likely reflects that this relatively young cohort (mean baseline age 64, maximum 69) had few participants reaching the typical dementia onset age in the earliest years of follow-up. In EPIC-Norfolk, where baseline ages extended up to 80, the association in the first 15 years showed a 29% increased risk, a magnitude comparable to that in the prior meta-analysis, and this was reduced to a 9% increased risk after 20 years of follow-up. This pattern suggests that although reverse causality may contribute to the strength of early associations, the persistence of a significant link beyond two decades strengthens confidence in its robustness and direction.

In the meta-analysis, the mean baseline age across studies ranged widely from under 60 to over 80 years, yet heterogeneity in the pooled estimates was non-significant.[103] The EPIC-Norfolk study was the first to stratify results by life stage and further supports the absence of age-specific variation in risk. It showed similar associations for participants who reported neuroticism in their 40s–60s, 60s–70s, and 70s–80s, indicating that the link between neuroticism and dementia risk is evident from midlife through later life and remains detectable over long follow-up periods, rather than simply reflecting pre-existing dementia-related changes.

Interaction with genetic risk

In UK Biobank, a younger cohort, the effect size for neuroticism was larger in *APOE* ε4 non-carriers, though no significant interaction was detected. In EPIC-Norfolk, with an older baseline sample and longer follow-up, a significant interaction emerged, with stronger associations in non-carriers. Similar patterns have been reported for other dementia risk factors. For example, in a UK Biobank study (mean age 64.1 years; mean follow-up 11.8 years), multimorbidity showed a stronger association with dementia risk in non-carriers;[348] whereas in an older cohort (mean age 75.0 years; mean follow-up 8.4 years), the association between multimorbidity and dementia risk was significantly stronger in *APOE* ε4 carriers.[349] Likewise, in UK Biobank, hypertension showed a stronger association with dementia in non-carriers despite no interaction;[350] yet in a cohort of functionally intact older adults (mean age 73.2 years), elevated pulse pressure was more strongly linked to lower Aβ42/40 plasma concentrations in *APOE* ε4 carriers.[351] A recent UK Biobank analysis further showed

APOE ε4 modified the association between 22 factors and dementia: for 20 factors (e.g., self-rated health, smoking, diet quality, HDL-C, neutrophil count, vitamin D, air pollution), associations were stronger in non-carriers, whereas only two factors (maternal dementia history and low C-reactive protein) showed stronger associations in carriers.[352] These findings suggest that in UK Biobank, *APOE* ε4 carriers may already have an elevated baseline risk, the additional contribution of other factors—such as neuroticism—may appear proportionally smaller.

The EPIC-Norfolk findings showed a stronger association between neuroticism and dementia risk in *APOE* ε4 carriers. This is biologically plausible, as the *APOE* gene encodes apolipoprotein E, a protein central to lipid transport and metabolism.[353] The common alleles—ε2, ε3, and ε4—have well-established quantitative effects on lipid and lipoprotein levels. In particular, the ε4 allele is consistently linked to higher plasma total and LDL cholesterol,[354-356] and triglycerides,[357,358] contributing to an elevated risk of vascular conditions. Indeed, *APOE* ε4 has been associated with increased risks of hypertension and IHD.[359,360] Given that neuroticism is also associated with these vascular risk factors, the two may interact, amplifying pathways that contribute to dementia risk.

Potential vascular pathway

Multiple lines of evidence from this thesis and previous studies converge to suggest that vascular pathways may underlie the neuroticism-dementia association. First, both Chapters 3 and 4 demonstrated that higher neuroticism was associated with an increased risk of VaD (15–16% increased risk after full adjustment). This is consistent with a previous study

(mean baseline age 56.4 years; mean follow-up 8.9 years), which reported a 24% higher risk of incident VaD when adjusting only for age and sex.[116] In contrast, a study with a much younger baseline sample (38–54 years) and an extended 38-year follow-up found no association.[127] This null finding may reflect limited statistical power due to the small number of VaD cases, or the possibility that individuals with high vascular risk at younger ages are more likely to die from CVD before reaching the age at which VaD typically manifests.

These findings are further supported by structural brain outcomes. WMH burden is a well-established marker of cerebrovascular injury.[113] Consistent with a prior ROI study linking higher neuroticism to greater WMH burden,[170] both Chapters 3 and 6 demonstrated that genetically predicted neuroticism was associated with increased WMH, with no evidence for the reverse direction. In addition, Chapter 6 revealed strong associations between neuroticism and alterations in white matter microstructure, which were more pronounced than those observed for grey matter. This pattern aligns with animal models of cerebrovascular conditions, which show early microstructural changes in white matter (e.g., demyelination and axonal damage) while cortical grey matter remains relatively spared at the same stage.[361,362]

The role of vascular pathways was further examined using formal mediation analyses—applied to incident dementia in Chapters 3 and 4, and to structural brain outcomes in Chapter 6—which indicated that both depression and vascular conditions partially accounted for the observed associations. Since depression has been shown to causally

increase CVD risk,[86] and that cerebrovascular disease may contribute to later-life depressive syndromes,[363] depression may act as a driver or marker of vascular burden.

Biological mechanisms underlying these findings may involve multiple pathways. First, high neuroticism increases exposure to stressors and amplifies negative responses to them,[364] and chronic stress can dysregulate the hypothalamic-pituitary-adrenal axis and promote inflammation,[365] both of which contribute to endothelial dysfunction, atherosclerosis, hypertension, and CVD through processes such as oxidative stress, altered lipid metabolism, and insulin resistance.[366,367] Second, neuroticism is linked to unhealthy behaviours, including smoking,[368] a poorer diet,[100] and lower physical activity,[369] which contribute to dyslipidemia (elevated LDL and triglycerides, reduced HDL). Importantly, Chapter 5 highlighted a novel link: individuals with higher neuroticism had lower circulating omega-3 levels, which are known to improve vascular endothelial function and lipid profiles,[370,371] thereby creating an indirect pathway from neuroticism to dementia risk.

7.3 PUBLIC HEALTH PERSPECTIVES

Neuroticism as a long-term risk indicator

It has been proposed that mental health clinicians could routinely administer brief five-factor personality inventories, enabling the identification of individuals with high neuroticism who may benefit from closer monitoring. Such screening could even be delivered at scale, potentially through inexpensive community-based platforms or internet-based assessments, to efficiently flag individuals at higher risk.[53]

Findings from this thesis show that the association between neuroticism and dementia risk remains detectable even after more than two decades of follow-up and is consistent among individuals reporting neuroticism in their 40s–60s, 60s–70s, and 70s–80s. These results underscore that the influence of neuroticism on dementia risk is not confined to later life and highlight the importance of identifying high-risk individuals from at least midlife onward—when preventive interventions have a longer window of opportunity, and many modifiable dementia risk factors, including those linked to neuroticism (e.g., hypertension), exert the greatest influence.[17]

Furthermore, the EPIC-Norfolk study revealed that the association between neuroticism and dementia risk was stronger among *APOE* ε4 carriers, which raises the possibility that personality-based risk stratification may be enhanced by incorporating genetic information.

Nevertheless, the potential benefits of neuroticism screening must be balanced against possible harms. Careful consideration of screening thresholds is crucial to avoid unnecessary anxiety among individuals incorrectly identified as high risk. In addition, it is important to communicate clearly that neuroticism reflects variation within normal personality rather than a disorder, to minimize any risk of stigma.[53]

Alternative modifiable targets

Direct attempts to modify neuroticism face challenges: clinical interventions, such as pharmacological treatments[108] and cognitive-behavioural therapy,[109] have shown modest effects on personality traits, but interpretation is complicated because participants all had psychiatric conditions (depression[108] or anxiety[109]) and lacked pre-illness baseline data, making it unclear whether observed changes reflect true trait modification or a return to pre-psychopathology levels.[372] Nonclinical approaches, including behavioural and digital interventions,[110,112,373,374] offer preliminary promise but are limited by small sample sizes,[112] selective samples (e.g., university students),[373,374] and lengthy sessions,[110] impacting their robustness and scalability.

Therefore, a logical next step after risk stratification might be to target modifiable factors along the pathways linking neuroticism to dementia, rather than attempting to alter neuroticism itself. This thesis demonstrates that mental and vascular conditions partially mediate the neuroticism-dementia association and further extends these insights to the molecular level, identifying lower omega-3 fatty acid levels as being linked to both neuroticism and dementia risk. These are considered modifiable risk factors because they can

be effectively influenced through practical and cost-effective interventions. Consequently, individuals identified with high neuroticism could be offered regular physical and mental health reviews informed by current evidence linking neuroticism to adverse outcomes. These reviews might include assessments of depressive symptoms, blood pressure, lipid profiles, dietary patterns, cognitive performance, and markers of cerebrovascular injury. Those identified with additional modifiable risks could then receive tailored interventions, such as psychological support, lifestyle changes (e.g., increased intake of omega-3 fatty acids through diet or supplements), and cardiovascular management (e.g., antihypertensive therapy). These provide more direct and scalable strategies for individuals with high neuroticism to mitigate downstream pathways that contribute to dementia.

Randomized controlled trials are increasingly used to identify preventative targets for dementia. Hypertension, a potential mediator between neuroticism and dementia, was targeted in the Systolic Blood Pressure Intervention Trial (SPRINT, N=9,361), which compared intensive (<120 mm Hg) versus standard (<140 mm Hg) blood pressure management. Intensive treatment significantly reduced the risk of MCI and a combined outcome of MCI or probable dementia.[375] Given neuroticism's multiple downstream pathways and the multifactorial etiology of dementia, a multimodal approach may be necessary for optimal prevention. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was a large randomized controlled trial (N = 1,260) demonstrated that a combination of healthy nutrition, physical exercise, cognitive training, social engagement, and vascular/metabolic risk management significantly improved cognition in at-risk older adults.[376] Furthermore, the US Study to Protect Brain

Health Through Lifestyle Intervention to Reduce Risk (US POINTER) trial (N=2,111) found that both structured and self-guided multidomain lifestyle programs improved cognition over 2 years, with modest but significant additional benefits in the structured arm.[377] Neuroticism levels could serve as a useful indicator for trial inclusion, with multimodal strategies adapted accordingly.

7.4 STRENGTHS AND LIMITATIONS

This thesis examined direct associations in two large, independent cohorts—UK Biobank and EPIC-Norfolk—capturing both short- and long-term relationships across the life course. The study design incorporated a comprehensive, standardized cognitive battery, hypothesis-free metabolomic profiling, and whole-brain structural imaging, making it one of the largest investigations to date integrating these modalities. Furthermore, this thesis conducted the first formal mediation analyses to investigate pathways through mental and vascular conditions and was also the first to apply MR to assess the robustness and directionality of neuroticism's associations with dementia, metabolites, and structural brain outcomes.

This thesis has several limitations, some of which have been discussed in earlier chapters. These include selection bias in UK Biobank and EPIC-Norfolk, where participants tend to be healthier, better educated, and less diverse than the general population. Dementia diagnoses were derived from hospital inpatient data and death records, which often lag behind initial documentation in primary care or specialist memory clinics,[378] likely missing milder or earlier-stage cases and showing lower positive predictive value for specific

dementia subtypes.[227] In addition, some UK Biobank participants may not have reached the typical age of onset for dementia.[379] Furthermore, evolving diagnostic criteria and recording practices across hospitals and over time—for instance, revisions to the National Institute on Aging-Alzheimer's Association framework that increasingly define AD biologically rather than purely syndromically[179]—introduce heterogeneity and reduce comparability across studies.

As with any observational study, all observational analyses in this thesis are subject to residual confounding. Some relevant factors were not fully controlled for because of limited data availability (e.g., adverse childhood experiences), and measurement error in selected covariates may also remain. Therefore, these observational analyses cannot establish causality. However, triangulating the findings with MR analyses provides additional support for the robustness of the observed associations.

Nevertheless, MR has its own limitations. Current GWAS for AD rely on clinically diagnosed cases, which are imperfect; some individuals lack sufficient Alzheimer's pathology at autopsy, while many show mixed pathologies such as cerebrovascular disease or Lewy bodies, complicating the specificity of genetic signals.[380] For VaD and all-cause dementia, diagnoses are largely syndromic and pathologically heterogeneous, limiting the availability and precision of genetic data. In addition, genetic studies often have lower statistical power compared with large observational studies. Potential biases such as horizontal pleiotropy and weak instrument bias cannot be fully ruled out.

7.5 FUTURE DIRECTIONS

Investigating sex-specific associations

Across 21 cohorts comprising 29,850 participants from Africa, Asia, Europe, North America, Australia and South America, women had a 12% higher risk of developing dementia than men.[195] This difference is likely multifactorial. Women may carry a greater burden of certain social and psychological risk factors, including longer life expectancy, lower educational attainment in older generations,[381] and higher prevalence of depression.[382] In this thesis, UK Biobank and EPIC-Norfolk also showed that women reported higher neuroticism scores than men, warranting assessment of whether sex differences in dementia risk are partly driven by differences in neuroticism.

The contribution of established dementia risk factors may also vary by sex. Although neuroticism showed similar associations with all-cause dementia in men and women in UK Biobank—consistent with previous research[121,122,125]—sex-specific patterns may still arise in the timing of risk, interaction with other factors, and underlying pathways. First, vascular and mental health conditions, which earlier chapters identified as key pathways linking neuroticism to dementia, tend to intensify during the menopausal transition,[383,384] potentially heightening vulnerability among women at this stage. Second, genetic susceptibility may operate differently by sex; for example, *APOE* ε4 confers a greater AD risk in women than in men,[385] underscoring the need for future genotype-by-sex analyses. Third, Alzheimer-related lipid alterations—such as reduced highly unsaturated fatty acids and increased saturated lipid species—have been observed predominantly in women,[386] raising the

possibility that metabolic pathways linking neuroticism to dementia may differ between sexes.

Extending analyses to diverse populations and contexts

As highlighted in Chapter 2, most prior studies have been conducted in Europe and other high-income settings with predominantly White populations. The cohorts used in this thesis—UK Biobank and EPIC-Norfolk—also reflect this demographic composition; although small numbers of participants from minority ethnic groups were included, these were underpowered for subgroup analyses. Analyses using genetic data were further restricted to individuals of European ancestry, and the two-sample MR relied on GWAS summary statistics derived from European populations.

However, low- and middle-income countries are home to nearly two-thirds of people living with dementia,[387] and these regions are projected to experience substantial increases in dementia burden due to population growth, ageing, and a higher prevalence of modifiable risk factors.[4] Extending research to non-White populations and under-represented geographic, economic, and cultural contexts is therefore crucial.

Achieving this will require several steps. First, personality assessments such as neuroticism scales need to be validated in non-Western contexts, as cultural differences in emotional expression, reporting styles, and interpretation may influence score validity.[388] Second, GWAS and large-scale biomarker studies—including brain imaging and metabolomics—should be expanded to include diverse ancestries, given that allele

frequencies. brain morphology, lipid metabolism, and other biological traits may vary across populations. Third, reliance on electronic health records for dementia ascertainment may not be feasible in many low- and middle-income countries; instead, there is a need for detailed, cross-culturally validated cognitive assessments, clinical interviews, and standardized dementia classification algorithms.[389]

Strengthening temporal inference with early and repeated measurement

This thesis demonstrated that the association between neuroticism and dementia is evident from midlife through later life. However, because neuroticism typically stabilizes in young adulthood,[51] assessing it even earlier could help determine whether the association extends into early life, further reduce potential reverse-causation bias, and identify developmental periods that may be especially important for risk stratification and early prevention.

Earlier measurement of neuroticism would also enable clearer temporal ordering between the exposure (neuroticism), potential mediators, and dementia outcomes. Repeated measurements of potential mediators—such as depressive symptoms, blood pressure, and lipid profiles (including omega-3 fatty acids)—or restricting analyses to incident chronic conditions rather than baseline histories could improve pathway modeling.

Linking early neuroticism measures to dementia outcomes requires long-term follow-up. To date, only one study has examined personality before midlife (mean age 15.8 years) with follow-up to a mean age of 69.5 years, reporting protective associations of traits

such as calmness and maturity with later dementia.[239] However, that cohort has not yet reached the ages at which most dementia cases occurred (mid-80s), and the cases identified likely represent a mixture of early- and later-onset disease, which differ in clinical and genetic profiles.[390] Future work could leverage preclinical biomarkers (e.g., CSF levels of Aβ and tau) or examine broader cognitive and brain-aging trajectories, thereby shortening the follow-up time required to detect meaningful associations. Repeated cognitive and imaging assessments would allow the modeling of both baseline levels (intercepts) and rates of change (slopes), helping to determine whether neuroticism is more closely linked to initial cognitive/brain reserve or to accelerated decline over time.

Broadening pathway discovery through detailed lifestyle data

To uncover additional pathways and identify further modifiable intermediate factors that could be targeted, it is important to assess a wider range of potential mediators. For instance, prior evidence links neuroticism to poorer dietary habits, and findings in Chapter 5 suggest a possible link between neuroticism, omega-3 fatty acids, and dementia. This raises the question of whether diets characterized by unhealthy fatty acid profiles may act as mediators. However, the dietary data available in UK Biobank are based on a brief food-frequency touchscreen questionnaire, which is susceptible to misclassification and coarse categorization of intake levels.[391] For example, fish intake was captured only by simple questions on the number of servings per week, without information on portion size or specific fish types. By contrast, EPIC-Norfolk employed a validated 130-item food-frequency questionnaire with detailed portion and frequency information (e.g., six separate fish/seafood items assessed on a nine-point scale from “never or less than once per

month" to "more than six times per day")[392] making it a valuable resource for examining dietary pathways. Although both cohorts also include 24-hour dietary recalls that can provide more accurate intake estimates, these are available only in subsets, limiting power and potentially introducing selection bias. Large cohorts with detailed, repeated dietary assessments are needed to better understand the role of diet and inform potential dietary interventions to reduce dementia risk in individuals with high neuroticism.

Advancing genome-wide association studies for neuroticism

The genetic architecture of neuroticism is highly polygenic, therefore, future GWAS with much larger sample sizes are needed to generate a larger number of stronger genetic instruments and thereby improve MR power. Ideally, such GWAS would also provide summary statistics independent of UK Biobank to minimise sample overlap in two-sample MR. A further challenge is that large biobanks often rely on brief personality measures—for example, the Million Veteran Program uses a very brief 10-item Big Five Inventory,[71] and cohorts within the Genetics of Personality Consortium apply heterogeneous measures. Future work would therefore benefit from standardised, deep personality phenotyping that captures the full facet structure of neuroticism and allows facet- or item-level GWAS.

In addition, the life-course-specific genetic architecture of neuroticism remains poorly characterised. Multivariable MR based on age-stratified GWAS of neuroticism would enable estimation of genetically predicted neuroticism at different developmental stages and its association with dementia, helping to identify periods of heightened vulnerability and opportunities for early intervention.

Finally, neuroticism GWAS in non-European populations remain much smaller, limiting power and restricting MR to European datasets. Larger ancestry-diverse GWAS and trans-ethnic MR,[393] typically conducted by performing MR within each ancestry group and comparing effect estimates across populations, will be essential for determining whether findings generalise beyond European ancestries.

7.6 CONCLUDING REMARKS

In conclusion, this DPhil thesis strengthens evidence that higher neuroticism is associated with an increased risk of developing dementia. This association was observed over long follow-up and across mid- to later life, and was reflected in poorer cognitive performance and brain structural profiles. These associations appear to operate partly through modifiable pathways involving vascular and mental health, with downstream molecular evidence implicating lower omega-3 fatty acid levels. These results improve understanding of the basic nature of both neuroticism and dementia, and highlight potential public health implications: neuroticism could help stratify risk to identify individuals who may benefit from closer monitoring, while practical intervention efforts may focus on modifiable factors such as hypertension, depression, and diet rather than on personality itself. The findings also emphasize the need to validate these findings in more diverse populations and to use longitudinal approaches that more clearly map temporal pathways. Overall, this thesis supports integrating a psychological dimension into dementia risk assessment, offering opportunities for more personalized and proactive prevention strategies.

References

1. World Health Organization. Dementia. Accessed July 01, 2025. https://www.who.int/news-room/fact-sheets/detail/dementia
2. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. *JAMA*. 2019;322(16):1589-1599. doi:10.1001/jama.2019.4782
3. Reitz C, Rogaeva E, Beecham GW. Late-onset vs nonmendelian early-onset Alzheimer disease: A distinction without a difference? *Neurol Genet*. Oct 2020;6(5):e512. doi:10.1212/nxg.0000000000000512
4. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health*. 2022;7(2):e105-e125. doi:10.1016/S2468-2667(21)00249-8
5. World Health Organization. *Global Health Estimates 2021: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2021*. 2024.
6. Alzheimer's Disease International. *World Alzheimer Report 2024: Global changes in attitudes to dementia.* 2024.
7. Alzheimer's Society. *The economic impact of dementia*. 2025.
8. Erkkinen MG, Kim MO, Geschwind MD. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. *Cold Spring Harb Perspect Biol*. Apr 2 2018;10(4)doi:10.1101/cshperspect.a033118
9. Sperling R, Mormino E, Johnson K. The Evolution of Preclinical Alzheimer's Disease: Implications for Prevention Trials. *Neuron*. 2014/11/05/ 2014;84(3):608-622. doi:https://doi.org/10.1016/j.neuron.2014.10.038
10. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. Feb 2013;12(2):207-16. doi:10.1016/s1474-4422(12)70291-0
11. Wolters FJ, Ikram MA. Epidemiology of Vascular Dementia. *Arterioscler Thromb Vasc Biol*. Aug 2019;39(8):1542-1549. doi:10.1161/atvbaha.119.311908
12. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. Feb 1993;43(2):250-60. doi:10.1212/wnl.43.2.250
13. O'Brien JT, Thomas A. Vascular dementia. *The Lancet*. 2015;386(10004):1698-1706. doi:10.1016/S0140-6736(15)00463-8
14. Elahi FM, Miller BL. A clinicopathological approach to the diagnosis of dementia. *Nat Rev Neurol*. Aug 2017;13(8):457-476. doi:10.1038/nrneurol.2017.96
15. van Dyck Christopher H, Swanson Chad J, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *New England Journal of Medicine*. 2023/01/04 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
16. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *Jama*. Aug 8 2023;330(6):512-527. doi:10.1001/jama.2023.13239

17. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet*. 2024;404(10452):572-628. doi:10.1016/S0140-6736(24)01296-0
18. Yang LG, March ZM, Stephenson RA, Narayan PS. Apolipoprotein E in lipid metabolism and neurodegenerative disease. *Trends Endocrinol Metab*. Aug 2023;34(8):430-445. doi:10.1016/j.tem.2023.05.002
19. Jackson RJ, Hyman BT, Serrano-Pozo A. Multifaceted roles of APOE in Alzheimer disease. *Nat Rev Neurol*. Aug 2024;20(8):457-474. doi:10.1038/s41582-024-00988-2
20. Lim YY, Mormino EC. APOE genotype and early β-amyloid accumulation in older adults without dementia. *Neurology*. Sep 5 2017;89(10):1028-1034. doi:10.1212/wnl.0000000000004336
21. Belloy ME, Andrews SJ, Le Guen Y, et al. APOE Genotype and Alzheimer Disease Risk Across Age, Sex, and Population Ancestry. *JAMA Neurology*. 2023;80(12):1284-1294. doi:10.1001/jamaneurol.2023.3599
22. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet*. Mar 2019;51(3):414-430. doi:10.1038/s41588-019-0358-2
23. The Mega Vascular Cognitive I, Dementia c. A genome-wide association meta-analysis of all-cause and vascular dementia. *Alzheimer's & Dementia*. 2024/09/01 2024;20(9):5973-5995. doi:https://doi.org/10.1002/alz.14115
24. Guerreiro R, Ross OA, Kun-Rodrigues C, et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. *Lancet Neurol*. Jan 2018;17(1):64-74. doi:10.1016/s1474-4422(17)30400-3
25. Ferrari R, Hernandez DG, Nalls MA, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. *Lancet Neurol*. Jul 2014;13(7):686-99. doi:10.1016/s1474-4422(14)70065-1
26. Cadar D. A Life Course Approach to Dementia Prevention. 04/24 2017;2017
27. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *The Lancet*. 2017;390(10113):2673-2734. doi:10.1016/S0140-6736(17)31363-6
28. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. Aug 8 2020;396(10248):413-446. doi:10.1016/s0140-6736(20)30367-6
29. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. doi:10.1136/bmj.k601
30. Anderson EL, Davies NM, Korologou-Linden R, Kivimäki M. Dementia prevention: the Mendelian randomisation perspective. *Journal of Neurology, Neurosurgery & Psychiatry*. 2024;95(4):384. doi:10.1136/jnnp-2023-332293
31. Desai R, John A, Saunders R, et al. Examining the Lancet Commission risk factors for dementia using Mendelian randomisation. *BMJ Ment Health*. Feb 2023;26(1)doi:10.1136/bmjment-2022-300555
32. Raffaitin C, Gin H, Empana JP, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. *Diabetes Care*. Jan 2009;32(1):169-74. doi:10.2337/dc08-0272

33. Yu JT, Xu W, Tan CC, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry*. Nov 2020;91(11):1201-1209. doi:10.1136/jnnp-2019-321913
34. Sharp SI, Aarsland D, Day S, Sønnesyn H, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. *Int J Geriatr Psychiatry*. Jul 2011;26(7):661-9. doi:10.1002/gps.2572
35. Thomassen JQ, Tolstrup JS, Benn M, Frikke-Schmidt R. Type-2 diabetes and risk of dementia: observational and Mendelian randomisation studies in 1 million individuals. *Epidemiol Psychiatr Sci*. Apr 24 2020;29:e118. doi:10.1017/s2045796020000347
36. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry*. May 2013;202(5):329-35. doi:10.1192/bjp.bp.112.118307
37. Luchetti M, Aschwanden D, Sesker AA, et al. A meta-analysis of loneliness and risk of dementia using longitudinal data from >600,000 individuals. *Nature Mental Health*. 2024/11/01 2024;2(11):1350-1361. doi:10.1038/s44220-024-00328-9
38. Proitsi P, Lupton MK, Velayudhan L, et al. Genetic predisposition to increased blood cholesterol and triglyceride lipid levels and risk of Alzheimer disease: a Mendelian randomization analysis. *PLoS Med*. Sep 2014;11(9):e1001713. doi:10.1371/journal.pmed.1001713
39. Sproviero W, Winchester L, Newby D, et al. High Blood Pressure and Risk of Dementia: A Two-Sample Mendelian Randomization Study in the UK Biobank. *Biol Psychiatry*. Apr 15 2021;89(8):817-824. doi:10.1016/j.biopsych.2020.12.015
40. Wang W, Zhang J, Zhang M, et al. Impact of diabetes mellitus on the risk of Alzheimer's disease: a mendelian randomization study. *BMC Neurology*. 2024/11/18 2024;24(1):448. doi:10.1186/s12883-024-03955-y
41. Xie Y, Liu S, Wang X, et al. Lipids, Apolipoproteins, Lipid-Lowering Drugs, and the Risk of Cerebral Small Vessel Disease: A Mendelian Randomization Study. *Journal of the American Heart Association*. 2024/08/20 2024;13(16):e032409. doi:10.1161/JAHA.123.032409
42. Andrews SJ, Fulton-Howard B, O'Reilly P, Marcora E, Goate AM. Causal Associations Between Modifiable Risk Factors and the Alzheimer's Phenome. *Ann Neurol*. Jan 2021;89(1):54-65. doi:10.1002/ana.25918
43. Georgakis MK, Harshfield EL, Malik R, et al. Diabetes Mellitus, Glycemic Traits, and Cerebrovascular Disease: A Mendelian Randomization Study. *Neurology*. Mar 30 2021;96(13):e1732-e1742. doi:10.1212/wnl.0000000000011555
44. Wishart DS. Emerging applications of metabolomics in drug discovery and precision medicine. *Nature Reviews Drug Discovery*. 2016/07/01 2016;15(7):473-484. doi:10.1038/nrd.2016.32
45. Rosenberg GA. Neurological diseases in relation to the blood-brain barrier. *J Cereb Blood Flow Metab*. Jul 2012;32(7):1139-51. doi:10.1038/jcbfm.2011.197
46. Kim M, Legido-Quigley C. Small molecule biomarkers in Alzheimer's disease. *OCL*. 07/01 2018;25doi:10.1051/ocl/2018027

47. Tiwari P, Gupta A, Kaushik M, et al. Comprehensive metabolomics profiling reveals novel biomarkers and pathways for early detection of Alzheimer's disease. *Brain Communications*. 2025;7(6):fcaf410. doi:10.1093/braincomms/fcaf410
48. Amin N, Liu J, Sproviero W, et al. Interplay between age, APOE Ɛ4 and the metabolome in plasma and brain in Alzheimer's disease. *Translational Psychiatry*. 2025/10/31 2025;15(1):460. doi:10.1038/s41398-025-03625-8
49. Liu Y, Abdolkarimi D, Gilchrist L, et al. Circulating Metabolites are Linked to Dementia and Brain Imaging Phenotypes, and Mediate Modifiable Risk Pathways. *medRxiv*. 2025:2025.10.31.25339240. doi:10.1101/2025.10.31.25339240
50. Friedman HS, Kern ML. Personality, Well-Being, and Health*. *Annual Review of Psychology*. 2014;65(Volume 65, 2014):719-742. doi:https://doi.org/10.1146/annurev-psych-010213-115123
51. Bleidorn W, Schwaba T, Zheng A, et al. Personality stability and change: A meta-analysis of longitudinal studies. *Psychol Bull*. Jul-Aug 2022;148(7-8):588-619. doi:10.1037/bul0000365
52. Friedman HS. Personality, disease, and self-healing. *The Oxford handbook of health psychology*. 2011:215-240.
53. Lahey BB. Public health significance of neuroticism. *Am Psychol*. May-Jun 2009;64(4):241-56. doi:10.1037/a0015309
54. Eysenck HJ. *Dimensions of personality*. Dimensions of personality. Kegan Paul; 1947:xi, 308-xi, 308.
55. Costa PT, McCrae RR, Psychological Assessment Resources I. *Revised NEO Personality Inventory (NEO PI-R) and NEO Five-Factor Inventory (NEO-FFI)*. Psychological Assessment Resources; 1992.
56. Leary M, Hoyle R. *Handbook of individual differences in social behavior*. 2009.
57. Costa PT, McCrae RR. Four ways five factors are basic. *Personality and Individual Differences*. 1992/06/01/ 1992;13(6):653-665. doi:https://doi.org/10.1016/0191-8869(92)90236-I
58. Goldberg LR. The structure of phenotypic personality traits. *American Psychologist*. 1993;48(1):26-34. doi:10.1037/0003-066X.48.1.26
59. Weiss A, Costa P. Domain and Facet Personality Predictors of All-Cause Mortality Among Medicare Patients Aged 65 to 100. *Psychosomatic medicine*. 09/01 2005;67:724-33. doi:10.1097/01.psy.0000181272.58103.18
60. Costa P, McCrae R. Neo PI-R professional manual. *Psychological Assessment Resources*. 01/01 1992;396
61. Eysenck SBG, Eysenck HJ, Barrett P. A revised version of the psychoticism scale. *Personality and Individual Differences*. 1985/01/01/ 1985;6(1):21-29. doi:https://doi.org/10.1016/0191-8869(85)90026-1
62. John OP, Donahue EM, Kentle RL. The Big Five Inventory---versions 4a and 5. 1991;
63. Goldberg LR. A broad-bandwidth, public domain, personality inventory measuring the lower-level facets of several five-factor models. *Personality psychology in Europe*. 1999;7(1):7-28.

64. McCrae RR, Kurtz JE, Yamagata S, Terracciano A. Internal consistency, retest reliability, and their implications for personality scale validity. *Pers Soc Psychol Rev*. Feb 2011;15(1):28-50. doi:10.1177/1088868310366253
65. Thalmayer AG, Saucier G, Eigenhuis A. Comparative validity of brief to medium-length Big Five and Big Six Personality Questionnaires. *Psychol Assess*. Dec 2011;23(4):995-1009. doi:10.1037/a0024165
66. Grucza RA, and Goldberg LR. The Comparative Validity of 11 Modern Personality Inventories: Predictions of Behavioral Acts, Informant Reports, and Clinical Indicators. *Journal of Personality Assessment*. 2007/11/01 2007;89(2):167-187. doi:10.1080/00223890701468568
67. Zuckerman M. Temperament and Personality: Trait Structure and Persistence. *Psychobiology of Personality*. 2 ed. Cambridge University Press; 2005:1-38.
68. van den Berg SM, de Moor MH, McGue M, et al. Harmonization of Neuroticism and Extraversion phenotypes across inventories and cohorts in the Genetics of Personality Consortium: an application of Item Response Theory. *Behav Genet*. Jul 2014;44(4):295-313. doi:10.1007/s10519-014-9654-x
69. Vukasović T, Bratko D. Heritability of personality: A meta-analysis of behavior genetic studies. *Psychol Bull*. Jul 2015;141(4):769-85. doi:10.1037/bul0000017
70. Nagel M, Jansen PR, Stringer S, et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nature Genetics*. 2018/07/01 2018;50(7):920-927. doi:10.1038/s41588-018-0151-7
71. Gupta P, Galimberti M, Liu Y, et al. A genome-wide investigation into the underlying genetic architecture of personality traits and overlap with psychopathology. *Nature Human Behaviour*. 2024/11/01 2024;8(11):2235-2249. doi:10.1038/s41562-024-01951-3
72. Binder EB, Nemeroff CB. The CRF system, stress, depression and anxiety-insights from human genetic studies. *Mol Psychiatry*. Jun 2010;15(6):574-88. doi:10.1038/mp.2009.141
73. Liu Z, Zhu F, Wang G, et al. Association of corticotropin-releasing hormone receptor1 gene SNP and haplotype with major depression. *Neurosci Lett*. Sep 1 2006;404(3):358-62. doi:10.1016/j.neulet.2006.06.016
74. Smith DJ, Escott-Price V, Davies G, et al. Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Mol Psychiatry*. Nov 2016;21(11):1644. doi:10.1038/mp.2016.177
75. Fletcher JM, Schurer S. Origins of adulthood personality: The role of adverse childhood experiences. *B E J Econom Anal Policy*. Apr 2017;17(2)doi:10.1515/bejeap-2015-0212
76. Ono K, Yoshikazu T, Yukiei N, et al. Associations among depressive symptoms, childhood abuse, neuroticism, and adult stressful life events in the general adult population. *Neuropsychiatric Disease and Treatment*. 2017/02/15 2017;13(null):477-482. doi:10.2147/NDT.S128557
77. Boillat C, Schwab N, Stutz M, Pflueger MO, Graf M, Rosburg T. Neuroticism as a risk factor for child abuse in victims of childhood sexual abuse. *Child Abuse Negl*. Jun 2017;68:44-54. doi:10.1016/j.chiabu.2017.03.018

78. Anusic I, Schimmack U. Stability and change of personality traits, self-esteem, and well-being: Introducing the meta-analytic stability and change model of retest correlations. *J Pers Soc Psychol*. May 2016;110(5):766-81. doi:10.1037/pspp0000066
79. Chopik WJ, Kitayama S. Personality change across the life span: Insights from a cross-cultural, longitudinal study. *J Pers*. Jun 2018;86(3):508-521. doi:10.1111/jopy.12332
80. Terracciano A, Costa PT, Jr., McCrae RR. Personality plasticity after age 30. *Pers Soc Psychol Bull*. Aug 2006;32(8):999-1009. doi:10.1177/0146167206288599
81. Ormel J, Jeronimus BF, Kotov R, et al. Neuroticism and common mental disorders: meaning and utility of a complex relationship. *Clin Psychol Rev*. Jul 2013;33(5):686-697. doi:10.1016/j.cpr.2013.04.003
82. Seifert IS, Rohrer JM, Schmukle SC. Using within-person change in three large panel studies to estimate personality age trajectories. *J Pers Soc Psychol*. Jan 2024;126(1):150-174. doi:10.1037/pspp0000482
83. Jeronimus BF, Kotov R, Riese H, Ormel J. Neuroticism's prospective association with mental disorders halves after adjustment for baseline symptoms and psychiatric history, but the adjusted association hardly decays with time: a meta-analysis on 59 longitudinal/prospective studies with 443 313 participants. *Psychological Medicine*. 2016;46(14):2883-2906. doi:10.1017/S0033291716001653
84. Christensen DS, Flensborg-Madsen T, Andersen NE, Rosenkær IB, Mortensen EL. Personality and risk of hospital diagnosed mental disorder: a 35 years' prospective study. *Soc Psychiatry Psychiatr Epidemiol*. Nov 2021;56(11):2073-2081. doi:10.1007/s00127-020-02001-9
85. Howard DM, Adams MJ, Clarke TK, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci*. Mar 2019;22(3):343-352. doi:10.1038/s41593-018-0326-7
86. Li H, Li S, Yang H, et al. Association of comprehensive mental health with incident cardiovascular disease: A prospective cohort study. *Journal of Affective Disorders*. 2022/02/01/ 2022;298:388-395. doi:https://doi.org/10.1016/j.jad.2021.11.008
87. Sun Y, Zhang H, Wang B, et al. Joint exposure to positive affect, life satisfaction, broad depression, and neuroticism and risk of cardiovascular diseases: A prospective cohort study. *Atherosclerosis*. 2022/10/01/ 2022;359:44-51. doi:https://doi.org/10.1016/j.atherosclerosis.2022.08.007
88. Dahlén AD, Miguet M, Schiöth HB, Rukh G. The influence of personality on the risk of myocardial infarction in UK Biobank cohort. *Sci Rep*. Apr 25 2022;12(1):6706. doi:10.1038/s41598-022-10573-6
89. Almas A, Moller J, Iqbal R, Forsell Y. Effect of neuroticism on risk of cardiovascular disease in depressed persons - a Swedish population-based cohort study. *BMC Cardiovascular Disorders*. 2017/07/11 2017;17(1):185. doi:10.1186/s12872-017-0604-4
90. Stephan Y, Sutin AR, Luchetti M, Aschwanden D, Terracciano A. Personality and Risk of Incident Stroke in 6 Prospective Studies. *Stroke*. Aug 2023;54(8):2069-2076. doi:10.1161/strokeaha.123.042617

91. Zhang F, Baranova A, Zhou C, et al. Causal influences of neuroticism on mental health and cardiovascular disease. *Human Genetics*. 2021/09/01 2021;140(9):1267-1281. doi:10.1007/s00439-021-02288-x
92. Liu Y, Cheng P, Liu N, et al. Neuroticism Increases the Risk of Stroke: Mendelian Randomization Study. *Stroke*. Nov 2021;52(11):e742-e743. doi:10.1161/strokeaha.121.036131
93. Huovinen E, Kaprio J, Koskenvuo M. Asthma in relation to personality traits, life satisfaction, and stress: a prospective study among 11,000 adults. *Allergy*. Oct 2001;56(10):971-7. doi:10.1034/j.1398-9995.2001.00112.x
94. Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: an overview. *Psychother Psychosom*. Jan-Feb 2001;70(1):6-16. doi:10.1159/000056219
95. Zarpour S, Besharat MA. Comparison of Personality Characteristics of Individuals with Irritable Bowel Syndrome and Healthy Individuals. *Procedia - Social and Behavioral Sciences*. 2011/01/01/ 2011;30:84-88. doi:https://doi.org/10.1016/j.sbspro.2011.10.017
96. Terracciano A, Stephan Y, Luchetti M, Gonzalez-Rothi R, Sutin AR. Personality and Lung Function in Older Adults. *J Gerontol B Psychol Sci Soc Sci*. Oct 1 2017;72(6):913-921. doi:10.1093/geronb/gbv161
97. Basten M, Pan KY, van Tuijl LA, et al. Psychosocial factors, health behaviors and risk of cancer incidence: Testing interaction and effect modification in an individual participant data meta-analysis. *Int J Cancer*. May 15 2024;154(10):1745-1759. doi:10.1002/ijc.34852
98. Finch JF, Graziano WG. Predicting depression from temperament, personality, and patterns of social relations. *J Pers*. Feb 2001;69(1):27-55. doi:10.1111/1467-6494.00135
99. Hakulinen C, Hintsanen M, Munafò MR, et al. Personality and smoking: individual-participant meta-analysis of nine cohort studies. *Addiction*. 2015/11/01 2015;110(11):1844-1852. doi:https://doi.org/10.1111/add.13079
100. Esposito CM, Ceresa A, Buoli M. The Association Between Personality Traits and Dietary Choices: A Systematic Review. *Adv Nutr*. Jul 30 2021;12(4):1149-1159. doi:10.1093/advances/nmaa166
101. Mõttus R, McNeill G, Jia X, Craig LC, Starr JM, Deary IJ. The associations between personality, diet and body mass index in older people. *Health Psychol*. Apr 2013;32(4):353-60. doi:10.1037/a0025537
102. Tiainen AM, Männistö S, Lahti M, et al. Personality and dietary intake - findings in the Helsinki birth cohort study. *PLoS One*. 2013;8(7):e68284. doi:10.1371/journal.pone.0068284
103. Aschwanden D, Strickhouser JE, Luchetti M, Stephan Y, Sutin AR, Terracciano A. Is personality associated with dementia risk? A meta-analytic investigation. *Ageing Res Rev*. May 2021;67:101269. doi:10.1016/j.arr.2021.101269
104. Eckerström M, Berg AI. Aspects of Personality Traits and Changes in Different Stages of Dementia Disorders. In: Garcia D, Archer T, Kostrzewa RM, eds. *Personality and Brain Disorders: Associations and Interventions*. Springer International Publishing; 2019:59-84.

105. Yang W, Li X, Pan KY, et al. Association of life-course depression with the risk of dementia in late life: A nationwide twin study. *Alzheimers Dement*. Aug 2021;17(8):1383-1390. doi:10.1002/alz.12303
106. Elser H, Horváth-Puhó E, Gradus JL, et al. Association of Early-, Middle-, and Late-Life Depression With Incident Dementia in a Danish Cohort. *JAMA Neurol*. Sep 1 2023;80(9):949-958. doi:10.1001/jamaneurol.2023.2309
107. Mirza SS, de Bruijn RF, Direk N, et al. Depressive symptoms predict incident dementia during short- but not long-term follow-up period. *Alzheimers Dement*. Oct 2014;10(5 Suppl):S323-S329.e1. doi:10.1016/j.jalz.2013.10.006
108. Tang TZ, DeRubeis RJ, Hollon SD, Amsterdam J, Shelton R, Schalet B. Personality change during depression treatment: a placebo-controlled trial. *Arch Gen Psychiatry*. Dec 2009;66(12):1322-30. doi:10.1001/archgenpsychiatry.2009.166
109. Sauer-Zavala S, Fournier JC, Jarvi Steele S, et al. Does the unified protocol really change neuroticism? Results from a randomized trial. *Psychol Med*. Oct 2021;51(14):2378-2387. doi:10.1017/s0033291720000975
110. Allan J, Leeson P, De Fruyt F, Martin S. Application of a 10 week coaching program designed to facilitate volitional personality change: Overall effects on personality and the impact of targeting. *International Journal of Evidence Based Coaching and Mentoring*. 2018;16(1):80-94.
111. Hudson NW, Briley DA, Chopik WJ, Derringer J. You have to follow through: Attaining behavioral change goals predicts volitional personality change. *J Pers Soc Psychol*. Oct 2019;117(4):839-857. doi:10.1037/pspp0000221
112. Stieger M, Flückiger C, Rüegger D, Kowatsch T, Roberts BW, Allemand M. Changing personality traits with the help of a digital personality change intervention. *Proceedings of the National Academy of Sciences*. 2021/02/23 2021;118(8):e2017548118. doi:10.1073/pnas.2017548118
113. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *Bmj*. Jul 26 2010;341:c3666. doi:10.1136/bmj.c3666
114. Luchetti M, Terracciano A, Stephan Y, Sutin AR. Personality and Cognitive Decline in Older Adults: Data From a Longitudinal Sample and Meta-Analysis. *The Journals of Gerontology: Series B*. 2016;71(4):591-601. doi:10.1093/geronb/gbu184
115. Chen YW, Canli T. "Nothing to see here": No structural brain differences as a function of the Big Five personality traits from a systematic review and meta-analysis. *Personal Neurosci*. 2022;5:e8. doi:10.1017/pen.2021.5
116. Terracciano A, Aschwanden D, Passamonti L, et al. Is neuroticism differentially associated with risk of Alzheimer's disease, vascular dementia, and frontotemporal dementia? *J Psychiatr Res*. Jun 2021;138:34-40. doi:10.1016/j.jpsychires.2021.03.039
117. Wilson RS, Barnes LL, Bennett DA, et al. Proneness to psychological distress and risk of Alzheimer disease in a biracial community. *Neurology*. Jan 25 2005;64(2):380-2. doi:10.1212/01.Wnl.0000149525.53525.E7
118. Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA. Chronic psychological distress and risk of Alzheimer's disease in old age. *Neuroepidemiology*. 2006;27(3):143-53. doi:10.1159/000095761

119. Wilson RS, Schneider JA, Arnold SE, Bienias JL, Bennett DA. Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. *Archives of general psychiatry*. 2007;64(10):1204-1212.
120. Duberstein PR, Chapman BP, Tindle HA, et al. Personality and risk for Alzheimer's disease in adults 72 years of age and older: a 6-year follow-up. *Psychol Aging*. Jun 2011;26(2):351-62. doi:10.1037/a0021377
121. Terracciano A, Sutin AR, An Y, et al. Personality and risk of Alzheimer's disease: New data and meta-analysis. *Alzheimer's & Dementia*. 2014/03/01 2014;10(2):179-186. doi:https://doi.org/10.1016/j.jalz.2013.03.002
122. Terracciano A, Stephan Y, Luchetti M, Albanese E, Sutin AR. Personality traits and risk of cognitive impairment and dementia. *J Psychiatr Res*. Jun 2017;89:22-27. doi:10.1016/j.jpsychires.2017.01.011
123. Duchek JM, Aschenbrenner AJ, Fagan AM, Benzinger TLS, Morris JC, Balota DA. The Relation Between Personality and Biomarkers in Sensitivity and Conversion to Alzheimer-Type Dementia. *J Int Neuropsychol Soc*. Jul 2020;26(6):596-606. doi:10.1017/s1355617719001358
124. Singh-Manoux A, Yerramalla MS, Sabia S, et al. Association of big-5 personality traits with cognitive impairment and dementia: a longitudinal study. *J Epidemiol Community Health*. Oct 2020;74(10):799-805. doi:10.1136/jech-2019-213014
125. Aschwanden D, Sutin AR, Luchetti M, Stephan Y, Terracciano A. Personality and Dementia Risk in England and Australia. *GeroPsych (Bern)*. Dec 2020;33(4):197-208. doi:10.1024/1662-9647/a000241
126. Wang HX, Karp A, Herlitz A, et al. Personality and lifestyle in relation to dementia incidence. *Neurology*. Jan 20 2009;72(3):253-9. doi:10.1212/01.wnl.0000339485.39246.87
127. Johansson L, Guo X, Duberstein PR, et al. Midlife personality and risk of Alzheimer disease and distress: a 38-year follow-up. *Neurology*. 2014;83(17):1538-1544.
128. Desai P, Beck T, Krueger KR, Wilson RS, Evans DA, Rajan KB. Neuroticism, physical activity, and cognitive functioning in a population-based cohort of older adults. *BMC Geriatr*. Nov 6 2023;23(1):717. doi:10.1186/s12877-023-04399-8
129. Hock RS, Lee HB, Bienvenu OJ, et al. Personality and cognitive decline in the Baltimore Epidemiologic Catchment Area follow-up study. *Am J Geriatr Psychiatry*. Sep 2014;22(9):917-25. doi:10.1016/j.jagp.2012.12.217
130. Wilson RS, Bennett DA, Mendes de Leon CF, Bienias JL, Morris MC, Evans DA. Distress proneness and cognitive decline in a population of older persons. *Psychoneuroendocrinology*. 2005/01/01/ 2005;30(1):11-17. doi:https://doi.org/10.1016/j.psyneuen.2004.04.005
131. Nishita Y, Tange C, Tomida M, Otsuka R, Ando F, Shimokata H. Personality and global cognitive decline in Japanese community-dwelling elderly people: A 10-year longitudinal study. *Journal of Psychosomatic Research*. 2016/12/01/ 2016;91:20-25. doi:https://doi.org/10.1016/j.jpsychores.2016.10.004
132. Iwasa H, Yoshida Y, Ishioka Y, Suzukamo Y. Association of Personality with Cognitive Failure among Japanese Middle-Aged and Older Adults. *Int J Environ Res Public Health*. Jun 12 2022;19(12)doi:10.3390/ijerph19127215
133. Foong HF, Hamid TA, Ibrahim R, Haron SA. Mediating role of neuroticism in the association between loneliness and cognitive function among community-dwelling older

adults. *Australasian Journal on Ageing*. 2018/12/01 2018;37(4):283-287. doi:https://doi.org/10.1111/ajag.12555
134. Sutin AR, Brown J, Luchetti M, Aschwanden D, Stephan Y, Terracciano A. Five-Factor Model Personality Traits and the Trajectory of Episodic Memory: Individual-Participant Meta-Analysis of 471,821 Memory Assessments from 120,640 Participants. *J Gerontol B Psychol Sci Soc Sci*. Mar 4 2023;78(3):421-433. doi:10.1093/geronb/gbac154
135. Bethell J, Andrew MK, Hothi S, et al. Does social connection mediate the association between neuroticism and cognition? Cross-sectional analysis of the Canadian Longitudinal Study on Aging. *Aging Ment Health*. Mar-Apr 2024;28(3):482-490. doi:10.1080/13607863.2023.2252369
136. Olaru G, Laukka EJ, Dekhtyar S, Sarwary A, Brehmer Y. Association between personality traits, leisure activities, and cognitive levels and decline across 12 years in older adults. *Psychol Aging*. Jun 2023;38(4):277-290. doi:10.1037/pag0000743
137. Terracciano A, Piras MR, Sutin AR, et al. Facets of Personality and Risk of Cognitive Impairment: Longitudinal Findings in a Rural Community from Sardinia. *J Alzheimers Dis*. 2022;88(4):1651-1661. doi:10.3233/jad-220400
138. Montoliu T, Pulopulos MM, Puig-Pérez S, Hidalgo V, Salvador A. Mediation of perceived stress and cortisol in the association between neuroticism and global cognition in older adults: A longitudinal study. *Stress and Health*. 2022/04/01 2022;38(2):290-303. doi:https://doi.org/10.1002/smi.3088
139. Crook Z, Booth T, Cox SR, et al. Apolipoprotein E genotype does not moderate the associations of depressive symptoms, neuroticism and allostatic load with cognitive ability and cognitive aging in the Lothian Birth Cohort 1936. *PLoS One*. 2018;13(2):e0192604. doi:10.1371/journal.pone.0192604
140. Dar-Nimrod I, Chapman BP, Robbins JA, Porsteinsson A, Mapstone M, Duberstein PR. Gene by neuroticism interaction and cognitive function among older adults. *International Journal of Geriatric Psychiatry*. 2012/11/01 2012;27(11):1147-1154. doi:https://doi.org/10.1002/gps.3759
141. Chapman B, Duberstein P, Tindle HA, et al. Personality predicts cognitive function over 7 years in older persons. *Am J Geriatr Psychiatry*. Jul 2012;20(7):612-21. doi:10.1097/JGP.0b013e31822cc9cb
142. Boyle LL, Lyness JM, Duberstein PR, et al. Trait Neuroticism, Depression, and Cognitive Function in Older Primary Care Patients. *The American Journal of Geriatric Psychiatry*. 2010/04/01/ 2010;18(4):305-312. doi:https://doi.org/10.1097/JGP.0b013e3181c2941b
143. Stephan Y, Sutin AR, Luchetti M, Aschwanden D, Cabibel V, Terracciano A. Measures of physical performance as mediators between personality and cognition in two prospective studies. *Arch Gerontol Geriatr*. Apr 2023;107:104902. doi:10.1016/j.archger.2022.104902
144. Stephan Y, Sutin AR, Luchetti M, Terracciano A. Personality and memory performance over twenty years: Findings from three prospective studies. *J Psychosom Res*. Jan 2020;128:109885. doi:10.1016/j.jpsychores.2019.109885
145. Klaming R, Veltman DJ, Comijs HC. The impact of personality on memory function in older adults—results from the Longitudinal Aging Study Amsterdam.

International Journal of Geriatric Psychiatry. 2017/07/01 2017;32(7):798-804. doi:https://doi.org/10.1002/gps.4527
146. Beaudreau SA, Gould CE, Hantke NC, et al. Insights about personality traits and cognitive performance and decline in adults 51–59 Years old from the Wisconsin longitudinal study. *International Journal of Geriatric Psychiatry*. 2023/01/01 2023;38(1):e5852. doi:https://doi.org/10.1002/gps.5852
147. Simon SS, Lee S, Stern Y. Personality-cognition associations across the adult life span and potential moderators: Results from two cohorts. *Journal of Personality*. 2020/10/01 2020;88(5):1025-1039. doi:https://doi.org/10.1111/jopy.12548
148. Wettstein M, Wahl HW, Siebert J, Schröder J. Still more to learn about late-life cognitive development: How personality and health predict 20-year cognitive trajectories. *Psychol Aging*. Aug 2019;34(5):714-728. doi:10.1037/pag0000374
149. Sutin AR, Stephan Y, Luchetti M, Terracciano A. Five-factor model personality traits and cognitive function in five domains in older adulthood. *BMC Geriatr*. Dec 5 2019;19(1):343. doi:10.1186/s12877-019-1362-1
150. Chapman BP, Benedict RH, Lin F, Roy S, Federoff HJ, Mapstone M. Personality and Performance in Specific Neurocognitive Domains Among Older Persons. *The American Journal of Geriatric Psychiatry*. 2017/08/01/ 2017;25(8):900-908. doi:https://doi.org/10.1016/j.jagp.2017.03.006
151. Wettstein M, Tauber B, Kuźma E, Wahl HW. The interplay between personality and cognitive ability across 12 years in middle and late adulthood: Evidence for reciprocal associations. *Psychol Aging*. May 2017;32(3):259-277. doi:10.1037/pag0000166
152. Caselli RJ, Dueck AC, Locke DEC, et al. Impact of Personality on Cognitive Aging: A Prospective Cohort Study. *Journal of the International Neuropsychological Society*. 2016;22(7):765-776. doi:10.1017/S1355617716000527
153. Sutin AR, Terracciano A, Kitner-Triolo MH, Uda M, Schlessinger D, Zonderman AB. Personality traits prospectively predict verbal fluency in a lifespan sample. *Psychol Aging*. Dec 2011;26(4):994-9. doi:10.1037/a0024276
154. Hagger-Johnson GE, Shickle DA, Roberts BA, Deary IJ. Neuroticism combined with slower and more variable reaction time: synergistic risk factors for 7-year cognitive decline in females. *J Gerontol B Psychol Sci Soc Sci*. Sep 2012;67(5):572-81. doi:10.1093/geronb/gbr151
155. Lewis GJ, Dickie DA, Cox SR, et al. Widespread associations between trait conscientiousness and thickness of brain cortical regions. *Neuroimage*. Aug 1 2018;176:22-28. doi:10.1016/j.neuroimage.2018.04.033
156. Li T, Yan X, Li Y, et al. Neuronal Correlates of Individual Differences in the Big Five Personality Traits: Evidences from Cortical Morphology and Functional Homogeneity. *Front Neurosci*. 2017;11:414. doi:10.3389/fnins.2017.00414
157. Kitamura S, Yasuno F, Yamamoto A, et al. A structural model of age, grey matter volumes, education, and personality traits. *Psychogeriatrics*. 2016/01/01 2016;16(1):46-53. doi:https://doi.org/10.1111/psyg.12118
158. Tuerk C, Zhang H, Sachdev P, et al. Regional Gray Matter Volumes Are Related to Concern About Falling in Older People: A Voxel-Based Morphometric Study. *The Journals of Gerontology: Series A*. 2016;71(1):138-144. doi:10.1093/gerona/glu242

159. Krishnadas R, Palaniyappan L, Lang J, McLean J, Cavanagh J. Psychoticism and salience network morphology. *Personality and Individual Differences*. 2014/01/01/ 2014;57:37-42. doi:https://doi.org/10.1016/j.paid.2013.09.016
160. Bjørnebekk A, Fjell AM, Walhovd KB, Grydeland H, Torgersen S, Westlye LT. Neuronal correlates of the five factor model (FFM) of human personality: Multimodal imaging in a large healthy sample. *Neuroimage*. Jan 15 2013;65:194-208. doi:10.1016/j.neuroimage.2012.10.009
161. Kapogiannis D, Sutin A, Davatzikos C, Costa P, Jr., Resnick S. The five factors of personality and regional cortical variability in the Baltimore longitudinal study of aging. *Hum Brain Mapp*. Nov 2013;34(11):2829-40. doi:10.1002/hbm.22108
162. Taki Y, Thyreau B, Kinomura S, et al. A longitudinal study of the relationship between personality traits and the annual rate of volume changes in regional gray matter in healthy adults. *Hum Brain Mapp*. Dec 2013;34(12):3347-53. doi:10.1002/hbm.22145
163. Cremers H, van Tol M-J, Roelofs K, et al. Extraversion Is Linked to Volume of the Orbitofrontal Cortex and Amygdala. *PLOS ONE*. 2011;6(12):e28421. doi:10.1371/journal.pone.0028421
164. Jackson J, Balota DA, Head D. Exploring the relationship between personality and regional brain volume in healthy aging. *Neurobiol Aging*. Dec 2011;32(12):2162-71. doi:10.1016/j.neurobiolaging.2009.12.009
165. Wright CI, Feczko E, Dickerson B, Williams D. Neuroanatomical correlates of personality in the elderly. *Neuroimage*. Mar 2007;35(1):263-72. doi:10.1016/j.neuroimage.2006.11.039
166. Knutson B, Momenan R, Rawlings RR, Fong GW, Hommer D. Negative association of neuroticism with brain volume ratio in healthy humans. *Biological Psychiatry*. 2001/11/01/ 2001;50(9):685-690. doi:https://doi.org/10.1016/S0006-3223(01)01220-3
167. Sweeney M, Tsapanou A, Stern Y. Regional cortical thickness and neuroticism across the lifespan. *Psychiatry Research: Neuroimaging*. 2019/04/30/ 2019;286:39-44. doi:https://doi.org/10.1016/j.pscychresns.2019.03.005
168. Booth T, Mõttus R, Corley J, et al. Personality, health, and brain integrity: the Lothian birth cohort study 1936. *Health Psychol*. Dec 2014;33(12):1477-86. doi:10.1037/hea0000012
169. Byun MS, Jung JH, Sohn BK, et al. Neuroticism, conscientiousness, and in vivo Alzheimer pathologies measured by amyloid PET and MRI. *Psychiatry and Clinical Neurosciences*. 2020/05/01 2020;74(5):303-310. doi:https://doi.org/10.1111/pcn.12983
170. Terracciano A, Cenatus B, Zhu X, et al. Neuroticism and white matter hyperintensities. *Journal of Psychiatric Research*. 2023/09/01/ 2023;165:174-179. doi:https://doi.org/10.1016/j.jpsychires.2023.07.026
171. Xu J, Potenza MN. White matter integrity and five-factor personality measures in healthy adults. *NeuroImage*. 2012/01/02/ 2012;59(1):800-807. doi:https://doi.org/10.1016/j.neuroimage.2011.07.040
172. McIntosh AM, Bastin ME, Luciano M, et al. Neuroticism, depressive symptoms and white-matter integrity in the Lothian Birth Cohort 1936. *Psychol Med*. Jun 2013;43(6):1197-206. doi:10.1017/s003329171200150x

173. Rodriguez C, Jagadish AK, Meskaldji DE, et al. Structural Correlates of Personality Dimensions in Healthy Aging and MCI. *Front Psychol*. 2018;9:2652. doi:10.3389/fpsyg.2018.02652
174. Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. *Am J Epidemiol*. Aug 1 2012;176(3):190-5. doi:10.1093/aje/kwr525
175. Tsoi KKF, Chan JYC, Hirai HW, Wong SYS, Kwok TCY. Cognitive Tests to Detect Dementia: A Systematic Review and Meta-analysis. *JAMA Internal Medicine*. 2015;175(9):1450-1458. doi:10.1001/jamainternmed.2015.2152
176. Wang X, Li F, Tian J, Gao Q, Zhu H. Bayesian estimation for the accuracy of three neuropsychological tests in detecting Alzheimer's disease and mild cognitive impairment: a retrospective analysis of the ADNI database. *European Journal of Medical Research*. 2023/10/12 2023;28(1):427. doi:10.1186/s40001-023-01265-6
177. Tromp D, Dufour A, Lithfous S, Pebayle T, Després O. Episodic memory in normal aging and Alzheimer disease: Insights from imaging and behavioral studies. *Ageing Research Reviews*. 2015/11/01/ 2015;24:232-262. doi:https://doi.org/10.1016/j.arr.2015.08.006
178. Josefsson M, Sundström A, Pudas S, Nordin Adolfsson A, Nyberg L, Adolfsson R. Memory profiles predict dementia over 23–28 years in normal but not successful aging. *International Psychogeriatrics*. 2023/07/01/ 2023;35(7):351-359. doi:https://doi.org/10.1017/S1041610219001844
179. Jack Jr CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's & Dementia*. 2024/08/01 2024;20(8):5143-5169. doi:https://doi.org/10.1002/alz.13859
180. Marek S, Tervo-Clemmens B, Calabro FJ, et al. Reproducible brain-wide association studies require thousands of individuals. *Nature*. Mar 2022;603(7902):654-660. doi:10.1038/s41586-022-04492-9
181. Vernooij MW, Ikram MA, Vrooman HA, et al. White Matter Microstructural Integrity and Cognitive Function in a General Elderly Population. *Archives of General Psychiatry*. 2009;66(5):545-553. doi:10.1001/archgenpsychiatry.2009.5
182. Baker E, Escott-Price V. Polygenic Risk Scores in Alzheimer's Disease: Current Applications and Future Directions. *Front Digit Health*. 2020;2:14. doi:10.3389/fdgth.2020.00014
183. Sauer-Zavala S, Wilner JG, Barlow DH. Addressing neuroticism in psychological treatment. *Personal Disord*. Jul 2017;8(3):191-198. doi:10.1037/per0000224
184. Navrady LB, Ritchie SJ, Chan SWY, et al. Intelligence and neuroticism in relation to depression and psychological distress: Evidence from two large population cohorts. *European Psychiatry*. 2017/06/01/ 2017;43:58-65. doi:https://doi.org/10.1016/j.eurpsy.2016.12.012
185. Weston SJ, Graham EK, Turiano NA, et al. Is Healthy Neuroticism Associated with Chronic Conditions? A Coordinated Integrative Data Analysis. *Collabra: Psychology*. 2020;6(1):42. doi:10.1525/collabra.267
186. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. Mar 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779

187. Littlejohns TJ, Holliday J, Gibson LM, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nature Communications*. 2020/05/26 2020;11(1):2624. doi:10.1038/s41467-020-15948-9
188. Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. *PLoS One*. 2020;15(4):e0231627. doi:10.1371/journal.pone.0231627
189. Gow AJ, Whiteman MC, Pattie A, Deary IJ. Goldberg's 'IPIP' Big-Five factor markers: Internal consistency and concurrent validation in Scotland. *Personality and Individual Differences*. 2005/07/01/ 2005;39(2):317-329. doi:https://doi.org/10.1016/j.paid.2005.01.011
190. Bowden SC, Saklofske DH, van de Vijver FJR, Sudarshan NJ, Eysenck SBG. Cross-cultural measurement invariance of the Eysenck Personality Questionnaire across 33 countries. *Personality and Individual Differences*. 2016/12/01/ 2016;103:53-60. doi:https://doi.org/10.1016/j.paid.2016.04.028
191. Mackinnon A, Jorm AF, Christensen H, Scott LR, Henderson AS, Korten AE. A latent trait analysis of the eysenck personality questionnaire in an elderly community sample. *Personality and Individual Differences*. 1995/06/01/ 1995;18(6):739-747. doi:https://doi.org/10.1016/0191-8869(95)00011-T
192. Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008-2016. *Alzheimers Dement*. Jul 2018;14(7):933-943. doi:10.1016/j.jalz.2018.02.012
193. UK Biobank Outcome Adjudication group. UK Biobank Algorithmically-defined outcomes (ADOs). Updated January 2022. Accessed February 6, 2023. https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/alg_outcome_main.pdf
194. Licher S, Darweesh SKL, Wolters FJ, et al. Lifetime risk of common neurological diseases in the elderly population. *Journal of Neurology, Neurosurgery & Psychiatry*. 2019;90(2):148. doi:10.1136/jnnp-2018-318650
195. Gong J, Harris K, Lipnicki DM, et al. Sex differences in dementia risk and risk factors: Individual-participant data analysis using 21 cohorts across six continents from the COSMIC consortium. *Alzheimer's & Dementia*. 2023/08/01 2023;19(8):3365-3378. doi:https://doi.org/10.1002/alz.12962
196. Donnellan MB, Lucas RE. Age differences in the Big Five across the life span: evidence from two national samples. *Psychol Aging*. Sep 2008;23(3):558-66. doi:10.1037/a0012897
197. Ormel J, Bastiaansen A, Riese H, et al. The biological and psychological basis of neuroticism: current status and future directions. *Neurosci Biobehav Rev*. Jan 2013;37(1):59-72. doi:10.1016/j.neubiorev.2012.09.004
198. Branigan AR, McCallum KJ, Freese J. Variation in the Heritability of Educational Attainment: An International Meta-Analysis. *Social Forces*. 2013;92(1):109-140. doi:10.1093/sf/sot076
199. Terracciano A, Costa PT, Jr. Smoking and the Five-Factor Model of personality. *Addiction*. Apr 2004;99(4):472-81. doi:10.1111/j.1360-0443.2004.00687.x

200. Luchetti M, Sutin AR, Delitala A, et al. Personality traits and facets linked with self-reported alcohol consumption and biomarkers of liver health. *Addict Behav*. Jul 2018;82:135-141. doi:10.1016/j.addbeh.2018.02.034
201. Sutin AR, Terracciano A. Personality traits and body mass index: Modifiers and mechanisms. *Psychol Health*. 2016;31(3):259-75. doi:10.1080/08870446.2015.1082561
202. Foster HME, Celis-Morales CA, Nicholl BI, et al. The effect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. *The Lancet Public Health*. 2018;3(12):e576-e585. doi:10.1016/S2468-2667(18)30200-7
203. Townsend P, Phillimore P, Beattie A. *Health and deprivation: inequality and the North*. Routledge; 1988.
204. Antal B, McMahon LP, Sultan SF, et al. Type 2 diabetes mellitus accelerates brain aging and cognitive decline: Complementary findings from UK Biobank and meta-analyses. *Elife*. May 24 2022;11doi:10.7554/eLife.73138
205. Lee JJ, Wedow R, Okbay A, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet*. Jul 23 2018;50(8):1112-1121. doi:10.1038/s41588-018-0147-3
206. Carter AR, Gill D, Davies NM, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. *BMJ*. 2019;365:l1855. doi:10.1136/bmj.l1855
207. World Health Organization. A healthy lifestyle - WHO recommendations. Updated May 2010. Accessed February 6, 2023. https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations
208. Ikram MA, Bersano A, Manso-Calderón R, et al. Genetics of vascular dementia – review from the ICVD working group. *BMC Medicine*. 2017/03/06 2017;15(1):48. doi:10.1186/s12916-017-0813-9
209. Patel B, Markus HS. Magnetic Resonance Imaging in Cerebral Small Vessel Disease and its Use as a Surrogate Disease Marker. *International Journal of Stroke*. 2011/02/01 2011;6(1):47-59. doi:10.1111/j.1747-4949.2010.00552.x
210. Iadecola C. The Pathobiology of Vascular Dementia. *Neuron*. 2013/11/20/ 2013;80(4):844-866. doi:https://doi.org/10.1016/j.neuron.2013.10.008
211. Hu H-Y, Ou Y-N, Shen X-N, et al. White matter hyperintensities and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 36 prospective studies. *Neuroscience & Biobehavioral Reviews*. 2021/01/01/ 2021;120:16-27. doi:https://doi.org/10.1016/j.neubiorev.2020.11.007
212. Smith SM, Douaud G, Chen W, et al. An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nat Neurosci*. May 2021;24(5):737-745. doi:10.1038/s41593-021-00826-4
213. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. Springer International Publishing; 2015.
214. White IR, Royston P. Imputing missing covariate values for the Cox model. *Statistics in medicine*. 2009;28(15):1982-1998.
215. Eekhout I, de Vet HCW, Twisk JWR, Brand JPL, de Boer MR, Heymans MW. Missing data in a multi-item instrument were best handled by multiple imputation at the

item score level. *Journal of Clinical Epidemiology*. 2014/03/01/ 2014;67(3):335-342. doi:https://doi.org/10.1016/j.jclinepi.2013.09.009
216. Rubin DB. *Multiple imputation for nonresponse in surveys*. vol 81. John Wiley & Sons; 2004.
217. Ebenau JL, van der Lee SJ, Hulsman M, et al. Risk of dementia in APOE ε4 carriers is mitigated by a polygenic risk score. *Alzheimers Dement (Amst)*. 2021;13(1):e12229. doi:10.1002/dad2.12229
218. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *International journal of epidemiology*. 2015;44(2):512-525.
219. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genetic epidemiology*. 2016;40(4):304-314.
220. Mounier N, Kutalik Z. Bias correction for inverse variance weighting Mendelian randomization. *Genet Epidemiol*. Jun 2023;47(4):314-331. doi:10.1002/gepi.22522
221. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLOS Genetics*. 2017;13(11):e1007081. doi:10.1371/journal.pgen.1007081
222. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife*. May 30 2018;7doi:10.7554/eLife.34408
223. Dar-Nimrod I, Chapman BP, Franks P, et al. Personality factors moderate the associations between apolipoprotein genotype and cognitive function as well as late onset Alzheimer disease. *Am J Geriatr Psychiatry*. Dec 2012;20(12):1026-35. doi:10.1097/JGP.0b013e318267016b
224. Batty GD, Catharine RG, Mika K, Ian JD, Steven B. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ*. 2020;368:m131. doi:10.1136/bmj.m131
225. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *American Journal of Epidemiology*. 2017;186(9):1026-1034. doi:10.1093/aje/kwx246
226. Lyall DM, Quinn T, Lyall LM, et al. Quantifying bias in psychological and physical health in the UK Biobank imaging sub-sample. *Brain Communications*. 2022;4(3):fcac119. doi:10.1093/braincomms/fcac119
227. Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol*. Jun 2019;34(6):557-565. doi:10.1007/s10654-019-00499-1
228. Polsinelli AJ, Logan PE, Lane KA, et al. APOE ε4 carrier status and sex differentiate rates of cognitive decline in early- and late-onset Alzheimer's disease. *Alzheimers Dement*. May 2023;19(5):1983-1993. doi:10.1002/alz.12831
229. Hayat SA, Luben R, Khaw KT, Brayne C. The Relationship Between Cognitive Performance Using Tests Assessing a Range of Cognitive Domains and Future Dementia Diagnosis in a British Cohort: A Ten-Year Prospective Study. *J Alzheimers Dis*. 2021;81(1):123-135. doi:10.3233/jad-210030

230. Hayat SA, Luben R, Dalzell N, et al. Cross Sectional Associations between Socio-Demographic Factors and Cognitive Performance in an Older British Population: The European Investigation of Cancer in Norfolk (EPIC-Norfolk) Study. *PLoS One*. 2016;11(12):e0166779. doi:10.1371/journal.pone.0166779
231. Day N, Oakes S, Luben R, et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer*. Jul 1999;80 Suppl 1:95-103.
232. Khaw K-T, Wareham N, Bingham S, Welch A, Luben R, Day N. Combined Impact of Health Behaviours and Mortality in Men and Women: The EPIC-Norfolk Prospective Population Study. *PLOS Medicine*. 2008;5(1):e12. doi:10.1371/journal.pmed.0050012
233. Surtees PG, Wainwright NW, Khaw KT, Day NE. Functional health status, chronic medical conditions and disorders of mood. *Br J Psychiatry*. Oct 2003;183:299-303. doi:10.1192/bjp.183.4.299
234. Hayat SA, Luben R, Keevil VL, et al. Cohort Profile: A prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3). *International Journal of Epidemiology*. 2014;43(4):1063-1072. doi:10.1093/ije/dyt086
235. Hayat S, Luben R, Khaw KT, Wareham N, Brayne C. Evaluation of routinely collected records for dementia outcomes in UK: a prospective cohort study. *BMJ Open*. Jun 15 2022;12(6):e060931. doi:10.1136/bmjopen-2022-060931
236. Jellinger KA, Attems J. Prevalence and Pathology of Vascular Dementia in the Oldest-Old1. *Journal of Alzheimer's Disease*. 2010/01/01 2010;21(4):1283-1293. doi:10.3233/JAD-2010-100603
237. Wilson RS, Krueger KR, Gu L, Bienias JL, Mendes de Leon CF, Evans DA. Neuroticism, extraversion, and mortality in a defined population of older persons. *Psychosom Med*. Nov-Dec 2005;67(6):841-5. doi:10.1097/01.psy.0000190615.20656.83
238. Shipley BA, Weiss A, Der G, Taylor MD, Deary IJ. Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: a 21-year prospective cohort study. *Psychosom Med*. Dec 2007;69(9):923-31. doi:10.1097/PSY.0b013e31815abf83
239. Chapman BP, Huang A, Peters K, et al. Association Between High School Personality Phenotype and Dementia 54 Years Later in Results From a National US Sample. *JAMA Psychiatry*. 2020;77(2):148-154. doi:10.1001/jamapsychiatry.2019.3120
240. Graham EK, Rutsohn JP, Turiano NA, et al. Personality predicts mortality risk: An integrative data analysis of 15 international longitudinal studies. *Journal of Research in Personality*. 2017/10/01/ 2017;70:174-186. doi:https://doi.org/10.1016/j.jrp.2017.07.005
241. Zaninotto P, Batty GD, Allerhand M, Deary IJ. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *J Epidemiol Community Health*. Aug 2018;72(8):685-694. doi:10.1136/jech-2017-210116
242. Mukadam N, Marston L, Lewis G, Mathur R, Rait G, Livingston G. Incidence, age at diagnosis and survival with dementia across ethnic groups in England: A longitudinal study using electronic health records. *Alzheimer's & Dementia*. 2023/04/01 2023;19(4):1300-1307. doi:https://doi.org/10.1002/alz.12774

243. Wishart DS. Metabolomics for Investigating Physiological and Pathophysiological Processes. *Physiological Reviews*. 2019/10/01 2019;99(4):1819-1875. doi:10.1152/physrev.00035.2018
244. Wright AJ, Weston SJ, Norton S, et al. Prospective self-and informant-personality associations with inflammation, health behaviors, and health indicators. *Health Psychology*. 2022;41(2):121.
245. Kim HN, Yun Y, Ryu S, et al. Correlation between gut microbiota and personality in adults: A cross-sectional study. *Brain Behav Immun*. Mar 2018;69:374-385. doi:10.1016/j.bbi.2017.12.012
246. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. Aug 11 2012;380(9841):581-90. doi:10.1016/s0140-6736(12)60367-5
247. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ*. 2016;355:i5953. doi:10.1136/bmj.i5953
248. Khan SU, Lone AN, Khan MS, et al. Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis. *eClinicalMedicine*. 2021;38doi:10.1016/j.eclinm.2021.100997
249. Qureshi D, Collister J, Allen NE, Kuźma E, Littlejohns T. Association between metabolic syndrome and risk of incident dementia in UK Biobank. *Alzheimer's & Dementia*. 2024/01/01 2024;20(1):447-458. doi:https://doi.org/10.1002/alz.13439
250. Phillips AC, Batty GD, Weiss A, et al. Neuroticism, cognitive ability, and the metabolic syndrome: The Vietnam Experience Study. *J Psychosom Res*. Aug 2010;69(2):193-201. doi:10.1016/j.jpsychores.2010.01.016
251. Sutin AR, Terracciano A, Deiana B, et al. Cholesterol, triglycerides, and the Five-Factor Model of personality. *Biol Psychol*. May 2010;84(2):186-91. doi:10.1016/j.biopsycho.2010.01.012
252. van Reedt Dortland AKB, Giltay EJ, van Veen T, Zitman FG, Penninx BWJH. Personality traits and childhood trauma as correlates of metabolic risk factors: The Netherlands Study of Depression and Anxiety (NESDA). *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2012/01/10/ 2012;36(1):85-91. doi:https://doi.org/10.1016/j.pnpbp.2011.10.001
253. Roh SJ, Kim HN, Shim U, et al. Association between blood lipid levels and personality traits in young Korean women. *PLoS One*. 2014;9(9):e108406. doi:10.1371/journal.pone.0108406
254. Armon G. Personality and Serum Lipids: Does Lifestyle Account for Their Concurrent and Long-term Relationships. *European Journal of Personality*. 2014/11/01 2014;28(6):550-559. doi:https://doi.org/10.1002/per.1943
255. Sutin AR, Stephan Y, Terracciano A. Personality and metabolic dysfunction in young adulthood: A cross-sectional study. *J Health Psychol*. Mar 2019;24(4):495-501. doi:10.1177/1359105316677294
256. Tanios V, Terracciano A, Luchetti M, Stephan Y, Sutin AR. Personality traits at age 16 and risk of metabolic syndrome at age 46. *J Psychosom Res*. Apr 2022;155:110744. doi:10.1016/j.jpsychores.2022.110744

257. Conklin SM, Manuck SB, Yao JK, Flory JD, Hibbeln JR, Muldoon MF. High omega-6 and low omega-3 fatty acids are associated with depressive symptoms and neuroticism. *Psychosom Med*. Dec 2007;69(9):932-4. doi:10.1097/PSY.0b013e31815aaa42
258. Thesing CS, Bot M, Milaneschi Y, Giltay EJ, Penninx BWJH. The association of omega-3 fatty acid levels with personality and cognitive reactivity. *Journal of Psychosomatic Research*. 2018/05/01/ 2018;108:93-101. doi:https://doi.org/10.1016/j.jpsychores.2018.02.016
259. Nightingale Health. Nightingale Health Metabolic Biomarkers Companion document. Accessed October 1, 2023. https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/NMR_companion_phase2.pdf
260. Elliott P, Peakman TC. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol*. Apr 2008;37(2):234-44. doi:10.1093/ije/dym276
261. Julkunen H, Cichońska A, Tiainen M, et al. Atlas of plasma NMR biomarkers for health and disease in 118,461 individuals from the UK Biobank. *Nature Communications*. 2023/02/03 2023;14(1):604. doi:10.1038/s41467-023-36231-7
262. Amin N, Liu J, Bonnechere B, et al. Interplay of Metabolome and Gut Microbiome in Individuals With Major Depressive Disorder vs Control Individuals. *JAMA Psychiatry*. Jun 1 2023;80(6):597-609. doi:10.1001/jamapsychiatry.2023.0685
263. Borges MC, Haycock PC, Zheng J, et al. Role of circulating polyunsaturated fatty acids on cardiovascular diseases risk: analysis using Mendelian randomization and fatty acid genetic association data from over 114,000 UK Biobank participants. *BMC Medicine*. 2022/06/13 2022;20(1):210. doi:10.1186/s12916-022-02399-w
264. Fiehn O. Metabolomics by Gas Chromatography-Mass Spectrometry: Combined Targeted and Untargeted Profiling. *Curr Protoc Mol Biol*. Apr 1 2016;114:30.4.1-30.4.32. doi:10.1002/0471142727.mb3004s114
265. Thomas A, Baillet M, Proust-Lima C, et al. Blood polyunsaturated omega-3 fatty acids, brain atrophy, cognitive decline, and dementia risk. *Alzheimer's & Dementia*. 2021/03/01 2021;17(3):407-416. doi:https://doi.org/10.1002/alz.12195
266. de Oliveira Otto MC, Wu JHY, Thacker EL, et al. Circulating Omega-3 and Omega-6 Fatty Acids, Cognitive Decline, and Dementia in Older Adults. *J Alzheimers Dis*. 2023;95(3):965-979. doi:10.3233/jad-230083
267. Samieri C, Féart C, Letenneur L, et al. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk1. *The American Journal of Clinical Nutrition*. 2008/09/01/ 2008;88(3):714-721. doi:https://doi.org/10.1093/ajcn/88.3.714
268. Belayev L, Hong SH, Menghani H, et al. Docosanoids Promote Neurogenesis and Angiogenesis, Blood-Brain Barrier Integrity, Penumbra Protection, and Neurobehavioral Recovery After Experimental Ischemic Stroke. *Mol Neurobiol*. Aug 2018;55(8):7090-7106. doi:10.1007/s12035-018-1136-3
269. Liu ZH, Chen NY, Tu PH, et al. DHA Attenuates Cerebral Edema Following Traumatic Brain Injury via the Reduction in Blood-Brain Barrier Permeability. *Int J Mol Sci*. Aug 31 2020;21(17)doi:10.3390/ijms21176291
270. Schwarz C, Wirth M, Gerischer L, et al. Effects of Omega-3 Fatty Acids on Resting Cerebral Perfusion in Patients with Mild Cognitive Impairment: A Randomized Controlled

Trial. *The Journal of Prevention of Alzheimer's Disease*. 2018/01/01 2018;5(1):26-30. doi:10.14283/jpad.2017.23
271. Tan ZS, Harris WS, Beiser AS, et al. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. *Neurology*. 2012/02/28 2012;78(9):658-664. doi:10.1212/WNL.0b013e318249f6a9
272. Rouch L, Virecoulon Giudici K, Cantet C, et al. Associations of erythrocyte omega-3 fatty acids with cognition, brain imaging and biomarkers in the Alzheimer's disease neuroimaging initiative: cross-sectional and longitudinal retrospective analyses. *The American Journal of Clinical Nutrition*. 2022/12/01/ 2022;116(6):1492-1506. doi:https://doi.org/10.1093/ajcn/nqac236
273. Schmitz G, Ecker J. The opposing effects of n−3 and n−6 fatty acids. *Progress in Lipid Research*. 2008/03/01/ 2008;47(2):147-155. doi:https://doi.org/10.1016/j.plipres.2007.12.004
274. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics*. Nov 1 2015;31(21):3555-7. doi:10.1093/bioinformatics/btv402
275. Messamore E, Almeida DM, Jandacek RJ, McNamara RK. Polyunsaturated fatty acids and recurrent mood disorders: Phenomenology, mechanisms, and clinical application. *Progress in Lipid Research*. 2017/04/01/ 2017;66:1-13. doi:https://doi.org/10.1016/j.plipres.2017.01.001
276. Reynolds LM, Howard TD, Ruczinski I, et al. Tissue-specific impact of FADS cluster variants on FADS1 and FADS2 gene expression. *PLoS One*. 2018;13(3):e0194610. doi:10.1371/journal.pone.0194610
277. Gilchrist L, Mutz J, Hysi P, et al. Evaluating metabolome-wide causal effects on risk for psychiatric and neurodegenerative disorders. *BMC Medicine*. 2025/06/02 2025;23(1):326. doi:10.1186/s12916-025-04129-4
278. Davyson E, Shen X, Gadd DA, et al. Metabolomic Investigation of Major Depressive Disorder Identifies a Potentially Causal Association With Polyunsaturated Fatty Acids. *Biol Psychiatry*. Oct 15 2023;94(8):630-639. doi:10.1016/j.biopsych.2023.01.027
279. Shadrin AA, Kaufmann T, van der Meer D, et al. Vertex-wise multivariate genome-wide association study identifies 780 unique genetic loci associated with cortical morphology. *NeuroImage*. 2021/12/01/ 2021;244:118603. doi:https://doi.org/10.1016/j.neuroimage.2021.118603
280. van der Meer D, Frei O, Kaufmann T, et al. Understanding the genetic determinants of the brain with MOSTest. *Nature Communications*. 2020/07/14 2020;11(1):3512. doi:10.1038/s41467-020-17368-1
281. Loef M, Walach H. The Omega-6/Omega-3 Ratio and Dementia or Cognitive Decline: A Systematic Review on Human Studies and Biological Evidence. *Journal of Nutrition in Gerontology and Geriatrics*. 2013/01/01 2013;32(1):1-23. doi:10.1080/21551197.2012.752335
282. Wei B-Z, Li L, Dong C-W, Tan C-C, Xu W. The Relationship of Omega-3 Fatty Acids with Dementia and Cognitive Decline: Evidence from Prospective Cohort Studies of Supplementation, Dietary Intake, and Blood Markers. *The American Journal of Clinical Nutrition*. 2023/06/01/ 2023;117(6):1096-1109. doi:https://doi.org/10.1016/j.ajcnut.2023.04.001

283. Andruchow ND, Konishi K, Shatenstein B, Bohbot VD. A lower ratio of omega-6 to omega-3 fatty acids predicts better hippocampus-dependent spatial memory and cognitive status in older adults. *Neuropsychology*. Oct 2017;31(7):724-734. doi:10.1037/neu0000373
284. Tynkkynen J, Chouraki V, van der Lee SJ, et al. Association of branched-chain amino acids and other circulating metabolites with risk of incident dementia and Alzheimer's disease: A prospective study in eight cohorts. *Alzheimers Dement*. Jun 2018;14(6):723-733. doi:10.1016/j.jalz.2018.01.003
285. Phillips MC. New insights into the determination of HDL structure by apolipoproteins1: Thematic Review Series: High Density Lipoprotein Structure, Function, and Metabolism. *Journal of Lipid Research*. 2013/08/01/ 2013;54(8):2034-2048. doi:https://doi.org/10.1194/jlr.R034025
286. Kjeldsen EW, Nordestgaard LT, Frikke-Schmidt R. HDL Cholesterol and Non-Cardiovascular Disease: A Narrative Review. *International Journal of Molecular Sciences*. 2021;22(9). doi:10.3390/ijms22094547
287. Jin Y, Chifodya K, Han G, et al. High-density lipoprotein in Alzheimer's disease: From potential biomarkers to therapeutics. *Journal of Controlled Release*. 2021/10/10/ 2021;338:56-70. doi:https://doi.org/10.1016/j.jconrel.2021.08.018
288. Martinez AE, Weissberger G, Kuklenyik Z, et al. The small HDL particle hypothesis of Alzheimer's disease. *Alzheimer's & Dementia*. 2023/02/01 2023;19(2):391-404. doi:https://doi.org/10.1002/alz.12649
289. Zhang X, Hu W, Wang Y, et al. Plasma metabolomic profiles of dementia: a prospective study of 110,655 participants in the UK Biobank. *BMC Medicine*. 2022/08/15 2022;20(1):252. doi:10.1186/s12916-022-02449-3
290. Harshfield EL, Markus HS. Association of Baseline Metabolomic Profiles With Incident Stroke and Dementia and With Imaging Markers of Cerebral Small Vessel Disease. *Neurology*. 2023/08/01 2023;101(5):e489-e501. doi:10.1212/WNL.0000000000207458
291. Lepara O, Valjevac A, Alajbegović A, Zaćiragić A, Nakas-Ićindić E. Decreased serum lipids in patients with probable Alzheimer's disease. *Bosn J Basic Med Sci*. Aug 2009;9(3):215-20. doi:10.17305/bjbms.2009.2809
292. Kivimäki M, Luukkonen R, Batty GD, et al. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement*. May 2018;14(5):601-609. doi:10.1016/j.jalz.2017.09.016
293. Jin D, Trichia E, Islam N, Bešević J, Lewington S, Lacey B. Lipoprotein Characteristics and Incident Coronary Heart Disease: Prospective Cohort of Nearly 90 000 Individuals in UK Biobank. *Journal of the American Heart Association*. 2023/10/17 2023;12(20):e029552. doi:10.1161/JAHA.123.029552
294. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. Aug 16 2014;384(9943):626-635. doi:10.1016/s0140-6736(14)61177-6
295. Ryals J, Lawton K, Stevens D, Milburn M. Metabolon, Inc. *Pharmacogenomics*. 2007/07/01 2007;8(7):863-866. doi:10.2217/14622416.8.7.863
296. Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. *Int J Epidemiol*. Feb 2012;41(1):161-76. doi:10.1093/ije/dyr233

297. Carter AR, Sanderson E, Hammerton G, et al. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. *Eur J Epidemiol*. May 2021;36(5):465-478. doi:10.1007/s10654-021-00757-1
298. Beck ED, Yoneda T, James BD, et al. Personality predictors of dementia diagnosis and neuropathological burden: An individual participant data meta-analysis. *Alzheimers Dement*. Mar 2024;20(3):1497-1514. doi:10.1002/alz.13523
299. DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR. Testing predictions from personality neuroscience. Brain structure and the big five. *Psychol Sci*. Jun 2010;21(6):820-8. doi:10.1177/0956797610370159
300. Lu F, Huo Y, Li M, et al. Relationship between Personality and Gray Matter Volume in Healthy Young Adults: A Voxel-Based Morphometric Study. *PLOS ONE*. 2014;9(2):e88763. doi:10.1371/journal.pone.0088763
301. Owens MM, Hyatt CS, Gray JC, et al. Cortical morphometry of the five-factor model of personality: findings from the Human Connectome Project full sample. *Soc Cogn Affect Neurosci*. May 17 2019;14(4):381-395. doi:10.1093/scan/nsz017
302. Power MC, Tingle JV, Reid RI, et al. Midlife and Late-Life Vascular Risk Factors and White Matter Microstructural Integrity: The Atherosclerosis Risk in Communities Neurocognitive Study. *J Am Heart Assoc*. May 18 2017;6(5)doi:10.1161/jaha.117.005608
303. Avinun R, Israel S, Knodt AR, Hariri AR. Little evidence for associations between the Big Five personality traits and variability in brain gray or white matter. *Neuroimage*. Oct 15 2020;220:117092. doi:10.1016/j.neuroimage.2020.117092
304. Delaparte L, Bartlett E, Grazioplene R, et al. Structural correlates of the orbitofrontal cortex and amygdala and personality in female adolescents. *Psychophysiology*. Aug 2019;56(8):e13376. doi:10.1111/psyp.13376
305. Kharabian Masouleh S, Eickhoff SB, Hoffstaedter F, Genon S, Alzheimer's Disease Neuroimaging I. Empirical examination of the replicability of associations between brain structure and psychological variables. *eLife*. 2019/03/13 2019;8:e43464. doi:10.7554/eLife.43464
306. Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed*. Aug 2010;23(7):803-20. doi:10.1002/nbm.1543
307. Nestor SM, Rupsingh R, Borrie M, et al. Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain*. Sep 2008;131(Pt 9):2443-54. doi:10.1093/brain/awn146
308. Guo CC, Tan R, Hodges JR, Hu X, Sami S, Hornberger M. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. *Brain*. 2016;139(5):1527-1538. doi:10.1093/brain/aww003
309. Miller KL, Alfaro-Almagro F, Bangerter NK, et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nat Neurosci*. Nov 2016;19(11):1523-1536. doi:10.1038/nn.4393
310. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. Jan 2001;20(1):45-57. doi:10.1109/42.906424

311. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage*. Jun 1 2011;56(3):907-22. doi:10.1016/j.neuroimage.2011.02.046
312. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage*. Jul 16 2012;61(4):1000-16. doi:10.1016/j.neuroimage.2012.03.072
313. Alfaro-Almagro F, McCarthy P, Afyouni S, et al. Confound modelling in UK Biobank brain imaging. *Neuroimage*. Jan 1 2021;224:117002. doi:10.1016/j.neuroimage.2020.117002
314. Kosuke I, Luke K, Teppei Y. Identification, Inference and Sensitivity Analysis for Causal Mediation Effects. *Statistical Science*. 2/1 2010;25(1):51-71. doi:10.1214/10-STS321
315. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. 2014;
316. Hiser J, Koenigs M. The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. *Biol Psychiatry*. Apr 15 2018;83(8):638-647. doi:10.1016/j.biopsych.2017.10.030
317. Apps MA, Rushworth MF, Chang SW. The Anterior Cingulate Gyrus and Social Cognition: Tracking the Motivation of Others. *Neuron*. May 18 2016;90(4):692-707. doi:10.1016/j.neuron.2016.04.018
318. Wong S, Flanagan E, Savage G, Hodges JR, Hornberger M. Contrasting prefrontal cortex contributions to episodic memory dysfunction in behavioural variant frontotemporal dementia and Alzheimer's disease. *PLoS One*. 2014;9(2):e87778. doi:10.1371/journal.pone.0087778
319. Nieuwenhuis ILC, Takashima A. The role of the ventromedial prefrontal cortex in memory consolidation. *Behavioural Brain Research*. 2011/04/15/ 2011;218(2):325-334. doi:https://doi.org/10.1016/j.bbr.2010.12.009
320. Echávarri C, Aalten P, Uylings HB, et al. Atrophy in the parahippocampal gyrus as an early biomarker of Alzheimer's disease. *Brain Struct Funct*. Jan 2011;215(3-4):265-71. doi:10.1007/s00429-010-0283-8
321. Krumm S, Kivisaari SL, Probst A, et al. Cortical thinning of parahippocampal subregions in very early Alzheimer's disease. *Neurobiology of Aging*. 2016/02/01/ 2016;38:188-196. doi:https://doi.org/10.1016/j.neurobiolaging.2015.11.001
322. Storsve AB, Fjell AM, Tamnes CK, et al. Differential Longitudinal Changes in Cortical Thickness, Surface Area and Volume across the Adult Life Span: Regions of Accelerating and Decelerating Change. *The Journal of Neuroscience*. 2014;34(25):8488. doi:10.1523/JNEUROSCI.0391-14.2014
323. Ahmad F, Javed M, Athar M, Shahzadi S. Determination of affected brain regions at various stages of Alzheimer's disease. *Neurosci Res*. Jul 2023;192:77-82. doi:10.1016/j.neures.2023.01.010
324. Hartikainen P, Räsänen J, Julkunen V, et al. Cortical thickness in frontotemporal dementia, mild cognitive impairment, and Alzheimer's disease. *J Alzheimers Dis*. 2012;30(4):857-74. doi:10.3233/jad-2012-112060

325. Bauer E, Toepper M, Gebhardt H, Gallhofer B, Sammer G. The significance of caudate volume for age-related associative memory decline. *Brain Research*. 2015/10/05/ 2015;1622:137-148. doi:https://doi.org/10.1016/j.brainres.2015.06.026
326. Grazioplene RG, S GR, Gray JR, Rustichini A, Jung RE, DeYoung CG. Subcortical intelligence: caudate volume predicts IQ in healthy adults. *Hum Brain Mapp*. Apr 2015;36(4):1407-16. doi:10.1002/hbm.22710
327. van der Velpen IF, Vlasov V, Evans TE, et al. Subcortical brain structures and the risk of dementia in the Rotterdam Study. *Alzheimers Dement*. Feb 2023;19(2):646-657. doi:10.1002/alz.12690
328. de Jong LW, van der Hiele K, Veer IM, et al. Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. *Brain*. Dec 2008;131(Pt 12):3277-85. doi:10.1093/brain/awn278
329. Habes M, Erus G, Toledo JB, et al. Regional tract-specific white matter hyperintensities are associated with patterns of aging-related brain atrophy via vascular risk factors, but also independently. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2018/01/01/ 2018;10:278-284. doi:https://doi.org/10.1016/j.dadm.2018.02.002
330. Bendlin BB, Ries ML, Canu E, et al. White matter is altered with parental family history of Alzheimer's disease. *Alzheimer's & Dementia*. 2010/09/01 2010;6(5):394-403. doi:https://doi.org/10.1016/j.jalz.2009.11.003
331. Mayo CD, Mazerolle EL, Ritchie L, Fisk JD, Gawryluk JR. Longitudinal changes in microstructural white matter metrics in Alzheimer's disease. *Neuroimage Clin*. 2017;13:330-338. doi:10.1016/j.nicl.2016.12.012
332. Mielke MM, Leoutsakos JM, Corcoran CD, et al. Effects of Food and Drug Administration-approved medications for Alzheimer's disease on clinical progression. *Alzheimers Dement*. May 2012;8(3):180-7. doi:10.1016/j.jalz.2011.02.011
333. Ringman JM, O'Neill J, Geschwind D, et al. Diffusion tensor imaging in preclinical and presymptomatic carriers of familial Alzheimer's disease mutations. *Brain*. Jul 2007;130(Pt 7):1767-76. doi:10.1093/brain/awm102
334. Schumacher J, Ray NJ, Hamilton CA, et al. Cholinergic white matter pathways in dementia with Lewy bodies and Alzheimer's disease. *Brain*. Jun 3 2022;145(5):1773-1784. doi:10.1093/brain/awab372
335. Sun X, Salat D, Upchurch K, Deason R, Kowall N, Budson A. Destruction of white matter integrity in patients with mild cognitive impairment and Alzheimer disease. *J Investig Med*. Oct 2014;62(7):927-33. doi:10.1097/jim.0000000000000102
336. Yin R-H, Tan L, Liu Y, et al. Multimodal Voxel-Based Meta-Analysis of White Matter Abnormalities in Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2015;47:495-507. doi:10.3233/JAD-150139
337. Yu J, Lam CLM, Lee TMC. White matter microstructural abnormalities in amnestic mild cognitive impairment: A meta-analysis of whole-brain and ROI-based studies. *Neuroscience & Biobehavioral Reviews*. 2017/12/01/ 2017;83:405-416. doi:https://doi.org/10.1016/j.neubiorev.2017.10.026
338. Baggeroer CE, Cambronero FE, Savan NA, Jefferson AL, Santisteban MM. Basic Mechanisms of Brain Injury and Cognitive Decline in Hypertension. *Hypertension*. 2024/01/01 2024;81(1):34-44. doi:10.1161/HYPERTENSIONAHA.123.19939

339. Heneka MT, Carson MJ, Khoury JE, et al. Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*. 2015/04/01/ 2015;14(4):388-405. doi:https://doi.org/10.1016/S1474-4422(15)70016-5
340. Rao JS, Kellom M, Kim HW, Rapoport SI, Reese EA. Neuroinflammation and synaptic loss. *Neurochem Res*. May 2012;37(5):903-10. doi:10.1007/s11064-012-0708-2
341. Shen X, Howard DM, Adams MJ, et al. A phenome-wide association and Mendelian Randomisation study of polygenic risk for depression in UK Biobank. *Nature Communications*. 2020/05/08 2020;11(1):2301. doi:10.1038/s41467-020-16022-0
342. Flinkenflügel K, Meinert S, Hirtsiefer C, et al. Associations between white matter microstructure and cognitive decline in major depressive disorder versus controls in Germany: a prospective case-control cohort study. *Lancet Psychiatry*. Nov 2024;11(11):899-909. doi:10.1016/s2215-0366(24)00291-8
343. Pariante CM. Risk factors for development of depression and psychosis. Glucocorticoid receptors and pituitary implications for treatment with antidepressant and glucocorticoids. *Ann N Y Acad Sci*. Oct 2009;1179:144-52. doi:10.1111/j.1749-6632.2009.04978.x
344. Jauregui-Huerta F, Ruvalcaba-Delgadillo Y, Gonzalez-Castañeda R, Garcia-Estrada J, Gonzalez-Perez O, Luquin S. Responses of glial cells to stress and glucocorticoids. *Curr Immunol Rev*. Aug 1 2010;6(3):195-204. doi:10.2174/157339510791823790
345. Yoneda T, Rush J, Berg AI, Johansson B, Piccinin AM. Trajectories of Personality Traits Preceding Dementia Diagnosis. *The Journals of Gerontology: Series B*. 2017;72(6):922-931. doi:10.1093/geronb/gbw006
346. Yoneda T, Rush J, Graham EK, et al. Increases in Neuroticism May Be an Early Indicator of Dementia: A Coordinated Analysis. *J Gerontol B Psychol Sci Soc Sci*. Jan 14 2020;75(2):251-262. doi:10.1093/geronb/gby034
347. Terracciano A, An Y, Sutin AR, Thambisetty M, Resnick SM. Personality Change in the Preclinical Phase of Alzheimer Disease. *JAMA Psychiatry*. 2017;74(12):1259-1265. doi:10.1001/jamapsychiatry.2017.2816
348. Calvin CM, Conroy MC, Moore SF, Kuźma E, Littlejohns TJ. Association of Multimorbidity, Disease Clusters, and Modification by Genetic Factors With Risk of Dementia. *JAMA Network Open*. 2022;5(9):e2232124-e2232124. doi:10.1001/jamanetworkopen.2022.32124
349. Grande G, Marengoni A, Vetrano DL, et al. Multimorbidity burden and dementia risk in older adults: The role of inflammation and genetics. *Alzheimer's & Dementia*. 2021/05/01 2021;17(5):768-776. doi:https://doi.org/10.1002/alz.12237
350. Littlejohns TJ, Collister JA, Liu X, Clifton L, Tapela NM, Hunter DJ. Hypertension, a dementia polygenic risk score, APOE genotype, and incident dementia. *Alzheimer's & Dementia*. 2023/02/01 2023;19(2):467-476. doi:https://doi.org/10.1002/alz.12680
351. VandeBunte AM, Ortiz BL, Paolillo EW, et al. Relationships between blood pressure indicators and fluid biomarkers of brain aging in functionally intact older adults. *Alzheimer's Research & Therapy*. 2025/04/21 2025;17(1):85. doi:10.1186/s13195-025-01731-9
352. Ye S, Roccati E, Wang W, et al. Leading determinants of incident dementia among individuals with and without the apolipoprotein E ε4 genotype: a retrospective cohort study. *BMC Neurology*. 2024/02/20 2024;24(1):71. doi:10.1186/s12883-024-03557-8

353. Yang LG, March ZM, Stephenson RA, Narayan PS. Apolipoprotein E in lipid metabolism and neurodegenerative disease. *Trends in Endocrinology & Metabolism*. 2023/08/01/ 2023;34(8):430-445. doi:https://doi.org/10.1016/j.tem.2023.05.002
354. Luc G, Bard JM, Arveiler D, et al. Impact of apolipoprotein E polymorphism on lipoproteins and risk of myocardial infarction. The ECTIM Study. *Arterioscler Thromb*. Sep 1994;14(9):1412-9. doi:10.1161/01.atv.14.9.1412
355. Schaefer EJ, Lamon-Fava S, Johnson S, et al. Effects of gender and menopausal status on the association of apolipoprotein E phenotype with plasma lipoprotein levels. Results from the Framingham Offspring Study. *Arterioscler Thromb*. Jul 1994;14(7):1105-13. doi:10.1161/01.atv.14.7.1105
356. Muros M, Rodríguez-Ferrer C. Apolipoprotein E polymorphism influence on lipids, apolipoproteins and Lp(a) in a Spanish population underexpressing apo E4. *Atherosclerosis*. Mar 1996;121(1):13-21. doi:10.1016/0021-9150(95)06643-8
357. Frikke-Schmidt R, Nordestgaard BG, Agerholm-Larsen B, Schnohr P, Tybjaerg-Hansen A. Context-dependent and invariant associations between lipids, lipoproteins, and apolipoproteins and apolipoprotein E genotype. *J Lipid Res*. Nov 2000;41(11):1812-22.
358. Leon AS, Togashi K, Rankinen T, et al. Association of apolipoprotein E polymorphism with blood lipids and maximal oxygen uptake in the sedentary state and after exercise training in the HERITAGE family study. *Metabolism*. Jan 2004;53(1):108-16. doi:10.1016/j.metabol.2003.08.013
359. Niu W, Qi Y, Qian Y, Gao P, Zhu D. The relationship between apolipoprotein E ε2/ε3/ε4 polymorphisms and hypertension: a meta-analysis of six studies comprising 1812 cases and 1762 controls. *Hypertension Research*. 2009/12/01 2009;32(12):1060-1066. doi:10.1038/hr.2009.164
360. Li M, Zhao JV, Kwok MK, Schooling CM. Age and sex specific effects of APOE genotypes on ischemic heart disease and its risk factors in the UK Biobank. *Scientific Reports*. 2021/04/29 2021;11(1):9229. doi:10.1038/s41598-021-88256-x
361. Wakita H, Tomimoto H, Akiguchi I, et al. Axonal damage and demyelination in the white matter after chronic cerebral hypoperfusion in the rat. *Brain Research*. 2002/01/04/ 2002;924(1):63-70. doi:https://doi.org/10.1016/S0006-8993(01)03223-1
362. Shibata M, Ohtani R, Ihara M, Tomimoto H. White matter lesions and glial activation in a novel mouse model of chronic cerebral hypoperfusion. *Stroke*. Nov 2004;35(11):2598-603. doi:10.1161/01.Str.0000143725.19053.60
363. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*. 2013/09/01 2013;18(9):963-974. doi:10.1038/mp.2013.20
364. Luo J, Zhang B, Cao M, Roberts BW. The Stressful Personality: A Meta-Analytical Review of the Relation Between Personality and Stress. *Personality and Social Psychology Review*. 2023/05/01 2022;27(2):128-194. doi:10.1177/10888683221104002
365. Rohleder N. Stress and inflammation – The need to address the gap in the transition between acute and chronic stress effects. *Psychoneuroendocrinology*. 2019/07/01/ 2019;105:164-171. doi:https://doi.org/10.1016/j.psyneuen.2019.02.021
366. Rosmond R, Björntorp P. The hypothalamic–pituitary–adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. *Journal of Internal*

Medicine. 2000/02/01 2000;247(2):188-197. doi:https://doi.org/10.1046/j.1365-2796.2000.00603.x
367. Glass CK, Olefsky JM. Inflammation and lipid signaling in the etiology of insulin resistance. *Cell Metab*. May 2 2012;15(5):635-45. doi:10.1016/j.cmet.2012.04.001
368. Hakulinen C, Hintsanen M, Munafò MR, et al. Personality and smoking: individual-participant meta-analysis of nine cohort studies. *Addiction*. Nov 2015;110(11):1844-52. doi:10.1111/add.13079
369. Sutin AR, Stephan Y, Luchetti M, Artese A, Oshio A, Terracciano A. The Five-Factor Model of Personality and Physical Inactivity: A Meta-Analysis of 16 Samples. *J Res Pers*. Aug 2016;63:22-28. doi:10.1016/j.jrp.2016.05.001
370. Colussi G, Catena C, Novello M, Bertin N, Sechi LA. Impact of omega-3 polyunsaturated fatty acids on vascular function and blood pressure: Relevance for cardiovascular outcomes. *Nutr Metab Cardiovasc Dis*. Mar 2017;27(3):191-200. doi:10.1016/j.numecd.2016.07.011
371. Poudyal H, Panchal SK, Diwan V, Brown L. Omega-3 fatty acids and metabolic syndrome: effects and emerging mechanisms of action. *Prog Lipid Res*. Oct 2011;50(4):372-87. doi:10.1016/j.plipres.2011.06.003
372. Roberts BW, Luo J, Briley DA, Chow PI, Su R, Hill PL. A systematic review of personality trait change through intervention. *Psychological bulletin*. 2017;143(2):117-141. doi:10.1037/bul0000088
373. Armstrong L, Rimes KA. Mindfulness-Based Cognitive Therapy for Neuroticism (Stress Vulnerability): A Pilot Randomized Study. *Behav Ther*. May 2016;47(3):287-98. doi:10.1016/j.beth.2015.12.005
374. Hanley AW, de Vibe M, Solhaug I, Gonzalez-Pons K, Garland EL. Mindfulness training reduces neuroticism over a 6-year longitudinal randomized control trial in Norwegian medical and psychology students. *Journal of Research in Personality*. 2019/10/01/ 2019;82:103859. doi:https://doi.org/10.1016/j.jrp.2019.103859
375. Williamson JD, Pajewski NM, Auchus AP, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *Jama*. Feb 12 2019;321(6):553-561. doi:10.1001/jama.2018.21442
376. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *The Lancet*. 2015/06/06/ 2015;385(9984):2255-2263. doi:https://doi.org/10.1016/S0140-6736(15)60461-5
377. Baker LD, Espeland MA, Whitmer RA, et al. Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function: The US POINTER Randomized Clinical Trial. *JAMA*. 2025;doi:10.1001/jama.2025.12923
378. Brown A, Kirichek O, Balkwill A, et al. Comparison of dementia recorded in routinely collected hospital admission data in England with dementia recorded in primary care. *Emerg Themes Epidemiol*. 2016;13:11. doi:10.1186/s12982-016-0053-z
379. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement*. Jan 2017;13(1):28-37. doi:10.1016/j.jalz.2016.04.002

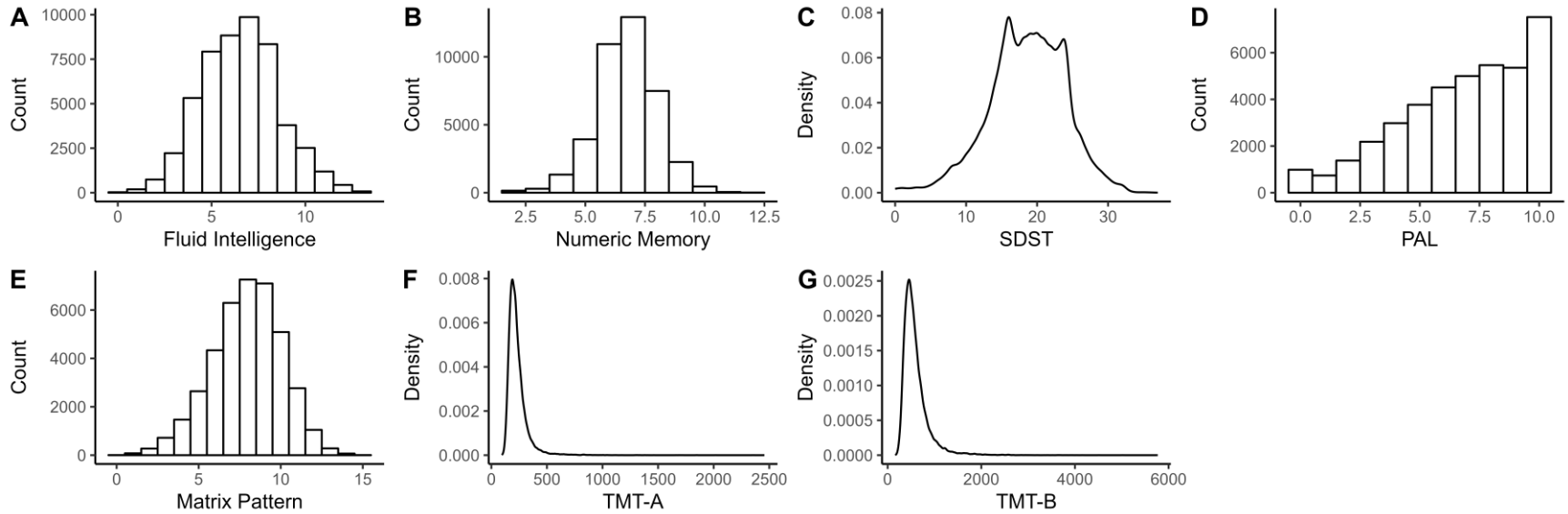
380. Neuropathology Group from Medical Research Council Cognitive Function and Aging Study. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet*. Jan 20 2001;357(9251):169-75. doi:10.1016/s0140-6736(00)03589-3
381. Huque H, Eramudugolla R, Chidiac B, et al. Could Country-Level Factors Explain Sex Differences in Dementia Incidence and Prevalence? A Systematic Review and Meta-Analysis. *J Alzheimers Dis*. 2023;91(4):1231-1241. doi:10.3233/jad-220724
382. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry*. 2022/02/01/ 2022;9(2):137-150. doi:https://doi.org/10.1016/S2215-0366(21)00395-3
383. Badawy Y, Spector A, Li Z, Desai R. The risk of depression in the menopausal stages: A systematic review and meta-analysis. *Journal of Affective Disorders*. 2024/07/15/ 2024;357:126-133. doi:https://doi.org/10.1016/j.jad.2024.04.041
384. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. *Circulation*. 2020/12/22 2020;142(25):e506-e532. doi:10.1161/CIR.0000000000000912
385. Altmann A, Tian L, Henderson VW, Greicius MD, Alzheimer's Disease Neuroimaging Initiative I. Sex modifies the APOE-related risk of developing Alzheimer disease. *Annals of Neurology*. 2014/04/01 2014;75(4):563-573. doi:https://doi.org/10.1002/ana.24135
386. Wretlind A, Xu J, Chen W, et al. Lipid profiling reveals unsaturated lipid reduction in women with Alzheimer's disease. *Alzheimers Dement*. Aug 2025;21(8):e70512. doi:10.1002/alz.70512
387. Siti Maisarah M, Devi M, Andrea Mary M, et al. The economic burden of dementia in low- and middle-income countries (LMICs): a systematic review. *BMJ Global Health*. 2022;7(4):e007409. doi:10.1136/bmjgh-2021-007409
388. Trnka R, Cabelkova I. Neuroticism across cultures: Macro-level insights into the worldwide distribution of neuroticism. *Neuroticism: Characteristics, impact on job performance, and health outcomes*. 2016:161-185.
389. Langa KM, Ryan LH, McCammon RJ, et al. The Health and Retirement Study Harmonized Cognitive Assessment Protocol Project: Study Design and Methods. *Neuroepidemiology*. 2020;54(1):64-74. doi:10.1159/000503004
390. Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA. Early-versus late-onset Alzheimer's disease: more than age alone. *J Alzheimers Dis*. 2010;19(4):1401-8. doi:10.3233/jad-2010-1337
391. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. *J Nutr Sci*. 2018;7:e6. doi:10.1017/jns.2017.66
392. Bingham SA, Gill C, Welch A, et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol*. 1997;26 Suppl 1:S137-51. doi:10.1093/ije/26.suppl_1.s137

393. Zheng J, Zhang Y, Rasheed H, et al. Trans-ethnic Mendelian-randomization study reveals causal relationships between cardiometabolic factors and chronic kidney disease. *International Journal of Epidemiology*. 2021;50(6):1995-2010. doi:10.1093/ije/dyab203

Appendices

Chapter 3

Appendix 3.1: Raw and transformed distributions of cognitive outcomes in UK Biobank



SDST, Symbol Digit Substitution Test; PAL, Paired Associate Learning; TMT-A/B, Trail Making Test A and B

Appendix 3.2: Baseline characteristics of participants by all-cause dementia case status

Characteristic	No dementia	Dementia
N	168190	5974
Age (mean (SD))	64.30 (2.95)	66.01 (2.82)
Female (%)	87488 (52.0)	2827 (47.3)
Townsend deprivation index quintile		
1 (Least deprived)	37017 (22.0)	1181 (19.8)
2	37005 (22.0)	1192 (20.0)
3	35121 (20.9)	1135 (19.0)
4	31685 (18.8)	1156 (19.4)
5 (Most deprived)	27362 (16.3)	1310 (21.9)
Education (%)		
Primary	42586 (25.3)	2155 (36.1)
Secondary	34973 (20.8)	1155 (19.3)
Post-secondary non-tertiary	23607 (14.0)	722 (12.1)
Tertiary	67024 (39.9)	1942 (32.5)
Ethnic group - White (%)	164207 (97.6)	5804 (97.2)
BMI (%)		
Normal (<25 kg/m^2)	50072 (29.8)	1786 (29.9)
Overweight (≥25–<30 kg/m^2)	76288 (45.4)	2595 (43.4)
Obese (≥30 kg/m^2)	41830 (24.9)	1593 (26.7)
Drinking ≤4 times weekly (%)	127499 (75.8)	4725 (79.1)
Smoking status (%)		
Never	83932 (49.9)	2723 (45.6)
Previous	70420 (41.9)	2698 (45.2)
Current	13838 (8.2)	553 (9.3)
APOE genotypes (%)		
APOE ε2 carriers	21816 (13.0)	420 (7.0)
APOE ε3/ε3 carriers	98085 (58.3)	2283 (38.2)
APOE ε4 carriers	40718 (24.2)	2965 (49.6)
Missing/Ambiguous genotypes[a]	7571 (4.5)	306 (5.1)
Non-*APOE* PRS (%)		
Low (lowest quintile)	27264 (16.2)	732 (12.3)
Intermediate (quintiles 2 to 4)	81983 (48.7)	2812 (47.1)
High (highest quintile)	27286 (16.2)	1273 (21.3)
Missing	31657 (18.8)	1157 (19.4)
Medical history (%)		
Depression	8248 (4.9)	496 (8.3)
Anxiety and stress disorder	2643 (1.6)	157 (2.6)
Hypertension	61527 (36.6)	2811 (47.1)
Ischaemic heart disease	14227 (8.5)	949 (15.9)
Diabetes	11250 (6.7)	833 (13.9)

N, number of participants; SD, standard deviation; BMI, body mass index; PRS, polygenic risk score.
[a] *APOE* ε1/ε3 and *APOE* ε2/ε4 genotypes.

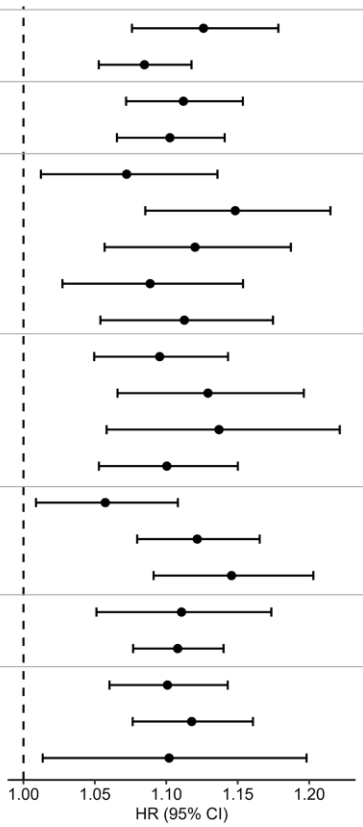
Appendix 3.3: Sensitivity analyses for the association between neuroticism z-score and incident dementia

Approach	HR (95% CI)		
	All-cause dementia	**AD**	**VaD**
Multiple imputation	1.12 (1.10 to 1.15)	1.07 (1.03 to 1.11)	1.16 (1.10 to 1.22)
Unrestricted baseline age	1.10 (1.08 to 1.13)	1.05 (1.01 to 1.08)	1.16 (1.11 to 1.22)

HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia. Sensitivity analyses include: multiple imputation of missing neuroticism scores and covariates using chained equations, with estimates pooled across five imputed datasets; and repeating the analysis without restricting baseline age. Hazard ratios represent the adjusted association per 1-SD increase in neuroticism score, and were derived from Cox proportional hazards models adjusted for age, sex, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index.

Appendix 3.4: Subgroup analyses for the association between neuroticism z-score and incident dementia

Subgroup		Cases / population	HR (95% CI)	*p* for interaction
Age	<65	1775 / 93861	1.13 (1.08 to 1.18)	0.219
	≥65	4199 / 80303	1.08 (1.05 to 1.12)	
Sex	Female	2827 / 90315	1.11 (1.07 to 1.15)	0.875
	Male	3147 / 83849	1.10 (1.07 to 1.14)	
TDI quintile	1 (Least deprived)	1181 / 38198	1.07 (1.01 to 1.14)	0.802
	2	1192 / 38197	1.15 (1.09 to 1.21)	
	3	1135 / 36256	1.12 (1.06 to 1.19)	
	4	1156 / 32841	1.09 (1.03 to 1.15)	
	5 (Most deprived)	1310 / 28672	1.11 (1.05 to 1.17)	
Education	Primary	2155 / 44741	1.10 (1.05 to 1.14)	0.666
	Secondary	1155 / 36128	1.13 (1.07 to 1.20)	
	Post-secondary non-tertiary	722 / 24329	1.14 (1.06 to 1.22)	
	Tertiary	1942 / 68966	1.10 (1.05 to 1.15)	
BMI	Normal	1786 / 51858	1.06 (1.01 to 1.11)	0.065
	Overweight	2595 / 78883	1.12 (1.08 to 1.17)	
	Obese	1593 / 43423	1.15 (1.09 to 1.20)	
Alcohol	Daily or almost daily	1249 / 41940	1.11 (1.05 to 1.17)	0.960
	≤4 times / week	4725 / 132224	1.11 (1.08 to 1.14)	
Smoking	Never	2723 / 86655	1.10 (1.06 to 1.14)	0.911
	Previous	2698 / 73118	1.12 (1.08 to 1.16)	
	Current	553 / 14391	1.10 (1.01 to 1.20)	



HR, hazard ratio; CI, confidence interval; TDI, Townsend deprivation index; BMI, body mass index. Models were adjusted for age, sex, education, TDI (quintiles), smoking status, alcohol consumption, and BMI, with follow-up time as the underlying timescale. Hazard ratios represent the adjusted association per 1-SD increase in neuroticism score within each subgroup. P-values correspond to Wald tests of interaction assessing heterogeneity in associations across subgroups. The dashed vertical line marks the reference HR of 1.0.

Appendix 3.5: Estimated direct and indirect effect sizes of neuroticism z-score with dementia through prevalent diseases at baseline

Mediator	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)	% Mediated
All-cause dementia				
Depression	1.11 (1.08 to 1.14)	1.07 (1.04 to 1.10)	1.04 (1.02 to 1.06)	38.5%
Anxiety and stress-related disorders	1.11 (1.08 to 1.14)	1.10 (1.07 to 1.13)	1.01 (1.00 to 1.03)	12.8%
Ischaemic heart disease	1.11 (1.08 to 1.14)	1.10 (1.07 to 1.13)	1.01 (1.00 to 1.02)	10.9%
Hypertension	1.11 (1.08 to 1.14)	1.10 (1.07 to 1.13)	1.01 (1.00 to 1.02)	10.4%
Diabetes	1.11 (1.08 to 1.14)	1.10 (1.08 to 1.13)	1.01 (1.00 to 1.02)	6.0%
AD				
Depression	1.05 (1.01 to 1.10)	1.03 (0.98 to 1.07)	1.03 (1.01 to 1.05)	51.0%
Anxiety and stress-related disorders	1.06 (1.01 to 1.10)	1.04 (1.00 to 1.09)	1.01 (0.99 to 1.03)	NA
Ischaemic heart disease	1.05 (1.01 to 1.10)	1.05 (1.01 to 1.09)	1.00 (0.99 to 1.02)	NA
Hypertension	1.05 (1.01 to 1.10)	1.05 (1.01 to 1.09)	1.00 (0.99 to 1.02)	NA
Diabetes	1.05 (1.01 to 1.10)	1.06 (1.02 to 1.10)	1.00 (0.98 to 1.01)	NA
VaD				
Depression	1.15 (1.09 to 1.22)	1.09 (1.03 to 1.16)	1.06 (1.02 to 1.09)	37.5%
Anxiety and stress-related disorders	1.16 (1.10 to 1.23)	1.14 (1.08 to 1.20)	1.02 (0.99 to 1.04)	NA
Ischaemic heart disease	1.15 (1.09 to 1.22)	1.13 (1.07 to 1.19)	1.02 (1.00 to 1.04)	13.8%
Hypertension	1.15 (1.09 to 1.22)	1.12 (1.07 to 1.18)	1.02 (1.00 to 1.05)	16.3%
Diabetes	1.15 (1.08 to 1.21)	1.13 (1.08 to 1.20)	1.01 (0.99 to 1.03)	NA

CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia. Estimates are adjusted for age, sex, ethnicity, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index. Total, direct, and indirect effects represent hazard ratios per 1-SD increase in neuroticism, estimated using the counterfactual framework and marginal structural models. The proportion mediated was calculated as the natural indirect effect divided by the total effect. In cases where the indirect effect was statistically insignificant, the corresponding proportion mediated was not calculated and is indicated as ‘NA’ (not applicable) in the table.

Appendix 3.6: Characteristics of the participants included in the cognitive function analyses

Characteristic	Overall	Neuroticism score tertile		
		1 (score 0–1)	2 (score 2–4)	3 (score 5–12)
N	39459	14382	12621	12456
Age [a] (mean (SD))	64.79 (7.75)	65.80 (7.61)	65.01 (7.66)	63.39 (7.77)
Female (%)	19761 (50.1)	8586 (59.7)	6006 (47.6)	5169 (41.5)
Townsend deprivation index quintile (%)				
1 (Least deprived)	9551 (24.2)	3620 (25.2)	3090 (24.5)	2841 (22.8)
2	9061 (23.0)	3324 (23.1)	2949 (23.4)	2788 (22.4)
3	8219 (20.8)	3007 (20.9)	2625 (20.8)	2587 (20.8)
4	7331 (18.6)	2623 (18.2)	2292 (18.2)	2416 (19.4)
5 (Most deprived)	5297 (13.4)	1808 (12.6)	1665 (13.2)	1824 (14.6)
Education[a] (%)				
Primary	2486 (6.3)	876 (6.1)	756 (6.0)	854 (6.9)
Secondary	7402 (18.8)	2387 (16.6)	2295 (18.2)	2720 (21.8)
Post-secondary non-tertiary	4414 (11.2)	1620 (11.3)	1492 (11.8)	1302 (10.5)
Tertiary	25157 (63.8)	9499 (66.0)	8078 (64.0)	7580 (60.9)
Ethnic group - White (%)	38376 (97.3)	13931 (96.9)	12294 (97.4)	12151 (97.6)
BMI[a] (%)				
Normal	16582 (42.0)	5782 (40.2)	5518 (43.7)	5282 (42.4)
Overweight	14862 (37.7)	5786 (40.2)	4666 (37.0)	4410 (35.4)
Obese	8015 (20.3)	2814 (19.6)	2437 (19.3)	2764 (22.2)
Drinking ≤4 times weekly[a] (%)	32683 (82.8)	11811 (82.1)	10498 (83.2)	10374 (83.3)
Smoking status[a] (%)				
Never	24613 (62.4)	9204 (64.0)	7879 (62.4)	7530 (60.5)
Previous	13504 (34.2)	4735 (32.9)	4318 (34.2)	4451 (35.7)
Current	1342 (3.4)	443 (3.1)	424 (3.4)	475 (3.8)

N, number of participants; SD, Standard deviation; BMI, body mass index.
[a] Measured at the imaging assessment.

Appendix 3.7: Summary of genetic instruments for phenotypes used in Mendelian Randomisation analyses

Phenotype	GWAS source	GWAS dataset	GWAS sample size	N_{snp}	R^2
Neuroticism	Nagel et al., 2018	UKB, GPC	390,278	91	0.010
AD	Kunkle et al., 2019	IGAP	21,982 cases and 41,944 controls	19	0.062
WMH	Smith et al., 2021	UKB	21,381	15	0.037

GWAS, genome-wide association studies; UKB, UK Biobank; GPC, Genetics of Personality Consortium; AD, Alzheimer's disease; IGAP, International Genomics of Alzheimer's Project; WMH, white matter hyperintensities; SNP, single nucleotide polymorphism; N_{SNP}, number of genetic variants used as instrumental variables; R^2, proportion of variance explained.

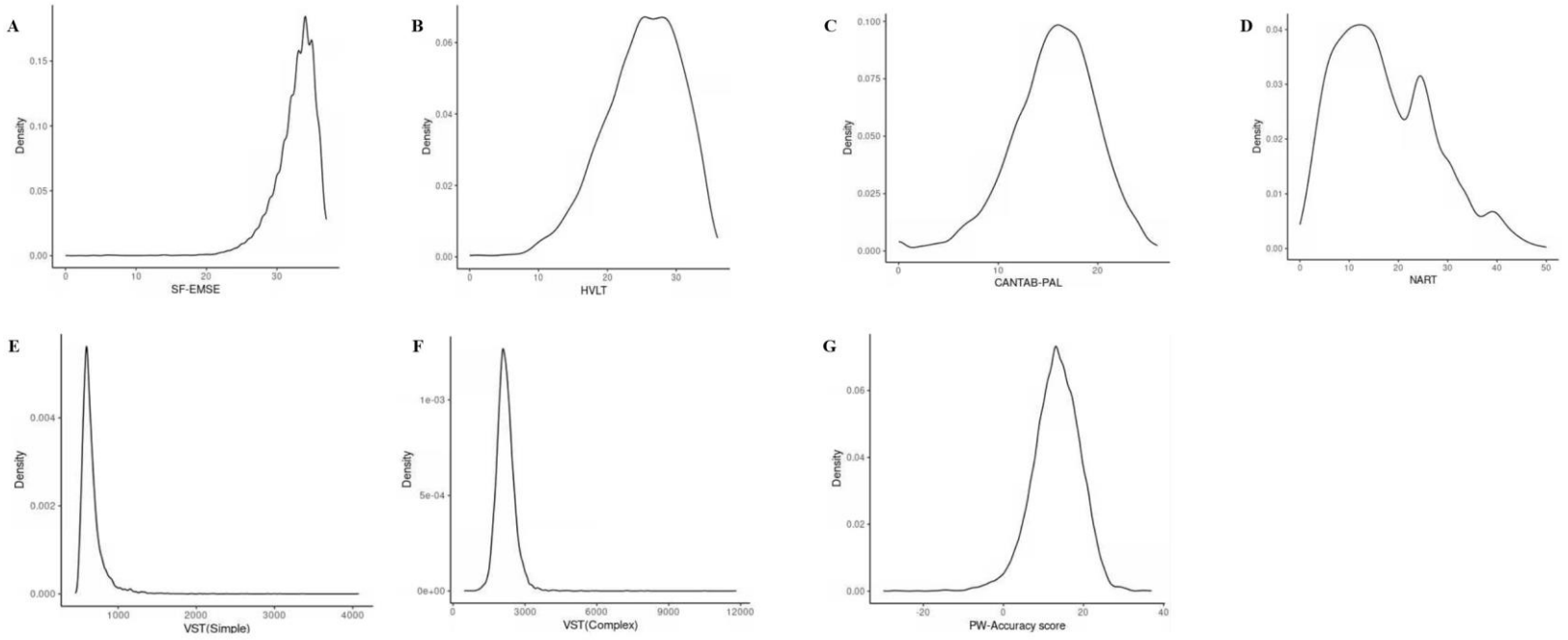
Appendix 3.8: Sensitivity analyses for bidirectional Mendelian randomisation

Exposure	Outcome	N_{snp}	p for Q (IVW)	p for Q (MR-Egger)	p for Egger intercept	R^2 exposure	R^2 outcome	p for Steiger
Neuroticism	AD	75	0.025	0.040	0.079	0.008	0.002	<0.001
AD	Neuroticism	15	<0.001	<0.001	0.774	0.034	<0.001	<0.001
Neuroticism	WMH	79	0.109	0.085	0.112	0.009	0.005	<0.001
WMH	Neuroticism	11	0.007	0.009	0.565	0.028	<0.001	<0.001

OR, odds ratio; CI, confidence interval; AD, Alzheimer's disease; WMH, white matter hyperintensities; IVW, inverse-variance weighted; N_{snp}, number of single nucleotide polymorphisms used as genetic instruments; Q, Cochran's Q-statistic for heterogeneity; R^2, proportion of variance explained; Steiger, Steiger directionality test. p for Q and p for Q (MR-Egger) assess heterogeneity across genetic instruments. p for Egger intercept tests for directional horizontal pleiotropy. R^2 exposure and R^2 outcome indicate the proportion of variance explained by the genetic instruments for the exposure and outcome, respectively. p for Steiger tests whether the genetic variants explain more variance in the exposure than in the outcome, supporting correct direction.

Chapter 4

Appendix 4.1: Distribution of cognitive test scores



Panels A–G display the distribution of raw scores for each cognitive test across participants included in the analysis: (A) Short Form of the Extended Mental State Examination (SF-EMSE), (B) Hopkins Verbal Learning Test (HVLT), (C) Cambridge Neuropsychological Test Automated Battery - Paired Associates Learning (CANTAB-PAL), (D) National Adult Reading Test (NART), (E, F) Verbal Similarities Test (VST), and (G) Paired Words Accuracy (PW-Accuracy).

Appendix 4.2: Sensitivity analyses for the association between neuroticism z-score and incident dementia

Approach	HR (95% CI)		
	All-cause dementia	**AD**	**VaD**
Multiple imputation	1.14 (1.10 to 1.19)	1.15 (1.08 to 1.23)	1.16 (1.07 to 1.26)
Fine-Gray subdistribution model [a]	1.08 (1.04 to 1.12)	1.09 (1.03 to 1.16)	1.08 (1.00 to 1.17)

HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia. The multiple imputation approach addresses missing exposure and covariate data, with estimates pooled across imputed datasets. The Fine-Gray subdistribution hazard model accounts for the competing risk of non-dementia death, given the older age structure and long follow-up in EPIC-Norfolk. Estimates are adjusted for age, sex, education, Townsend deprivation index (quintiles), smoking status, alcohol consumption, and body mass index.

[a] Fine-Gray subdistribution model was fitted in R using the crr function in the cmprsk package.

Appendix 4.3: Characteristics of participants included in the analyses of cognitive outcomes

Characteristic	Overall	Neuroticism score tertile		
		1 (score 0–1)	2 (score 2–4)	3 (score 5–12)
N	7446	2531	2470	2445
Age (mean [SD])	68.20 (8.05)	69.41 (8.05)	68.43 (7.98)	66.73 (7.89)
Female (%)	4112 (55.2)	1095 (43.3)	1416 (57.3)	1601 (65.5)
Townsend deprivation index quintile (%)				
1 (Least deprived)	1860 (25.0)	645 (25.5)	628 (25.4)	587 (24.0)
2	1573 (21.1)	561 (22.2)	495 (20.0)	517 (20.1)
3	1478 (19.8)	514 (20.3)	488 (19.8)	476 (19.5)
4	1284 (17.2)	388 (15.3)	459 (18.6)	437 (17.9)
5 (Most deprived)	1232 (16.5)	417 (16.5)	394 (16.0)	421 (17.2)
Missing	19 (0.3)	6 (0.2)	6 (0.2)	7 (0.3)
Education (%)				
Less than O-level	1866 (25.1)	624 (24.7)	589 (23.8)	653 (26.7)
O-level	902 (12.1)	284 (11.2)	298 (12.1)	320 (13.1)
A-level	3328 (44.7)	1136 (44.9)	1117 (45.2)	1075 (44.0)
Degree	1349 (18.1)	487 (19.2)	465 (18.8)	397 (16.2)
Missing	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Body mass index category (%)				
Normal	2633 (35.4)	830 (32.8)	931 (37.7)	872 (35.7)
Overweight	2262 (30.4)	878 (34.7)	700 (28.3)	684 (28.0)
Obese	1419 (19.1)	454 (17.9)	461 (18.7)	504 (20.6)
Missing	1132 (15.2)	369 (14.6)	378 (15.3)	385 (15.7)
Alcohol intake (%)				
Never	373 (5.0)	133 (5.3)	114 (4.6)	126 (5.2)
Previous	780 (10.5)	264 (10.4)	228 (9.2)	288 (11.8)
Current (≤14 units/week)	5199 (69.8)	1739 (68.7)	1767 (71.5)	1693 (69.2)
Current (>14 units/week)	822 (11.0)	298 (11.8)	280 (11.3)	244 (10.0)
Missing	272 (3.7)	97 (3.8)	81 (3.3)	94 (3.8)
Smoking (%)				
Never	3661 (49.2)	1214 (48.0)	1245 (50.4)	1202 (49.2)
Previous	3378 (45.4)	1205 (47.6)	1079 (43.7)	1094 (44.7)
Current	302 (4.1)	79 (3.1)	108 (4.4)	115 (4.7)
Missing	105 (1.4)	33 (1.3)	38 (1.5)	34 (1.4)

N, number of participants; SD, standard deviation

Chapter 5

Appendix 5.1: Regression coefficients for linear associations between neuroticism and metabolites

Outcome	β	t	p
Monounsaturated Fatty Acids to Total Fatty Acids percentage	0.017	8.401	4.5E−17
Citrate	−0.018	−8.139	4.0E−16
Average Diameter for VLDL Particles	0.016	8.070	7.1E−16
Docosahexaenoic Acid to Total Fatty Acids percentage	−0.016	−7.658	1.9E−14
Glycine	0.016	7.420	1.2E−13
Linoleic Acid	0.015	7.330	2.3E−13
Total Lipids in Large VLDL	0.014	6.553	5.6E−11
Free Cholesterol in Very Large HDL	−0.013	−6.521	7.0E−11
Triglycerides to Phosphoglycerides ratio	0.013	6.503	7.9E−11
Triglycerides in Medium VLDL	0.014	6.495	8.3E−11
Monounsaturated Fatty Acids	0.014	6.432	1.3E−10
Phospholipids to Total Lipids in Very Large HDL percentage	−0.013	−6.414	1.4E−10
Triglycerides in VLDL	0.013	6.377	1.8E−10
Concentration of Large VLDL Particles	0.013	6.296	3.1E−10
Phospholipids in Very Large HDL	−0.012	−6.257	3.9E−10
Concentration of Very Large VLDL Particles	0.013	6.208	5.4E−10
Triglycerides in Large VLDL	0.013	6.199	5.7E−10
Total Lipids in VLDL	0.013	6.193	5.9E−10
Free Cholesterol in Large VLDL	0.013	6.186	6.2E−10
Average Diameter for HDL Particles	−0.011	−6.142	8.2E−10
Omega-6 Fatty Acids	0.013	6.114	9.8E−10
Polyunsaturated Fatty Acids to Monounsaturated Fatty Acids ratio	−0.012	−6.093	1.1E−09
Saturated Fatty Acids to Total Fatty Acids percentage	−0.013	−6.057	1.4E−09
Cholesterol in Very Large VLDL	0.013	6.047	1.5E−09
Total Lipids in Very Large VLDL	0.013	6.039	1.6E−09
Omega-3 Fatty Acids to Total Fatty Acids percentage	−0.013	−6.012	1.8E−09
Total Lipids in Very Large HDL	−0.011	−6.009	1.9E−09
Cholesterol in Large VLDL	0.013	5.994	2.1E−09
Cholesterol in Very Large HDL	−0.011	−5.943	2.8E−09
Phospholipids in Large VLDL	0.013	5.938	2.9E−09
Triglycerides in Small VLDL	0.013	5.914	3.3E−09
Total Triglycerides	0.012	5.908	3.5E−09
Phospholipids in Large HDL	−0.011	−5.877	4.2E−09
Free Cholesterol in Large HDL	−0.011	−5.873	4.3E−09
Cholesteryl Esters in Very Large HDL	−0.011	−5.836	5.4E−09

Total Lipids in Medium VLDL	0.012	5.802	6.6E−09
Phospholipids in VLDL	0.012	5.800	6.7E−09
Total Lipids in Large HDL	−0.011	−5.791	7.0E−09
Concentration of Small VLDL Particles	0.012	5.748	9.0E−09
Concentration of Chylomicrons and Extremely Large VLDL Particles	0.012	5.712	1.1E−08
Cholesterol in Large HDL	−0.010	−5.693	1.2E−08
Total Lipids in Small VLDL	0.012	5.661	1.5E−08
Total Lipids in Chylomicrons and Extremely Large VLDL	0.012	5.647	1.6E−08
Cholesteryl Esters to Total Lipids in Very Small VLDL percentage	−0.011	−5.644	1.7E−08
Cholesterol to Total Lipids in Very Small VLDL percentage	−0.011	−5.638	1.7E−08
Cholesteryl Esters in Very Large VLDL	0.012	5.618	1.9E−08
Triglycerides to Total Lipids in Very Small VLDL percentage	0.011	5.581	2.4E−08
Cholesteryl Esters in Large HDL	−0.010	−5.571	2.5E−08
Glycoprotein Acetyls	0.012	5.531	3.2E−08
Cholesterol in Chylomicrons and Extremely Large VLDL	0.013	5.499	3.8E−08
Cholesteryl Esters in Large VLDL	0.012	5.474	4.4E−08
Free Cholesterol in VLDL	0.011	5.452	5.0E−08
Triglycerides in Very Large VLDL	0.012	5.443	5.2E−08
Cholesteryl Esters to Total Lipids in Small LDL percentage	0.012	5.412	6.2E−08
Concentration of Large HDL Particles	−0.010	−5.366	8.1E−08
Concentration of Medium VLDL Particles	0.011	5.253	1.5E−07
Triglycerides in Small HDL	0.011	5.202	2.0E−07
Concentration of Very Large HDL Particles	−0.010	−5.096	3.5E−07
Cholesteryl Esters in Small LDL	0.011	5.088	3.6E−07
Phospholipids to Total Lipids in Small LDL percentage	−0.011	−5.053	4.4E−07
Triglycerides in Medium LDL	0.011	5.024	5.1E−07
Cholesteryl Esters in Chylomicrons and Extremely Large VLDL	0.012	5.018	5.2E−07
Triglycerides to Total Lipids in Small HDL percentage	0.010	4.949	7.5E−07
Phospholipids in Medium VLDL	0.010	4.948	7.5E−07
Phospholipids in Small VLDL	0.010	4.921	8.6E−07
Free Cholesterol in Very Large VLDL	0.012	4.890	1.0E−06
Triglycerides in Small LDL	0.011	4.887	1.0E−06
Concentration of VLDL Particles	0.010	4.872	1.1E−06
Omega-6 Fatty Acids to Omega-3 Fatty Acids ratio	0.010	4.849	1.2E−06
Triglycerides to Total Lipids in Medium VLDL percentage	0.009	4.845	1.3E−06
Free Cholesterol to Total Lipids in Medium HDL percentage	−0.009	−4.793	1.6E−06
Free Cholesterol to Total Lipids in Large LDL percentage	−0.009	−4.743	2.1E−06
VLDL Cholesterol	0.010	4.732	2.2E−06
Free Cholesterol to Total Lipids in Medium LDL percentage	−0.010	−4.729	2.3E−06
Total Fatty Acids	0.010	4.725	2.3E−06
Cholesteryl Esters to Total Lipids in Medium VLDL percentage	−0.009	−4.724	2.3E−06
Free Cholesterol in Chylomicrons and Extremely Large VLDL	0.012	4.723	2.3E−06
Cholesteryl Esters to Total Lipids in Large VLDL percentage	−0.010	−4.720	2.4E−06
Phospholipids in Very Large VLDL	0.011	4.651	3.3E−06

Phospholipids to Total Lipids in Small HDL percentage	−0.010	−4.650	3.3E−06
Free Cholesterol to Total Lipids in Large HDL percentage	−0.009	−4.625	3.8E−06
Polyunsaturated Fatty Acids	0.010	4.616	3.9E−06
Degree of Unsaturation	−0.009	−4.615	3.9E−06
Phospholipids to Total Lipids in Large VLDL percentage	0.010	4.590	4.4E−06
Phospholipids in Chylomicrons and Extremely Large VLDL	0.011	4.570	4.9E−06
Total Lipids in Small LDL	0.009	4.493	7.0E−06
Cholesteryl Esters in Medium LDL	0.009	4.486	7.3E−06
Docosahexaenoic Acid	−0.009	−4.466	8.0E−06
Free Cholesterol to Total Lipids in IDL percentage	−0.010	−4.452	8.5E−06
Free Cholesterol to Total Lipids in Small LDL percentage	−0.010	−4.448	8.7E−06
Triglycerides in Chylomicrons and Extremely Large VLDL	0.010	4.440	9.0E−06
Free Cholesterol to Total Lipids in Medium VLDL percentage	−0.009	−4.434	9.2E−06
Cholesterol to Total Lipids in Very Large VLDL percentage	−0.009	−4.419	9.9E−06
Phospholipids in Medium LDL	0.009	4.384	1.2E−05
Cholesteryl Esters in Small VLDL	0.009	4.382	1.2E−05
Cholesterol in Small LDL	0.009	4.366	1.3E−05
Apolipoprotein B to Apolipoprotein A1 ratio	0.009	4.359	1.3E−05
Total Lipids in Medium LDL	0.009	4.344	1.4E−05
Triglycerides in LDL	0.009	4.314	1.6E−05
Cholesterol to Total Lipids in Medium VLDL percentage	−0.008	−4.295	1.8E−05
Free Cholesterol in HDL	−0.008	−4.260	2.0E−05
Cholesterol in Small VLDL	0.009	4.256	2.1E−05
Triglycerides in Very Small VLDL	0.009	4.208	2.6E−05
Free Cholesterol in Medium VLDL	0.009	4.179	2.9E−05
Concentration of Small LDL Particles	0.009	4.164	3.1E−05
Cholesteryl Esters to Total Lipids in Very Large VLDL percentage	−0.009	−4.140	3.5E−05
Linoleic Acid to Total Fatty Acids percentage	0.008	4.111	3.9E−05
HDL Cholesterol	−0.008	−4.098	4.2E−05
Triglycerides to Total Lipids in Large HDL percentage	0.008	4.090	4.3E−05
Phospholipids to Total Lipids in Very Small VLDL percentage	0.008	4.029	5.6E−05
Cholesteryl Esters in VLDL	0.008	4.027	5.6E−05
Cholesterol in Medium LDL	0.008	4.022	5.8E−05
Cholesteryl Esters in HDL	−0.008	−4.020	5.8E−05
Free Cholesterol in Small VLDL	0.008	3.978	7.0E−05
Free Cholesterol to Total Lipids in Very Small VLDL percentage	−0.008	−3.946	7.9E−05
Cholesteryl Esters to Total Lipids in Large LDL percentage	0.009	3.863	1.1E−04
Concentration of LDL Particles	0.008	3.782	1.6E−04
Concentration of Medium LDL Particles	0.008	3.766	1.7E−04
Triglycerides to Total Lipids in Medium HDL percentage	0.008	3.734	1.9E−04
Cholesteryl Esters to Total Lipids in Medium LDL percentage	0.008	3.713	2.0E−04
Free Cholesterol to Total Lipids in Very Large HDL percentage	0.007	3.676	2.4E−04
Triglycerides to Total Lipids in Very Large VLDL percentage	0.008	3.645	2.7E−04
Free Cholesterol to Total Lipids in Small VLDL percentage	−0.007	−3.620	2.9E−04

Phospholipids in Small LDL	0.008	3.568	3.6E−04
Total Lipids in HDL	−0.007	−3.561	3.7E−04
Cholesterol to Total Lipids in Very Large HDL percentage	0.008	3.550	3.9E−04
Triglycerides to Total Lipids in IDL percentage	0.007	3.541	4.0E−04
Apolipoprotein B	0.007	3.518	4.4E−04
Concentration of Large LDL Particles	0.007	3.488	4.9E−04
Phospholipids in HDL	−0.007	−3.483	5.0E−04
Triglycerides in Large LDL	0.007	3.428	6.1E−04
Triglycerides to Total Lipids in Small VLDL percentage	0.007	3.414	6.4E−04
Cholesterol to Total Lipids in Medium HDL percentage	−0.007	−3.404	6.6E−04
Creatinine	−0.006	−3.361	7.8E−04
Free Cholesterol in Medium HDL	−0.006	−3.245	1.2E−03
Cholesteryl Esters in LDL	0.007	3.223	1.3E−03
Cholesterol to Total Lipids in Large VLDL percentage	−0.007	−3.184	1.5E−03
Phospholipids to Total Lipids in Medium VLDL percentage	−0.006	−3.124	1.8E−03
Cholesterol in Medium HDL	−0.006	−3.078	2.1E−03
Cholesterol to Total Lipids in Small VLDL percentage	−0.006	−3.042	2.3E−03
Phospholipids to Total Lipids in Small VLDL percentage	−0.006	−3.039	2.4E−03
Concentration of Small HDL Particles	0.007	3.025	2.5E−03
Triglycerides in IDL	0.007	3.002	2.7E−03
Cholesteryl Esters in Medium HDL	−0.006	−2.996	2.7E−03
Free Cholesterol to Total Lipids in Small HDL percentage	−0.006	−2.985	2.8E−03
Cholesterol to Total Lipids in IDL percentage	−0.006	−2.984	2.8E−03
Cholesterol in Medium VLDL	0.006	2.978	2.9E−03
Total Lipids in LDL	0.006	2.953	3.1E−03
Phospholipids in LDL	0.006	2.833	4.6E−03
Glucose	−0.006	−2.811	4.9E−03
Total Lipids in Lipoprotein Particles	0.006	2.780	5.4E−03
Triglycerides to Total Lipids in Small LDL percentage	0.006	2.742	6.1E−03
Triglycerides to Total Lipids in Very Large HDL percentage	0.014	2.739	6.2E−03
LDL Cholesterol	0.006	2.682	7.3E−03
Cholesteryl Esters to Total Lipids in Medium HDL percentage	−0.006	−2.666	7.7E−03
Concentration of Medium HDL Particles	−0.005	−2.630	8.5E−03
Polyunsaturated Fatty Acids to Total Fatty Acids percentage	−0.005	−2.618	8.9E−03
Cholesteryl Esters in Small HDL	0.006	2.605	9.2E−03
Total Cholesterol Minus HDL-C	0.005	2.591	9.6E−03
Acetoacetate	−0.006	−2.587	9.7E−03
Cholesterol to Total Lipids in Large HDL percentage	−0.005	−2.575	1.0E−02
Saturated Fatty Acids	0.005	2.554	1.1E−02
Valine	−0.005	−2.548	1.1E−02
Apolipoprotein A1	−0.005	−2.544	1.1E−02
Total Lipids in Small HDL	0.006	2.538	1.1E−02
Total Lipids in Medium HDL	−0.005	−2.514	1.2E−02
Free Cholesterol in Medium LDL	0.005	2.450	1.4E−02
Phospholipids to Total Lipids in Medium HDL percentage	0.005	2.415	1.6E−02

Cholesterol in Small HDL	0.005	2.388	1.7E−02
Triglycerides in HDL	0.005	2.368	1.8E−02
Glutamine	0.005	2.360	1.8E−02
Remnant Cholesterol (Non-HDL, Non-LDL -Cholesterol)	0.005	2.331	2.0E−02
Cholesterol to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	−0.005	−2.297	2.2E−02
Cholesteryl Esters in Large LDL	0.005	2.272	2.3E−02
Triglycerides in Medium HDL	0.005	2.267	2.3E−02
Total Concentration of Branched-Chain Amino Acids (Leucine+Isoleucine+Valine)	−0.005	−2.247	2.5E−02
Phospholipids in Medium HDL	−0.005	−2.243	2.5E−02
Omega-3 Fatty Acids	−0.005	−2.185	2.9E−02
Cholesteryl Esters to Total Lipids in Small VLDL percentage	−0.005	−2.136	3.3E−02
Acetone	−0.005	−2.035	4.2E−02
Leucine	−0.004	−2.010	4.4E−02
Total Lipids in Large LDL	0.004	1.998	4.6E−02
Tyrosine	−0.004	−1.947	5.2E−02
Clinical LDL Cholesterol	0.004	1.946	5.2E−02
Cholesteryl Esters to Total Lipids in Large HDL percentage	−0.004	−1.908	5.6E−02
Phospholipids in Small HDL	0.004	1.836	6.6E−02
Free Cholesterol in Small LDL	0.004	1.833	6.7E−02
Cholesterol in Large LDL	0.004	1.831	6.7E−02
3-Hydroxybutyrate	−0.004	−1.825	6.8E−02
Phospholipids to Total Lipids in Large LDL percentage	−0.004	−1.807	7.1E−02
Total Free Cholesterol	0.004	1.768	7.7E−02
Phospholipids in Large LDL	0.004	1.755	7.9E−02
Cholesteryl Esters in Medium VLDL	0.004	1.748	8.1E−02
Triglycerides to Total Lipids in Large LDL percentage	0.004	1.747	8.1E−02
Acetate	−0.004	−1.713	8.7E−02
Cholesterol to Total Lipids in Medium LDL percentage	−0.003	−1.672	9.4E−02
Phospholipids to Total Lipids in IDL percentage	0.004	1.652	9.8E−02
Free Cholesterol in Small HDL	0.004	1.639	1.0E−01
Free Cholesterol to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	−0.004	−1.634	1.0E−01
Free Cholesterol in IDL	−0.003	−1.634	1.0E−01
Sphingomyelins	−0.003	−1.598	1.1E−01
Cholesteryl Esters to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	−0.004	−1.542	1.2E−01
Cholesteryl Esters to Total Lipids in IDL percentage	−0.003	−1.521	1.3E−01
Cholesteryl Esters to Total Lipids in Very Large HDL percentage	0.003	1.476	1.4E−01
Phospholipids in Very Small VLDL	0.003	1.470	1.4E−01
Triglycerides to Total Lipids in Medium LDL percentage	0.003	1.421	1.6E−01
Cholesterol to Total Lipids in Small LDL percentage	0.003	1.419	1.6E−01
Cholesteryl Esters in Very Small VLDL	−0.003	−1.405	1.6E−01
Free Cholesterol to Total Lipids in Very Large VLDL percentage	−0.003	−1.204	2.3E−01
Free Cholesterol in LDL	0.002	1.180	2.4E−01

Average Diameter for LDL Particles	−0.003	−1.176	2.4E−01
Concentration of Very Small VLDL Particles	0.002	1.130	2.6E−01
Phospholipids to Total Lipids in Very Large VLDL percentage	0.003	1.118	2.6E−01
Cholesterol in IDL	−0.002	−1.088	2.8E−01
Total Lipids in Very Small VLDL	0.002	1.083	2.8E−01
Free Cholesterol to Total Lipids in Large VLDL percentage	0.002	1.082	2.8E−01
Total Cholesterol	0.002	1.029	3.0E−01
Isoleucine	−0.002	−1.016	3.1E−01
Triglycerides in Large HDL	−0.002	−0.888	3.7E−01
Cholesteryl Esters in IDL	−0.002	−0.887	3.7E−01
Phospholipids to Total Lipids in Large HDL percentage	0.002	0.871	3.8E−01
Concentration of HDL Particles	−0.002	−0.856	3.9E−01
Pyruvate	−0.002	−0.850	4.0E−01
Total Phospholipids in Lipoprotein Particles	0.002	0.791	4.3E−01
Cholesterol to Total Lipids in Large LDL percentage	−0.002	−0.791	4.3E−01
Cholesterol in Very Small VLDL	−0.002	−0.787	4.3E−01
Lactate	0.002	0.736	4.6E−01
Concentration of IDL Particles	0.001	0.732	4.6E−01
Total Esterified Cholesterol	0.001	0.727	4.7E−01
Albumin	−0.002	−0.723	4.7E−01
Total Cholines	0.001	0.705	4.8E−01
Phosphoglycerides	0.001	0.688	4.9E−01
Triglycerides in Very Large HDL	0.004	0.616	5.4E−01
Total Lipids in IDL	−0.001	−0.584	5.6E−01
Free Cholesterol in Very Small VLDL	0.001	0.552	5.8E−01
Phospholipids to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	0.001	0.546	5.8E−01
Free Cholesterol in Large LDL	0.001	0.515	6.1E−01
Triglycerides to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	0.001	0.501	6.2E−01
Omega-6 Fatty Acids to Total Fatty Acids percentage	−0.001	−0.454	6.5E−01
Cholesteryl Esters to Total Lipids in Small HDL percentage	0.001	0.448	6.5E−01
Cholesterol to Total Lipids in Small HDL percentage	−0.001	−0.387	7.0E−01
Phosphatidylcholines	0.001	0.359	7.2E−01
Histidine	−0.001	−0.321	7.5E−01
Phenylalanine	−0.001	−0.316	7.5E−01
Total Concentration of Lipoprotein Particles	−0.001	−0.298	7.7E−01
Phospholipids to Total Lipids in Medium LDL percentage	0.001	0.271	7.9E−01
Alanine	0.001	0.269	7.9E−01
Triglycerides to Total Lipids in Large VLDL percentage	0.001	0.261	7.9E−01
Phospholipids in IDL	0.000	−0.210	8.3E−01

Linear regression coefficients represent associations between neuroticism z-scores and metabolite levels, adjusted for sex, age, assessment centre, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, body mass index, and medication use.

Appendix 5.2: Cox regression for the associations between neuroticism-related metabolites and incident all-cause dementia

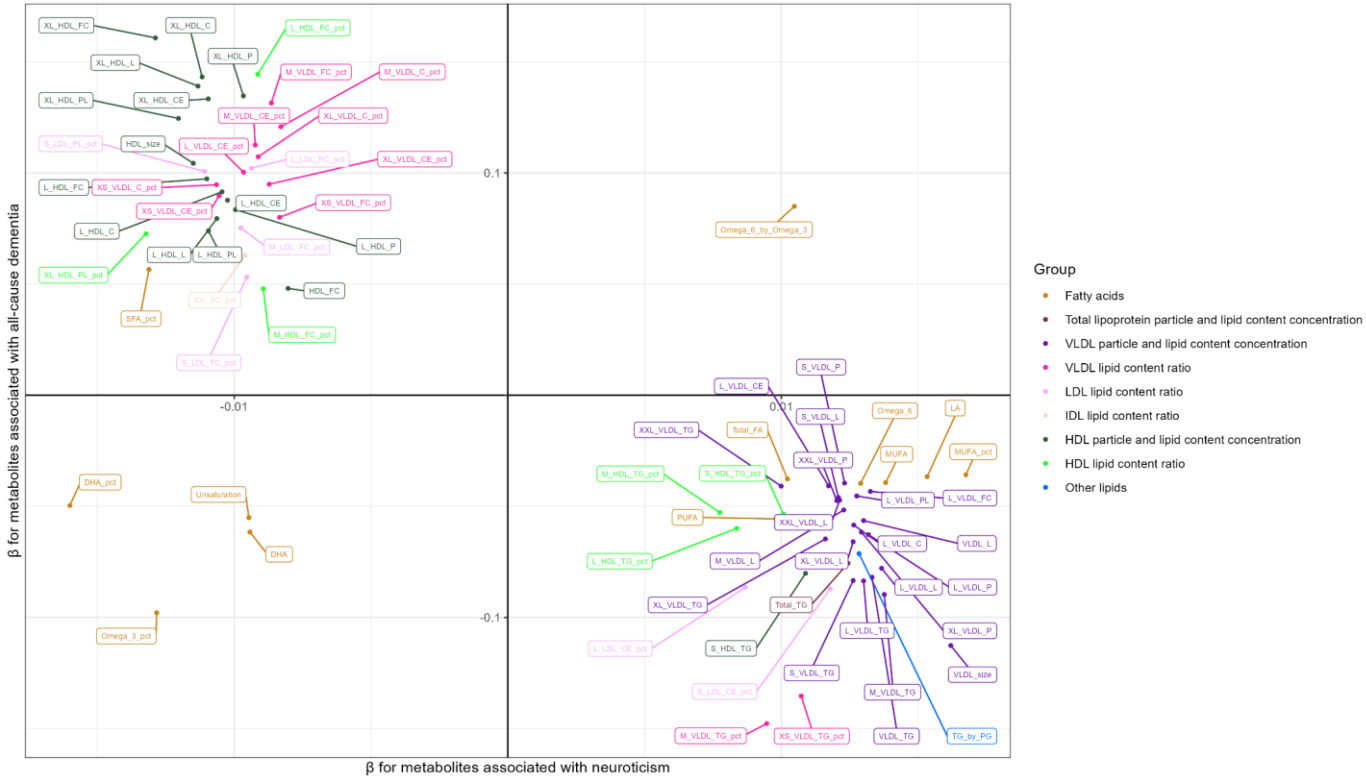
Metabolites	HR (95% CI)	p
Monounsaturated Fatty Acids to Total Fatty Acids percentage	0.96 (0.93 to 1.00)	4.8E−02
Citrate	1.00 (0.97 to 1.03)	9.9E−01
Average Diameter for VLDL Particles	0.89 (0.86 to 0.92)	1.2E−10
Docosahexaenoic Acid to Total Fatty Acids percentage	0.95 (0.92 to 0.98)	3.8E−03
Glycine	1.03 (0.99 to 1.07)	1.2E−01
Linoleic Acid	0.96 (0.93 to 1.00)	4.1E−02
Total Lipids in Large VLDL	0.93 (0.89 to 0.96)	1.3E−05
Free Cholesterol in Very Large HDL	1.17 (1.13 to 1.22)	3.4E−19
Triglycerides to Phosphoglycerides ratio	0.93 (0.90 to 0.97)	1.0E−04
Triglycerides in Medium VLDL	0.91 (0.88 to 0.95)	3.9E−07
Monounsaturated Fatty Acids	0.96 (0.93 to 0.99)	2.3E−02
Phospholipids to Total Lipids in Very Large HDL percentage	1.08 (1.04 to 1.12)	8.6E−05
Triglycerides in VLDL	0.92 (0.89 to 0.95)	3.8E−06
Concentration of Large VLDL Particles	0.94 (0.91 to 0.97)	4.6E−04
Phospholipids in Very Large HDL	1.13 (1.09 to 1.18)	3.5E−11
Concentration of Very Large VLDL Particles	0.94 (0.91 to 0.97)	6.1E−04
Triglycerides in Large VLDL	0.92 (0.89 to 0.95)	2.5E−06
Total Lipids in VLDL	0.95 (0.91 to 0.98)	1.3E−03
Free Cholesterol in Large VLDL	0.96 (0.92 to 0.99)	1.7E−02
Average Diameter for HDL Particles	1.11 (1.07 to 1.15)	5.6E−08
Omega-6 Fatty Acids	0.96 (0.93 to 1.00)	2.7E−02
Polyunsaturated Fatty Acids to Monounsaturated Fatty Acids ratio	1.02 (0.98 to 1.05)	3.9E−01
Saturated Fatty Acids to Total Fatty Acids percentage	1.06 (1.02 to 1.09)	5.5E−04
Cholesterol in Very Large VLDL	0.97 (0.94 to 1.01)	1.1E−01
Total Lipids in Very Large VLDL	0.94 (0.90 to 0.97)	2.4E−04
Omega-3 Fatty Acids to Total Fatty Acids percentage	0.91 (0.88 to 0.94)	1.9E−08
Total Lipids in Very Large HDL	1.15 (1.11 to 1.19)	1.2E−13
Cholesterol in Large VLDL	0.94 (0.91 to 0.98)	1.2E−03
Cholesterol in Very Large HDL	1.15 (1.11 to 1.20)	1.8E−14
Phospholipids in Large VLDL	0.96 (0.92 to 0.99)	1.2E−02
Triglycerides in Small VLDL	0.92 (0.89 to 0.95)	2.4E−06
Total Triglycerides	0.93 (0.90 to 0.96)	1.9E−05
Phospholipids in Large HDL	1.08 (1.04 to 1.12)	1.6E−04
Free Cholesterol in Large HDL	1.10 (1.06 to 1.14)	5.1E−07
Cholesteryl Esters in Very Large HDL	1.14 (1.10 to 1.19)	1.8E−12
Total Lipids in Medium VLDL	0.95 (0.92 to 0.98)	3.7E−03
Phospholipids in VLDL	0.97 (0.93 to 1.00)	5.9E−02
Total Lipids in Large HDL	1.08 (1.04 to 1.13)	5.6E−05
Concentration of Small VLDL Particles	0.96 (0.93 to 1.00)	2.5E−02

Concentration of Chylomicrons and Extremely Large VLDL Particles	0.95 (0.92 to 0.99)	7.3E−03
Cholesterol in Large HDL	1.10 (1.05 to 1.14)	2.8E−06
Total Lipids in Small VLDL	0.96 (0.92 to 0.99)	9.4E−03
Total Lipids in Chylomicrons and Extremely Large VLDL	0.95 (0.92 to 0.99)	8.6E−03
Cholesteryl Esters to Total Lipids in Very Small VLDL percentage	1.09 (1.05 to 1.13)	1.8E−06
Cholesterol to Total Lipids in Very Small VLDL percentage	1.10 (1.06 to 1.14)	4.9E−07
Cholesteryl Esters in Very Large VLDL	0.98 (0.95 to 1.02)	3.3E−01
Triglycerides to Total Lipids in Very Small VLDL percentage	0.87 (0.84 to 0.91)	4.3E−12
Cholesteryl Esters in Large HDL	1.09 (1.05 to 1.13)	7.0E−06
Glycoprotein Acetyls	0.99 (0.95 to 1.02)	4.3E−01
Cholesterol in Chylomicrons and Extremely Large VLDL	0.97 (0.94 to 1.01)	1.4E−01
Cholesteryl Esters in Large VLDL	0.96 (0.93 to 0.99)	2.5E−02
Free Cholesterol in VLDL	0.98 (0.94 to 1.01)	1.7E−01
Triglycerides in Very Large VLDL	0.94 (0.90 to 0.97)	3.4E−04
Cholesteryl Esters to Total Lipids in Small LDL percentage	0.92 (0.89 to 0.95)	1.2E−07
Concentration of Large HDL Particles	1.09 (1.05 to 1.13)	1.7E−05
Concentration of Medium VLDL Particles	0.98 (0.94 to 1.01)	2.1E−01
Triglycerides in Small HDL	0.92 (0.89 to 0.96)	7.7E−06
Concentration of Very Large HDL Particles	1.14 (1.10 to 1.19)	5.0E−13
Cholesteryl Esters in Small LDL	1.01 (0.98 to 1.05)	5.0E−01
Phospholipids to Total Lipids in Small LDL percentage	1.11 (1.07 to 1.14)	1.3E−09
Triglycerides in Medium LDL	0.99 (0.96 to 1.02)	5.4E−01
Cholesteryl Esters in Chylomicrons and Extremely Large VLDL	0.99 (0.95 to 1.02)	4.7E−01
Triglycerides to Total Lipids in Small HDL percentage	0.95 (0.91 to 0.98)	3.6E−03
Phospholipids in Medium VLDL	0.98 (0.95 to 1.02)	3.8E−01
Phospholipids in Small VLDL	0.98 (0.95 to 1.02)	3.0E−01
Free Cholesterol in Very Large VLDL	0.98 (0.94 to 1.01)	2.3E−01
Triglycerides in Small LDL	0.99 (0.96 to 1.03)	6.9E−01
Concentration of VLDL Particles	0.99 (0.95 to 1.02)	4.2E−01
Omega-6 Fatty Acids to Omega-3 Fatty Acids ratio	1.09 (1.05 to 1.13)	8.7E−07
Triglycerides to Total Lipids in Medium VLDL percentage	0.86 (0.83 to 0.89)	3.2E−15
Free Cholesterol to Total Lipids in Medium HDL percentage	1.05 (1.01 to 1.09)	1.4E−02
Free Cholesterol to Total Lipids in Large LDL percentage	1.11 (1.07 to 1.15)	1.5E−08
VLDL Cholesterol	0.99 (0.96 to 1.03)	6.6E−01
Free Cholesterol to Total Lipids in Medium LDL percentage	1.08 (1.04 to 1.12)	1.8E−05
Total Fatty Acids	0.96 (0.93 to 1.00)	2.9E−02
Cholesteryl Esters to Total Lipids in Medium VLDL percentage	1.12 (1.08 to 1.16)	4.4E−10
Free Cholesterol in Chylomicrons and Extremely Large VLDL	0.98 (0.94 to 1.01)	2.0E−01
Cholesteryl Esters to Total Lipids in Large VLDL percentage	1.11 (1.07 to 1.15)	2.4E−08
Phospholipids in Very Large VLDL	0.97 (0.93 to 1.00)	7.2E−02
Phospholipids to Total Lipids in Small HDL percentage	1.00 (0.96 to 1.03)	7.8E−01
Free Cholesterol to Total Lipids in Large HDL percentage	1.16 (1.11 to 1.20)	1.2E−14
Polyunsaturated Fatty Acids	0.95 (0.91 to 0.98)	1.8E−03
Degree of Unsaturation	0.95 (0.92 to 0.98)	1.2E−03
Phospholipids to Total Lipids in Large VLDL percentage	0.98 (0.95 to 1.02)	3.4E−01

Phospholipids in Chylomicrons and Extremely Large VLDL	0.97 (0.94 to 1.01)	1.8E−01
Total Lipids in Small LDL	1.03 (0.99 to 1.07)	1.2E−01
Cholesteryl Esters in Medium LDL	0.99 (0.95 to 1.02)	4.8E−01
Docosahexaenoic Acid	0.94 (0.91 to 0.97)	4.0E−04
Free Cholesterol to Total Lipids in IDL percentage	1.06 (1.03 to 1.10)	8.8E−05
Free Cholesterol to Total Lipids in Small LDL percentage	1.05 (1.02 to 1.09)	1.7E−03
Triglycerides in Chylomicrons and Extremely Large VLDL	0.96 (0.93 to 1.00)	2.7E−02
Free Cholesterol to Total Lipids in Medium VLDL percentage	1.14 (1.10 to 1.18)	9.5E−13
Cholesterol to Total Lipids in Very Large VLDL percentage	1.11 (1.07 to 1.15)	6.1E−09
Phospholipids in Medium LDL	1.01 (0.97 to 1.04)	7.0E−01
Cholesteryl Esters in Small VLDL	1.00 (0.96 to 1.03)	8.8E−01
Cholesterol in Small LDL	1.02 (0.99 to 1.06)	2.2E−01
Apolipoprotein B to Apolipoprotein A1 ratio	1.04 (1.00 to 1.07)	5.3E−02
Total Lipids in Medium LDL	1.00 (0.96 to 1.03)	8.5E−01
Triglycerides in LDL	1.00 (0.97 to 1.03)	9.3E−01
Cholesterol to Total Lipids in Medium VLDL percentage	1.13 (1.09 to 1.17)	2.6E−11
Free Cholesterol in HDL	1.05 (1.01 to 1.09)	1.4E−02
Cholesterol in Small VLDL	1.00 (0.96 to 1.03)	9.2E−01
Triglycerides in Very Small VLDL	0.97 (0.94 to 1.00)	7.1E−02
Free Cholesterol in Medium VLDL	1.00 (0.96 to 1.04)	9.4E−01
Concentration of Small LDL Particles	1.03 (1.00 to 1.07)	9.2E−02
Cholesteryl Esters to Total Lipids in Very Large VLDL percentage	1.10 (1.06 to 1.14)	4.0E−07
Linoleic Acid to Total Fatty Acids percentage	1.00 (0.96 to 1.03)	9.6E−01
HDL Cholesterol	1.03 (0.99 to 1.07)	1.8E−01
Triglycerides to Total Lipids in Large HDL percentage	0.94 (0.91 to 0.98)	9.0E−04
Phospholipids to Total Lipids in Very Small VLDL percentage	1.02 (0.99 to 1.06)	2.1E−01
Cholesteryl Esters in VLDL	1.01 (0.98 to 1.05)	5.3E−01
Cholesterol in Medium LDL	1.00 (0.96 to 1.03)	8.4E−01
Cholesteryl Esters in HDL	1.02 (0.98 to 1.06)	3.0E−01
Free Cholesterol in Small VLDL	1.01 (0.97 to 1.04)	6.9E−01
Free Cholesterol to Total Lipids in Very Small VLDL percentage	1.08 (1.05 to 1.12)	4.5E−06
Cholesteryl Esters to Total Lipids in Large LDL percentage	0.92 (0.89 to 0.95)	2.8E−08
Concentration of LDL Particles	1.03 (1.00 to 1.07)	7.1E−02
Concentration of Medium LDL Particles	1.01 (0.97 to 1.04)	7.4E−01
Triglycerides to Total Lipids in Medium HDL percentage	0.95 (0.92 to 0.98)	3.5E−03

HR, hazard ratio; CI, confidence interval. Cox models estimate the hazard ratio for incident all-cause dementia per 1-SD increase in each metabolite, adjusted for sex, age, assessment centre, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, body mass index, and medication use.

Appendix 5.3: Estimates of the associations of metabolites with neuroticism and all-cause dementia



Scatter plots show effect estimates from the linear regression between neuroticism and metabolites, and the Cox regression between metabolites and incident all-cause dementia, adjusted for sex, age, assessment centre, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, body mass index, and medication use. Only the 74 metabolites that reached Bonferroni-adjusted significance ($p<0.05$) for the association with neuroticism and were also significantly associated with incident all-cause dementia are displayed. DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; SFA, saturated fatty acids; LA, linoleic acid; TG, triglycerides; PG, phosphoglycerides; Prefixes 'XXL_', 'XL_', 'L_', 'M_' , 'S_' , 'XS_' indicate particle sizes. Suffixes '_FC', '_PL', '_L', '_C', '_CE', '_TG' denote specific lipid types: free cholesterol, phospholipids, total lipids, cholesterol, cholesteryl esters, and triglycerides, respectively. '_pct' indicates lipid-to-total lipid ratio.

Appendix 5.4: Summary of genetic instruments for phenotypes used in Mendelian Randomisation analyses

Phenotype	GWAS source	GWAS dataset	GWAS sample size	N_{snp}	R^2
Neuroticism	Nagel et al., 2018	UKB, GPC	390,278	91	0.010
AD	Kunkle et al., 2019	IGAP	21,982 cases and 41,944 controls	19	0.062
WMH	Smith et al., 2021	UKB	21,381	15	0.037
DHA	Borges et al., 2022	UKB	114,999	45	0.070
DHA_pct	Borges et al., 2022	UKB	114,999	28	0.050
Omega_3_pct	Borges et al., 2022	UKB	114,999	39	0.064
Omega_6_by_Omega_3	Borges et al., 2022	UKB	114,999	40	0.062
Unsaturation	Borges et al., 2022	UKB	114,999	45	0.070

GWAS, genome-wide association studies; UKB, UK Biobank; GPC, Genetics of Personality Consortium; AD, Alzheimer's disease; IGAP, International Genomics of Alzheimer's Project; WMH, white matter hyperintensities; DHA, docosahexaenoic acid; DHA_pct, docosahexaenoic acid to total fatty acids percentage; Omega_3_pct; omega-3 fatty acids to total fatty acids percentage; Omega_6_by_Omega_3; omega-6 fatty acids to omega-3 fatty acids ratio; Unsaturation; degree of unsaturation; SNP, single nucleotide polymorphism; N_{SNP}, number of genetic variants used as instrumental variables; R^2, proportion of variance explained.

Appendix 5.5: Mendelian randomisation analyses between neuroticism, metabolites, and dementia-related outcomes

Exposure	Outcome	Method	N_{snp}	β	SE	p
neuroticism	DHA	MR-Egger	79	−0.712	0.242	0.004
neuroticism	DHA	Weighted median	79	−0.116	0.052	0.027
neuroticism	DHA	Inverse-variance weighted	79	−0.125	0.049	0.011
neuroticism	DHA	MRlap	73	−0.153	0.069	0.027
neuroticism	DHA_pct	MR-Egger	79	−0.782	0.249	0.002
neuroticism	DHA_pct	Weighted median	79	−0.207	0.051	<0.001
neuroticism	DHA_pct	Inverse-variance weighted	79	−0.187	0.050	<0.001
neuroticism	DHA_pct	MRlap	73	−0.222	0.072	0.002
neuroticism	Omega_3_pct	MR-Egger	79	−0.723	0.233	0.003
neuroticism	Omega_3_pct	Weighted median	79	−0.109	0.051	0.032
neuroticism	Omega_3_pct	Inverse-variance weighted	79	−0.129	0.047	0.007
neuroticism	Omega_3_pct	MRlap	73	−0.154	0.066	0.020
neuroticism	Omega_6_by_Omega_3	MR-Egger	79	0.654	0.225	0.005
neuroticism	Omega_6_by_Omega_3	Weighted median	79	0.020	0.047	0.665
neuroticism	Omega_6_by_Omega_3	Inverse-variance weighted	79	0.093	0.046	0.042
neuroticism	Omega_6_by_Omega_3	MRlap	73	0.112	0.061	0.067
neuroticism	Unsaturation	MR-Egger	79	−0.523	0.232	0.027
neuroticism	Unsaturation	Weighted median	79	−0.200	0.050	<0.001
neuroticism	Unsaturation	Inverse-variance weighted	79	−0.136	0.046	0.003
neuroticism	Unsaturation	MRlap	73	−0.159	0.065	0.015
DHA	AD	MR-Egger	32	−0.069	0.191	0.719
DHA	AD	Weighted median	32	0.038	0.051	0.456
DHA	AD	Inverse-variance weighted	32	0.116	0.140	0.408
DHA_pct	AD	MR-Egger	20	0.318	0.502	0.535
DHA_pct	AD	Weighted median	20	0.056	0.075	0.455
DHA_pct	AD	Inverse-variance weighted	20	−0.144	0.342	0.675
Omega_3_pct	AD	MR-Egger	28	−0.236	0.104	0.032
Omega_3_pct	AD	Weighted median	28	−0.041	0.090	0.648
Omega_3_pct	AD	Inverse-variance weighted	28	−0.026	0.071	0.713

Omega_6_by_Omega_3	AD	MR-Egger	30	0.059	0.114	0.612
Omega_6_by_Omega_3	AD	Weighted median	30	−0.066	0.089	0.458
Omega_6_by_Omega_3	AD	Inverse-variance weighted	30	−0.037	0.069	0.592
Unsaturation	AD	MR-Egger	37	0.141	0.252	0.581
Unsaturation	AD	Weighted median	37	0.018	0.071	0.801
Unsaturation	AD	Inverse-variance weighted	37	0.158	0.161	0.325
DHA_pct	WMH	MR-Egger	24	−0.086	0.074	0.258
DHA_pct	WMH	Weighted median	24	−0.119	0.049	0.014
DHA_pct	WMH	Inverse-variance weighted	24	−0.060	0.048	0.208
DHA_pct	WMH	MRlap	20	−0.107	0.040	0.008
DHA	WMH	MR-Egger	39	−0.120	0.048	0.017
DHA	WMH	Weighted median	39	−0.109	0.033	0.001
DHA	WMH	Inverse-variance weighted	39	−0.075	0.034	0.030
DHA	WMH	MRlap	33	−0.083	0.039	0.033
Omega_3_pct	WMH	MR-Egger	33	−0.069	0.050	0.179
Omega_3_pct	WMH	Weighted median	33	−0.065	0.040	0.109
Omega_3_pct	WMH	Inverse-variance weighted	33	−0.057	0.035	0.106
Omega_3_pct	WMH	MRlap	26	−0.065	0.052	0.216
Omega_6_by_Omega_3	WMH	MR-Egger	35	0.020	0.139	0.886
Omega_6_by_Omega_3	WMH	Weighted median	35	0.053	0.054	0.330
Omega_6_by_Omega_3	WMH	Inverse-variance weighted	35	0.082	0.082	0.319
Omega_6_by_Omega_3	WMH	MRlap	27	0.081	0.033	0.015
Unsaturation	WMH	MR-Egger	43	−0.098	0.059	0.107
Unsaturation	WMH	Weighted median	43	−0.104	0.048	0.029
Unsaturation	WMH	Inverse-variance weighted	43	−0.048	0.038	0.204
Unsaturation	WMH	MRlap	31	−0.052	0.030	0.081

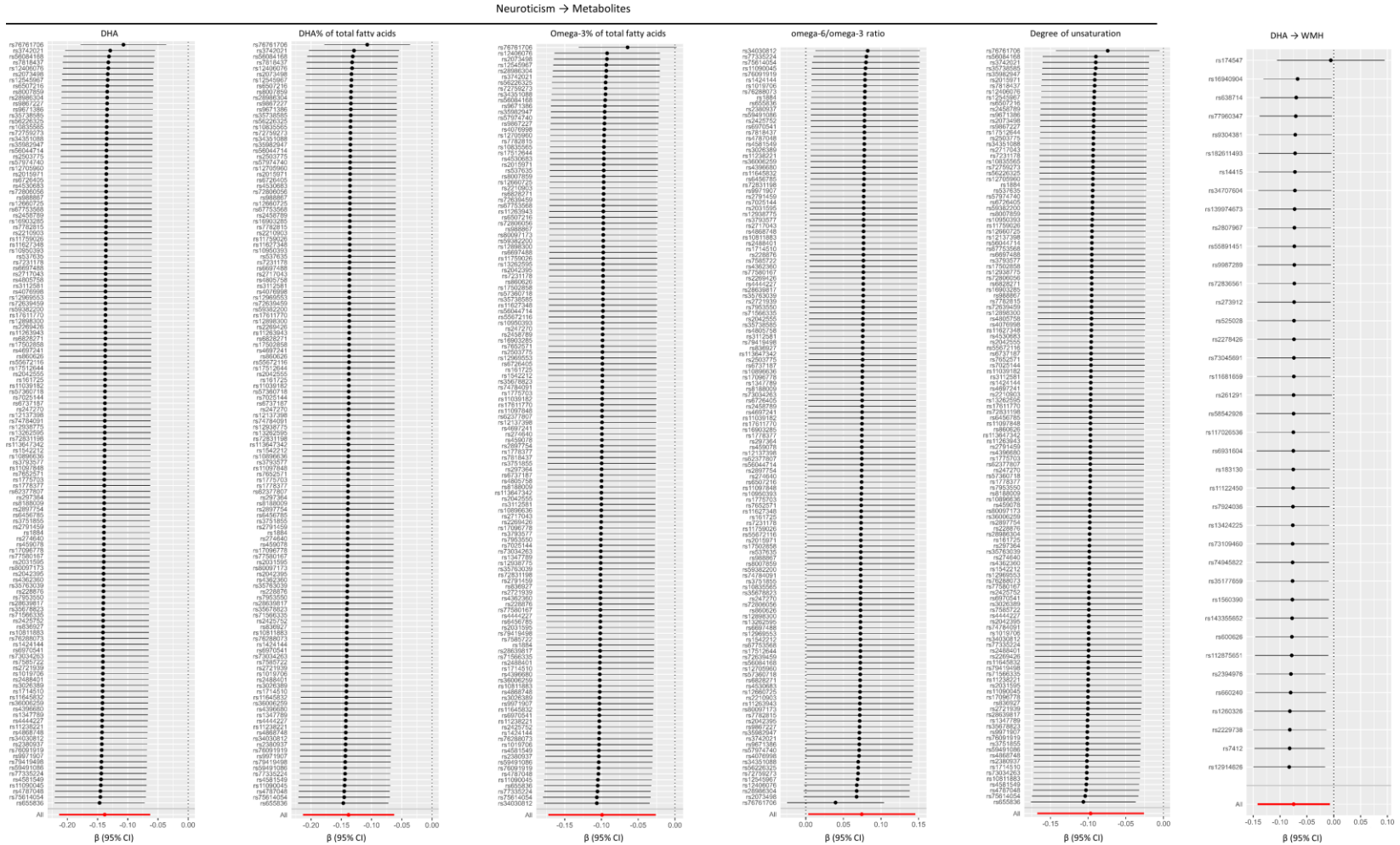
DHA, docosahexaenoic acid; DHA_pct, docosahexaenoic acid to total fatty acids percentage; Omega_3_pct; omega-3 fatty acids to total fatty acids percentage; Omega_6_by_Omega_3; omega-6 fatty acids to omega-3 fatty acids ratio; Unsaturation; degree of unsaturation; AD; Alzheimer's disease; WMH; white matter hyperintensities; N_{snp}, number of single nucleotide polymorphisms used as genetic instruments; SE, standard error.

Appendix 5.6: Sensitivity analyses for Mendelian randomisation

Exposure	Outcome	p for Q (IVW)	p for Q (MR-Egger)	p for Egger intercept	R^2 exposure	R^2 outcome	p for Steiger
neuroticism	DHA	<0.001	<0.001	0.016	0.009	0.002	<0.001
neuroticism	DHA_pct	<0.001	<0.001	0.017	0.009	0.002	<0.001
neuroticism	Omega_3_pct	<0.001	<0.001	0.011	0.009	0.002	<0.001
neuroticism	Omega_6_by_Omega_3	<0.001	<0.001	0.013	0.009	0.002	<0.001
neuroticism	Unsaturation	<0.001	<0.001	0.092	0.009	0.002	<0.001
DHA	AD	<0.001	<0.001	0.170	0.035	0.006	<0.001
DHA_pct	AD	<0.001	<0.001	0.231	0.020	0.009	<0.001
Omega_3_pct	AD	0.088	0.270	0.017	0.031	0.001	<0.001
Omega_6_by_Omega_3	AD	0.100	0.110	0.301	0.034	0.001	<0.001
Unsaturation	AD	<0.001	<0.001	0.929	0.036	0.006	<0.001
DHA_pct	WMH	0.038	0.030	0.650	0.024	0.002	<0.001
DHA	WMH	0.006	0.009	0.191	0.039	0.003	<0.001
Omega_3_pct	WMH	0.042	0.034	0.727	0.041	0.002	<0.001
Omega_6_by_Omega_3	WMH	<0.001	<0.001	0.587	0.037	0.008	<0.001
Unsaturation	WMH	0.053	0.057	0.284	0.039	0.003	<0.001

DHA, docosahexaenoic acid; DHA_pct, docosahexaenoic acid to total fatty acids percentage; Omega_3_pct; omega-3 fatty acids to total fatty acids percentage; Omega_6_by_Omega_3; omega-6 fatty acids to omega-3 fatty acids ratio; Unsaturation; degree of unsaturation; AD; Alzheimer's disease; WMH; white matter hyperintensities; IVW, inverse-variance weighted; Q, Cochran's Q-statistic for heterogeneity; R^2, proportion of variance explained; Steiger, Steiger directionality test.

Appendix 5.7: Leave-one-out analyses applied to metabolites with significant inverse-variance weighted associations



DHA, docosahexaenoic acid; WMH; white matter hyperintensities; CI, confidence interval. Each point shows the causal estimate with one variant removed, and the error bars represent the 95% confidence interval. The red point and error bar show the inverse-variance weighted estimate with its 95% confidence interval. The vertical dotted line marks β=0.

Chapter 6

Appendix 6.1: Associations between neuroticism and 1,747 IDPs estimated in a linear regression model

Outcome	Category	Model/atlas	β	t	p
Mean radial diffusivity in posterior thalamic radiation (right)	Thalamic radiations	dMRI diffusivity	0.028	5.459	4.8E−08
Mean FA in posterior thalamic radiation (right)	Thalamic radiations	dMRI FA	−0.028	−5.395	6.9E−08
Mean axial diffusivity in posterior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.027	5.187	2.2E−07
Area of Parahippocampal Gyrus (left)	Temporal	Freesurfer DKT	0.028	5.061	4.2E−07
Volume of grey matter in Frontal Medial Cortex (left)	Frontal	FAST	−0.027	−5.024	5.1E−07
Mean FA in posterior thalamic radiation (left)	Thalamic radiations	dMRI FA	−0.026	−4.921	8.7E−07
Mean ICVF in posterior thalamic radiation (right)	Thalamic radiations	dMRI ICVF	−0.026	−4.917	8.8E−07
Mean radial diffusivity in posterior thalamic radiation (left)	Thalamic radiations	dMRI diffusivity	0.025	4.912	9.1E−07
Volume of WMhypointensities (whole brain)	NA	Freesurfer ASEG	0.023	4.821	1.4E−06
Mean axial diffusivity in posterior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.023	4.715	2.4E−06
Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	NA	FLAIR	0.022	4.581	4.7E−06
Volume of grey matter in Caudate (left)	Striatum	FAST	0.025	4.564	5.0E−06
Mean MD in fornix cres+stria terminalis (right)	Limbic system fibres	dMRI diffusivity	0.023	4.564	5.1E−06
Mean ISOVF in fornix cres+stria terminalis (right)	Limbic system fibres	dMRI ISOVF	0.023	4.524	6.1E−06
Mean MD in tapetum (right)	Commissural fibres	dMRI diffusivity	0.023	4.518	6.3E−06
Volume of grey matter in Subcallosal Cortex (left)	Frontal	FAST	−0.024	−4.515	6.3E−06
Mean MD in posterior thalamic radiation (right)	Thalamic radiations	dMRI diffusivity	0.024	4.513	6.4E−06
thickness of Parahippocampal Gyrus (left)	Temporal	Freesurfer desikan white	−0.025	−4.500	6.8E−06
Volume of grey matter in Putamen (right)	Striatum	FAST	0.024	4.494	7.0E−06
Mean ICVF in posterior thalamic radiation (left)	Thalamic radiations	dMRI ICVF	−0.024	−4.489	7.2E−06
thickness of Parahippocampal Gyrus (left)	Temporal	Freesurfer DKT	−0.025	−4.467	8.0E−06
Volume of grey matter in Putamen (left)	Striatum	FAST	0.024	4.454	8.5E−06
Area of Parahippocampal Gyrus (left)	Temporal	Freesurfer desikan pial	0.024	4.451	8.6E−06

Area of Parahippocampal Gyrus (left)	Temporal	Freesurfer desikan white	0.024	4.446	8.8E−06
Mean ICVF in tapetum (right)	Commissural fibres	dMRI ICVF	−0.024	−4.440	9.0E−06
Volume of grey matter in Caudate (right)	Striatum	FAST	0.024	4.439	9.1E−06
Mean OD in posterior corona radiata (left)	Thalamic radiations	dMRI OD	−0.024	−4.403	1.1E−05
Mean axial diffusivity in tapetum (right)	Commissural fibres	dMRI diffusivity	0.023	4.379	1.2E−05
Mean MD in posterior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.023	4.362	1.3E−05
Volume of caudalAntcingulate (left)	Limbic	Freesurfer DKT	−0.024	−4.357	1.3E−05
Mean axial diffusivity in superior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.023	4.340	1.4E−05
Volume of GScingulAnt (right)	Limbic	Freesurfer a2009s	−0.023	−4.303	1.7E−05
Mean axial diffusivity in external capsule (right)	Association fibres	dMRI diffusivity	0.022	4.278	1.9E−05
Mean MD in superior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.021	4.262	2.0E−05
Area of Pericalcarine cortex (left)	Occipital	Freesurfer desikan white	−0.024	−4.260	2.1E−05
Volume of grey matter in Ventral Striatum (left)	Striatum	FAST	0.021	4.257	2.1E−05
Area of Scalcarine (left)	Occipital	Freesurfer a2009s	−0.023	−4.245	2.2E−05
Volume of Medorbitofrontal (left)	Frontal	Freesurfer DKT	−0.023	−4.239	2.3E−05
Area of Pericalcarine cortex (left)	Occipital	Freesurfer desikan pial	−0.023	−4.230	2.3E−05
Area of Pericalcarine cortex (left)	Occipital	Freesurfer DKT	−0.023	−4.190	2.8E−05
Mean MD in superior cerebellar peduncle (left)	Brainstem fibres	dMRI diffusivity	0.023	4.174	3.0E−05
Volume of grey matter in Paracingulate Gyrus (right)	Limbic	FAST	−0.021	−4.142	3.5E−05
Volume of Scalcarine (left)	Occipital	Freesurfer a2009s	−0.023	−4.122	3.8E−05
Mean radial diffusivity in fornix cres+stria terminalis (right)	Limbic system fibres	dMRI diffusivity	0.020	4.119	3.8E−05
Mean axial diffusivity in body of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.022	4.096	4.2E−05
Mean MD in superior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.020	4.089	4.3E−05
Mean radial diffusivity in tapetum (right)	Commissural fibres	dMRI diffusivity	0.021	4.075	4.6E−05
Volume of Medorbitofrontal (right)	Frontal	Freesurfer desikan white	−0.022	−4.062	4.9E−05
Mean MD in posterior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.021	4.061	4.9E−05
Mean MD in posterior thalamic radiation (left)	Thalamic radiations	dMRI diffusivity	0.021	4.032	5.5E−05
Mean axial diffusivity in superior longitudinal fasciculus (right)	Association fibres	dMRI diffusivity	0.021	4.016	5.9E−05

Volume of grey matter in Occipital Pole (left)	Occipital	FAST	−0.021	−4.012	6.0E−05
Volume of GScingulMidAnt (left)	Limbic	Freesurfer a2009s	−0.022	−4.004	6.2E−05
Volume of Pericalcarine cortex (left)	Occipital	Freesurfer desikan white	−0.022	−3.983	6.8E−05
thickness of Gsubcallosal (left)	Frontal	Freesurfer a2009s	−0.022	−3.973	7.1E−05
Mean MD in body of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.020	3.973	7.1E−05
Mean OD in cerebral peduncle (right)	Brainstem fibres	dMRI OD	0.021	3.964	7.4E−05
Volume of Scalcarine (right)	Occipital	Freesurfer a2009s	−0.022	−3.956	7.6E−05
Mean axial diffusivity in retrolenticular part of internal capsule (right)	Internal capsule	dMRI diffusivity	0.021	3.931	8.5E−05
Mean OD in posterior corona radiata (right)	Thalamic radiations	dMRI OD	−0.021	−3.928	8.6E−05
Volume of Pericalcarine cortex (left)	Occipital	Freesurfer DKT	−0.022	−3.924	8.7E−05
Area of Brodmann Area V1 (left)	Occipital	Freesurfer BA exvivo	−0.022	−3.919	8.9E−05
Area of Scalcarine (right)	Occipital	Freesurfer a2009s	−0.022	−3.906	9.4E−05
Area of Medorbitofrontal (right)	Frontal	Freesurfer desikan pial	−0.021	−3.894	9.9E−05
Mean radial diffusivity in superior cerebellar peduncle (left)	Brainstem fibres	dMRI diffusivity	0.021	3.889	1.0E−04
Mean ICVF in tapetum (left)	Commissural fibres	dMRI ICVF	−0.021	−3.879	1.1E−04
Volume of Grectus (right)	Frontal	Freesurfer a2009s	−0.021	−3.878	1.1E−04
Mean axial diffusivity in fornix cres+stria terminalis (right)	Limbic system fibres	dMRI diffusivity	0.021	3.872	1.1E−04
Volume of VA (left)	Thalamus	Freesurfer subsegmentation	0.021	3.835	1.3E−04
Mean radial diffusivity in superior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.019	3.813	1.4E−04
Volume of grey matter in Frontal Medial Cortex (right)	Frontal	FAST	−0.020	−3.745	1.8E−04
Mean ICVF in splenium of corpus callosum on FA skeleton	Commissural fibres	dMRI ICVF	−0.020	−3.744	1.8E−04
Volume of caudate (left)	Striatum	FIRST	0.020	3.738	1.9E−04
Area of Brodmann Area V1 (right)	Occipital	Freesurfer BA exvivo	−0.021	−3.736	1.9E−04
Mean OD in cerebral peduncle (left)	Brainstem fibres	dMRI OD	0.020	3.733	1.9E−04
Mean axial diffusivity in external capsule (left)	Association fibres	dMRI diffusivity	0.019	3.724	2.0E−04
Volume of Gprecentral (left)	Frontal	Freesurfer a2009s	−0.019	−3.719	2.0E−04
Grey-white contrast in Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer desikan gw	−0.018	−3.690	2.2E−04
Volume of Paralaminarnucleus (left)	Amygdala	Freesurfer subsegmentation	0.020	3.677	2.4E−04

thickness of SoctempmedLingual (left)	Temporal	Freesurfer a2009s	−0.020	−3.674	2.4E−04
Mean MD in superior fronto-occipital fasciculus (left)	Association fibres	dMRI diffusivity	0.018	3.672	2.4E−04
Volume of grey matter in Paracingulate Gyrus (left)	Limbic	FAST	−0.019	−3.654	2.6E−04
Mean ICVF in superior longitudinal fasciculus (left)	Association fibres	dMRI ICVF	−0.019	−3.648	2.6E−04
Grey-white contrast in Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer desikan gw	−0.018	−3.636	2.8E−04
Area of GScingulMidAnt (left)	Limbic	Freesurfer a2009s	−0.020	−3.621	2.9E−04
Volume of LSg (right)	Thalamus	Freesurfer subsegmentation	0.019	3.613	3.0E−04
Mean intensity of Accumbensarea (left)	Striatum	Freesurfer ASEG	−0.019	−3.608	3.1E−04
Mean MD in superior fronto-occipital fasciculus (right)	Association fibres	dMRI diffusivity	0.018	3.597	3.2E−04
Area of Pericalcarine cortex (right)	Occipital	Freesurfer DKT	−0.020	−3.584	3.4E−04
Area of SoctempmedLingual (left)	Temporal	Freesurfer a2009s	0.019	3.564	3.7E−04
Mean MD in posterior limb of internal capsule (right)	Internal capsule	dMRI diffusivity	0.018	3.564	3.7E−04
Mean axial diffusivity in fornix on FA skeleton	Limbic system fibres	dMRI diffusivity	0.017	3.547	3.9E−04
Area of GScingulAnt (right)	Limbic	Freesurfer a2009s	−0.019	−3.545	3.9E−04
Mean axial diffusivity in superior fronto-occipital fasciculus (left)	Association fibres	dMRI diffusivity	0.018	3.545	3.9E−04
Mean radial diffusivity in superior cerebellar peduncle (right)	Brainstem fibres	dMRI diffusivity	0.019	3.542	4.0E−04
Volume of grey matter in Precentral Gyrus (right)	Frontal	FAST	−0.018	−3.483	5.0E−04
Mean MD in retrolenticular part of internal capsule (right)	Internal capsule	dMRI diffusivity	0.019	3.477	5.1E−04
Area of Cuneal Cortex (left)	Occipital	Freesurfer desikan pial	−0.019	−3.476	5.1E−04
Area of Cuneal Cortex (left)	Occipital	Freesurfer desikan white	−0.019	−3.472	5.2E−04
Volume of Brodmann Area V1 (left)	Occipital	Freesurfer BA exvivo	−0.019	−3.464	5.3E−04
Mean radial diffusivity in posterior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.018	3.464	5.3E−04
Mean MD in superior longitudinal fasciculus (right)	Association fibres	dMRI diffusivity	0.018	3.459	5.4E−04
Volume of Pericalcarine cortex (right)	Occipital	Freesurfer DKT	−0.019	−3.445	5.7E−04
Mean MD in anterior limb of internal capsule (right)	Internal capsule	dMRI diffusivity	0.017	3.445	5.7E−04
Volume of ventricular CSF	NA	FAST	0.016	3.443	5.8E−04
Volume of Gprecuneus (right)	Occipital	Freesurfer a2009s	0.018	3.439	5.9E−04
Volume of grey matter in Frontal Operculum Cortex (left)	Insular	FAST	−0.018	−3.435	5.9E−04

Area of Pericalcarine cortex (right)	Occipital	Freesurfer desikan white	−0.019	−3.432	6.0E−04
Volume of Sparietooccipital (left)	Occipital	Freesurfer a2009s	−0.019	−3.431	6.0E−04
Mean ICVF in superior fronto-occipital fasciculus (left)	Association fibres	dMRI ICVF	−0.017	−3.430	6.0E−04
Mean ISOVF in anterior limb of internal capsule (right)	Internal capsule	dMRI ISOVF	0.018	3.425	6.2E−04
Volume of GScingulMidPost (right)	Limbic	Freesurfer a2009s	−0.019	−3.423	6.2E−04
Mean ICVF in superior fronto-occipital fasciculus (right)	Association fibres	dMRI ICVF	−0.017	−3.410	6.5E−04
Volume of Caudate (left)	Striatum	Freesurfer ASEG	0.019	3.403	6.7E−04
Mean radial diffusivity in superior fronto-occipital fasciculus (left)	Association fibres	dMRI diffusivity	0.017	3.399	6.8E−04
Volume of grey matter in Precentral Gyrus (left)	Frontal	FAST	−0.017	−3.396	6.8E−04
Mean FA in superior cerebellar peduncle (right)	Brainstem fibres	dMRI FA	−0.019	−3.392	6.9E−04
Volume of grey matter in Vermis IX Cerebellum	Cerebellum	FAST	0.018	3.379	7.3E−04
Mean MD in superior longitudinal fasciculus (left)	Association fibres	dMRI diffusivity	0.018	3.368	7.6E−04
Volume of Cuneal Cortex (left)	Occipital	Freesurfer DKT	−0.018	−3.362	7.8E−04
Volume of presubiculumbody (left)	Hippocampus	Freesurfer subsegmentation	0.017	3.361	7.8E−04
Area of GScingulMidPost (right)	Limbic	Freesurfer a2009s	−0.018	−3.356	7.9E−04
Volume of Caudate (right)	Striatum	Freesurfer ASEG	0.019	3.349	8.1E−04
Volume of GScingulAnt (left)	Limbic	Freesurfer a2009s	−0.018	−3.342	8.3E−04
Volume of grey matter in Ventral Striatum (right)	Striatum	FAST	0.017	3.339	8.4E−04
Area of Cuneal Cortex (left)	Occipital	Freesurfer DKT	−0.018	−3.338	8.5E−04
Area of Pericalcarine cortex (right)	Occipital	Freesurfer desikan pial	−0.018	−3.330	8.7E−04
Mean radial diffusivity in superior fronto-occipital fasciculus (right)	Association fibres	dMRI diffusivity	0.016	3.325	8.9E−04
Volume of Medorbitofrontal (left)	Frontal	Freesurfer desikan white	−0.018	−3.315	9.2E−04
Mean FA in medial lemniscus (right)	Brainstem fibres	dMRI FA	−0.018	−3.315	9.2E−04
Volume of Paralaminarnucleus (right)	Amygdala	Freesurfer subsegmentation	0.018	3.311	9.3E−04
thickness of Spericallosal (left)	Limbic	Freesurfer a2009s	−0.018	−3.310	9.3E−04
Mean MD in splenium of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.017	3.302	9.6E−04
thickness of Insular Cortex (left)	Insular	Freesurfer desikan white	−0.018	−3.299	9.7E−04

Volume of presubiculumhead (right)	Hippocampus	Freesurfer subsegmentation	0.017	3.295	9.9E−04
Area of Gcuneus (left)	Occipital	Freesurfer a2009s	−0.018	−3.280	1.0E−03
thickness of Medorbitofrontal (left)	Frontal	Freesurfer DKT	−0.018	−3.279	1.0E−03
Volume of Cuneal Cortex (left)	Occipital	Freesurfer desikan white	−0.018	−3.268	1.1E−03
Volume of Pericalcarine cortex (right)	Occipital	Freesurfer desikan white	−0.018	−3.260	1.1E−03
Mean MD in superior cerebellar peduncle (right)	Brainstem fibres	dMRI diffusivity	0.018	3.241	1.2E−03
Mean intensity of choroidplexus (left)	NA	Freesurfer ASEG	−0.016	−3.239	1.2E−03
Mean ISOVF in fornix on FA skeleton	Limbic system fibres	dMRI ISOVF	0.015	3.229	1.2E−03
Mean radial diffusivity in tapetum (left)	Commissural fibres	dMRI diffusivity	0.017	3.226	1.3E−03
Volume of Ssubparietal (right)	Parietal	Freesurfer a2009s	0.018	3.218	1.3E−03
Mean ICVF in superior corona radiata (left)	Thalamic radiations	dMRI ICVF	−0.017	−3.214	1.3E−03
Area of Parahippocampal Gyrus (right)	Temporal	Freesurfer desikan pial	0.018	3.214	1.3E−03
Grey-white contrast in Precentral Gyrus (left)	Frontal	Freesurfer desikan gw	−0.017	−3.213	1.3E−03
Mean axial diffusivity in superior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.017	3.211	1.3E−03
Mean OD in superior corona radiata (right)	Thalamic radiations	dMRI OD	−0.017	−3.192	1.4E−03
Area of Gfrontmiddle (right)	Frontal	Freesurfer a2009s	−0.018	−3.188	1.4E−03
Mean ICVF in medial lemniscus (right)	Brainstem fibres	dMRI ICVF	−0.017	−3.183	1.5E−03
thickness of Scircularinsulainf (left)	Insular	Freesurfer a2009s	−0.017	−3.170	1.5E−03
Volume of Brodmann Area 4a (left)	Frontal	Freesurfer BA exvivo	−0.017	−3.170	1.5E−03
Mean ICVF in superior cerebellar peduncle (left)	Brainstem fibres	dMRI ICVF	−0.017	−3.169	1.5E−03
Mean MD in fornix on FA skeleton	Limbic system fibres	dMRI diffusivity	0.015	3.165	1.6E−03
thickness of GStransvfrontopol (left)	Frontal	Freesurfer a2009s	−0.017	−3.158	1.6E−03
Mean ICVF in sagittal stratum (left)	Association fibres	dMRI ICVF	−0.017	−3.149	1.6E−03
thickness of Grectus (left)	Frontal	Freesurfer a2009s	−0.017	−3.136	1.7E−03
Volume of LateralVentricle (left)	NA	Freesurfer ASEG	0.016	3.133	1.7E−03
thickness of Sparietooccipital (left)	Occipital	Freesurfer a2009s	−0.017	−3.131	1.7E−03

Volume of Basalnucleus (left)	Amygdala	Freesurfer subsegmentation	0.016	3.123	1.8E−03
Mean radial diffusivity in anterior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.015	3.121	1.8E−03
Volume of LD (left)	Thalamus	Freesurfer subsegmentation	−0.017	−3.120	1.8E−03
Mean FA in tapetum (right)	Commissural fibres	dMRI FA	−0.017	−3.119	1.8E−03
Mean axial diffusivity in superior longitudinal fasciculus (left)	Association fibres	dMRI diffusivity	0.017	3.113	1.9E−03
Mean radial diffusivity in superior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.016	3.111	1.9E−03
Mean axial diffusivity in superior fronto-occipital fasciculus (right)	Association fibres	dMRI diffusivity	0.016	3.108	1.9E−03
thickness of Lateral orbitofrontal cortex (left)	Frontal	Freesurfer DKT	−0.017	−3.108	1.9E−03
Mean radial diffusivity in anterior limb of internal capsule (right)	Internal capsule	dMRI diffusivity	0.016	3.106	1.9E−03
thickness of Insular Cortex (left)	Insular	Freesurfer DKT	−0.017	−3.093	2.0E−03
Mean radial diffusivity in posterior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.016	3.093	2.0E−03
Volume of parasubiculum (right)	Hippocampus	Freesurfer subsegmentation	0.017	3.090	2.0E−03
Mean MD in external capsule (right)	Association fibres	dMRI diffusivity	0.015	3.072	2.1E−03
Mean ICVF in posterior corona radiata (left)	Thalamic radiations	dMRI ICVF	−0.016	−3.068	2.2E−03
Volume of peripheral cortical grey matter	NA	FAST	−0.013	−3.066	2.2E−03
Mean radial diffusivity in medial lemniscus (right)	Brainstem fibres	dMRI diffusivity	0.017	3.059	2.2E−03
Mean ISOVF in posterior corona radiata (right)	Thalamic radiations	dMRI ISOVF	0.016	3.048	2.3E−03
Mean ICVF in superior corona radiata (right)	Thalamic radiations	dMRI ICVF	−0.016	−3.042	2.4E−03
thickness of GInslgScentins (left)	Insular	Freesurfer a2009s	−0.017	−3.040	2.4E−03
Mean ISOVF in posterior limb of internal capsule (right)	Internal capsule	dMRI ISOVF	0.016	3.035	2.4E−03
thickness of rostralAntcingulate (left)	Limbic	Freesurfer DKT	−0.017	−3.032	2.4E−03
Mean FA in tapetum (left)	Commissural fibres	dMRI FA	−0.017	−3.030	2.5E−03
Mean OD in external capsule (left)	Association fibres	dMRI OD	−0.017	−3.008	2.6E−03
Grey-white contrast in Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer desikan gw	−0.015	−3.005	2.7E−03
Volume of Brodmann Area V1 (right)	Occipital	Freesurfer BA exvivo	−0.017	−3.004	2.7E−03
Volume of white matter	NA	FAST	0.016	2.999	2.7E−03
Mean FA in superior cerebellar peduncle (left)	Brainstem fibres	dMRI FA	−0.016	−2.997	2.7E−03
Mean FA in anterior corona radiata (left)	Thalamic radiations	dMRI FA	−0.015	−2.988	2.8E−03

Mean MD in tapetum (left)	Commissural fibres	dMRI diffusivity	0.016	2.983	2.9E−03
Volume of Insular Cortex (left)	Insular	Freesurfer desikan white	−0.016	−2.980	2.9E−03
Area of Postcentral Gyrus (left)	Parietal	Freesurfer desikan pial	−0.016	−2.979	2.9E−03
Mean ICVF in superior longitudinal fasciculus (right)	Association fibres	dMRI ICVF	−0.016	−2.977	2.9E−03
Volume of Brodmann Area 44 (left)	Frontal	Freesurfer BA exvivo	−0.016	−2.973	3.0E−03
Grey-white contrast in Precentral Gyrus (right)	Frontal	Freesurfer desikan gw	−0.015	−2.970	3.0E−03
thickness of Medorbitofrontal (left)	Frontal	Freesurfer desikan white	−0.016	−2.969	3.0E−03
thickness of rostralAntcingulate (left)	Limbic	Freesurfer desikan white	−0.016	−2.966	3.0E−03
Mean radial diffusivity in fornix cres+stria terminalis (left)	Limbic system fibres	dMRI diffusivity	0.014	2.961	3.1E−03
Mean radial diffusivity in fornix on FA skeleton	Limbic system fibres	dMRI diffusivity	0.014	2.959	3.1E−03
Volume of CerebralWhiteMatter (right)	NA	Freesurfer ASEG	0.015	2.958	3.1E−03
Volume of Sparietooccipital (right)	Occipital	Freesurfer a2009s	−0.016	−2.955	3.1E−03
Mean FA in medial lemniscus (left)	Brainstem fibres	dMRI FA	−0.016	−2.954	3.1E−03
Volume of Pallidum (left)	Pallidum	Freesurfer ASEG	0.016	2.945	3.2E−03
Volume of Precentral Gyrus (left)	Frontal	Freesurfer DKT	−0.016	−2.942	3.3E−03
Grey-white contrast in Paracentral lobule (right)	Frontal	Freesurfer desikan gw	−0.015	−2.939	3.3E−03
thickness of GScingulMidPost (left)	Limbic	Freesurfer a2009s	−0.016	−2.934	3.3E−03
Grey-white contrast in Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer desikan gw	−0.015	−2.930	3.4E−03
Volume of Medorbitofrontal (right)	Frontal	Freesurfer DKT	−0.016	−2.923	3.5E−03
Mean radial diffusivity in body of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.015	2.922	3.5E−03
Volume of rostralAntcingulate (left)	Limbic	Freesurfer DKT	−0.016	−2.920	3.5E−03
Area of Ssubparietal (right)	Parietal	Freesurfer a2009s	0.016	2.914	3.6E−03
Volume of VAmc (left)	Thalamus	Freesurfer subsegmentation	0.016	2.913	3.6E−03
Volume of Precentral Gyrus (left)	Frontal	Freesurfer desikan white	−0.015	−2.909	3.6E−03
Area of Gpostcentral (left)	Parietal	Freesurfer a2009s	−0.016	−2.888	3.9E−03

Volume of Frontal Pole (left)	Frontal	Freesurfer desikan white	−0.016	−2.879	4.0E−03
Mean intensity of CCPosterior (whole brain)	NA	Freesurfer ASEG	−0.015	−2.874	4.0E−03
Volume of LatFisantVertical (left)	NA	Freesurfer a2009s	−0.016	−2.874	4.1E−03
Mean FA in sagittal stratum (right)	Association fibres	dMRI FA	−0.016	−2.872	4.1E−03
Volume of VentricleChoroid (whole brain)	NA	Freesurfer ASEG	0.014	2.867	4.1E−03
Volume of grey matter in Hippocampus (left)	Hippocampus	FAST	0.015	2.863	4.2E−03
Volume of Grectus (left)	Frontal	Freesurfer a2009s	−0.016	−2.862	4.2E−03
Mean ICVF in posterior corona radiata (right)	Thalamic radiations	dMRI ICVF	−0.015	−2.855	4.3E−03
Volume of Gfrontmiddle (right)	Frontal	Freesurfer a2009s	−0.015	−2.854	4.3E−03
Mean ICVF in body of corpus callosum on FA skeleton	Commissural fibres	dMRI ICVF	−0.016	−2.841	4.5E−03
thickness of Superior Parietal Lobule (right)	Parietal	Freesurfer desikan white	0.015	2.835	4.6E−03
Area of caudalAntcingulate (left)	Limbic	Freesurfer DKT	−0.016	−2.835	4.6E−03
Volume of Cortex (left)	NA	Freesurfer ASEG	−0.014	−2.816	4.9E−03
Grey-white contrast in Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer desikan gw	−0.014	−2.811	4.9E−03
Volume of caudate (right)	Striatum	FIRST	0.015	2.807	5.0E−03
Volume of VLa (left)	Thalamus	Freesurfer subsegmentation	0.015	2.807	5.0E−03
Mean axial diffusivity in anterior limb of internal capsule (right)	Internal capsule	dMRI diffusivity	0.014	2.796	5.2E−03
Volume of Gcuneus (left)	Occipital	Freesurfer a2009s	−0.015	−2.791	5.3E−03
Mean ISOVF in posterior corona radiata (left)	Thalamic radiations	dMRI ISOVF	0.015	2.790	5.3E−03
Volume of grey matter in Temporal Occipital Fusiform Cortex (left)	Temporal	FAST	0.015	2.771	5.6E−03
Mean radial diffusivity in posterior limb of internal capsule (right)	Internal capsule	dMRI diffusivity	0.015	2.768	5.6E−03
Area of Sparietooccipital (right)	Occipital	Freesurfer a2009s	−0.015	−2.767	5.7E−03
Mean ISOVF in external capsule (right)	Association fibres	dMRI ISOVF	0.015	2.760	5.8E−03
Mean MD in fornix cres+stria terminalis (left)	Limbic system fibres	dMRI diffusivity	0.014	2.752	5.9E−03
Volume of CA1body (left)	Hippocampus	Freesurfer subsegmentation	−0.014	−2.752	5.9E−03
Area of Postcentral Gyrus (left)	Parietal	Freesurfer desikan white	−0.015	−2.751	5.9E−03

Mean OD in retrolenticular part of internal capsule (right)	Internal capsule	dMRI OD	−0.015	−2.749	6.0E−03
Volume of InfLatVent (left)	NA	Freesurfer ASEG	0.014	2.736	6.2E−03
thickness of Superior Parietal Lobule (right)	Parietal	Freesurfer DKT	0.014	2.717	6.6E−03
Mean FA in sagittal stratum (left)	Association fibres	dMRI FA	−0.015	−2.708	6.8E−03
Area of Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer desikan white	−0.015	−2.703	6.9E−03
Mean radial diffusivity in superior longitudinal fasciculus (left)	Association fibres	dMRI diffusivity	0.014	2.700	6.9E−03
Mean axial diffusivity in splenium of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.014	2.698	7.0E−03
Mean intensity of CCMidAnt (whole brain)	NA	Freesurfer ASEG	−0.015	−2.698	7.0E−03
Volume of Brodmann Area 4p (left)	Frontal	Freesurfer BA exvivo	−0.015	−2.681	7.4E−03
Area of Postcentral Gyrus (left)	Parietal	Freesurfer DKT	−0.015	−2.678	7.4E−03
Volume of grey matter in Hippocampus (right)	Hippocampus	FAST	0.014	2.676	7.5E−03
Area of Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer DKT	−0.015	−2.667	7.7E−03
Volume of LD (right)	Thalamus	Freesurfer subsegmentation	−0.015	−2.666	7.7E−03
Area of Parahippocampal Gyrus (right)	Temporal	Freesurfer desikan white	0.015	2.663	7.7E−03
Area of Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer desikan pial	0.015	2.660	7.8E−03
Volume of CA1head (right)	Hippocampus	Freesurfer subsegmentation	0.014	2.659	7.8E−03
Volume of CerebralWhiteMatter (left)	NA	Freesurfer ASEG	0.014	2.656	7.9E−03
Mean ISOVF in tapetum (right)	Commissural fibres	dMRI ISOVF	0.014	2.649	8.1E−03
Area of Brodmann Area V2 (left)	Occipital	Freesurfer BA exvivo	−0.014	−2.647	8.1E−03
Area of Gprecuneus (left)	Occipital	Freesurfer a2009s	0.014	2.630	8.5E−03
Mean ICVF in sagittal stratum (right)	Association fibres	dMRI ICVF	−0.014	−2.621	8.8E−03
thickness of GoctempmedParahip (left)	Temporal	Freesurfer a2009s	−0.014	−2.618	8.8E−03
Mean radial diffusivity in sagittal stratum (right)	Association fibres	dMRI diffusivity	0.014	2.617	8.9E−03
Mean MD in genu of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.013	2.608	9.1E−03
Area of Inferior Parietal Lobule (left)	Parietal	Freesurfer desikan pial	−0.014	−2.597	9.4E−03
Mean intensity of Amygdala (right)	Amygdala	Freesurfer ASEG	0.014	2.597	9.4E−03
Mean radial diffusivity in sagittal stratum (left)	Association fibres	dMRI diffusivity	0.014	2.594	9.5E−03

Volume of MDm (left)	Thalamus	Freesurfer subsegmentation	−0.013	−2.592	9.6E−03
Volume of Wholeamygdala (left)	Amygdala	Freesurfer subsegmentation	0.013	2.591	9.6E−03
Volume of CM (right)	Thalamus	Freesurfer subsegmentation	0.014	2.591	9.6E−03
Volume of PuM (left)	Thalamus	Freesurfer subsegmentation	−0.014	−2.588	9.7E−03
Mean axial diffusivity in cerebral peduncle (left)	Brainstem fibres	dMRI diffusivity	−0.014	−2.584	9.8E−03
Mean radial diffusivity in anterior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.013	2.583	9.8E−03
Mean OD in fornix on FA skeleton	Limbic system fibres	dMRI OD	0.013	2.582	9.8E−03
Volume of GStransvfrontopol (left)	Frontal	Freesurfer a2009s	−0.014	−2.572	1.0E−02
Area of Frontal Pole (left)	Frontal	Freesurfer desikan pial	−0.014	−2.559	1.1E−02
Area of SocmiddleLunatus (left)	Occipital	Freesurfer a2009s	−0.014	−2.557	1.1E−02
Volume of Pallidum (right)	Pallidum	Freesurfer ASEG	0.014	2.556	1.1E−02
Mean radial diffusivity in splenium of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.014	2.550	1.1E−02
Mean axial diffusivity in cingulum cingulate gyrus (left)	Limbic system fibres	dMRI diffusivity	0.014	2.544	1.1E−02
Mean MD in medial lemniscus (right)	Brainstem fibres	dMRI diffusivity	0.014	2.531	1.1E−02
thickness of SocmiddleLunatus (left)	Occipital	Freesurfer a2009s	0.014	2.531	1.1E−02
Volume of GInslgScentins (left)	Insular	Freesurfer a2009s	−0.014	−2.527	1.1E−02
Grey-white contrast in Paracentral lobule (left)	Frontal	Freesurfer desikan gw	−0.013	−2.526	1.2E−02
Area of Parahippocampal Gyrus (right)	Temporal	Freesurfer DKT	0.014	2.521	1.2E−02
Volume of Gsubcallosal (left)	Frontal	Freesurfer a2009s	−0.014	−2.517	1.2E−02
Mean ISOVF in body of corpus callosum on FA skeleton	Commissural fibres	dMRI ISOVF	0.013	2.514	1.2E−02
Mean MD in anterior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.013	2.508	1.2E−02
Volume of CA1body (right)	Hippocampus	Freesurfer subsegmentation	−0.013	−2.508	1.2E−02
Mean FA in anterior corona radiata (right)	Thalamic radiations	dMRI FA	−0.013	−2.503	1.2E−02
Area of Superior Frontal Gyrus (right)	Frontal	Freesurfer desikan white	−0.014	−2.501	1.2E−02
Area of Precentral Gyrus (left)	Frontal	Freesurfer desikan pial	−0.014	−2.494	1.3E−02

thickness of Grectus (right)	Frontal	Freesurfer a2009s	−0.014	−2.493	1.3E−02
Mean ISOVF in superior fronto-occipital fasciculus (left)	Association fibres	dMRI ISOVF	0.013	2.493	1.3E−02
Mean ISOVF in superior corona radiata (left)	Thalamic radiations	dMRI ISOVF	0.013	2.491	1.3E−02
Volume of subiculumhead (right)	Hippocampus	Freesurfer subsegmentation	0.013	2.491	1.3E−02
Mean axial diffusivity in cerebral peduncle (right)	Brainstem fibres	dMRI diffusivity	−0.014	−2.489	1.3E−02
Area of Superior Frontal Gyrus (right)	Frontal	Freesurfer desikan pial	−0.014	−2.488	1.3E−02
Volume of LSg (left)	Thalamus	Freesurfer subsegmentation	0.013	2.488	1.3E−02
Grey-white contrast in Pericalcarine cortex (right)	Occipital	Freesurfer desikan gw	0.013	2.480	1.3E−02
Volume of Hippocampaltail (left)	Hippocampus	Freesurfer subsegmentation	0.013	2.480	1.3E−02
Volume of Wholehippocampalhead (right)	Hippocampus	Freesurfer subsegmentation	0.012	2.480	1.3E−02
thickness of SorbitalHShaped (left)	Frontal	Freesurfer a2009s	−0.014	−2.475	1.3E−02
Volume of choroidplexus (left)	NA	Freesurfer ASEG	0.012	2.473	1.3E−02
Volume of Centralnucleus (left)	Amygdala	Freesurfer subsegmentation	0.013	2.471	1.3E−02
Area of Goctemplatfusifor (right)	Temporal	Freesurfer a2009s	−0.014	−2.471	1.3E−02
Mean ICVF in cerebral peduncle (right)	Brainstem fibres	dMRI ICVF	0.013	2.470	1.4E−02
Volume of LateralVentricle (right)	NA	Freesurfer ASEG	0.012	2.469	1.4E−02
Volume of Gparietalsup (right)	Parietal	Freesurfer a2009s	0.013	2.468	1.4E−02
Mean ISOVF in superior cerebellar peduncle (left)	Brainstem fibres	dMRI ISOVF	0.013	2.467	1.4E−02
Volume of grey matter in Juxtapositional Lobule Cortex (formerly Supplementary Motor Cortex) (right)	Frontal	FAST	−0.013	−2.464	1.4E−02
Mean intensity of WMhypointensities (whole brain)	NA	Freesurfer ASEG	0.013	2.461	1.4E−02
Mean MD in posterior limb of internal capsule (left)	Internal capsule	dMRI diffusivity	0.013	2.452	1.4E−02
Volume of Insular Cortex (left)	Insular	Freesurfer DKT	−0.013	−2.451	1.4E−02
Area of Brodmann Area 3b (left)	Parietal	Freesurfer BA exvivo	−0.013	−2.446	1.4E−02
Area of Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer desikan pial	−0.013	−2.438	1.5E−02
Volume of Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer desikan white	−0.013	−2.433	1.5E−02
Mean axial diffusivity in genu of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.013	2.432	1.5E−02

Volume of Sfrontinf (left)	Frontal	Freesurfer a2009s	−0.013	−2.428	1.5E−02
Mean intensity of Hippocampus (right)	Hippocampus	Freesurfer ASEG	0.013	2.427	1.5E−02
thickness of LatFisantVertical (left)	NA	Freesurfer a2009s	−0.013	−2.420	1.6E−02
Volume of grey matter in Intracalcarine Cortex (left)	Occipital	FAST	−0.013	−2.420	1.6E−02
Grey-white contrast in Superior Frontal Gyrus (left)	Frontal	Freesurfer desikan gw	−0.011	−2.415	1.6E−02
Mean radial diffusivity in superior longitudinal fasciculus (right)	Association fibres	dMRI diffusivity	0.013	2.415	1.6E−02
Volume of grey matter in Frontal Pole (left)	Frontal	FAST	−0.012	−2.413	1.6E−02
Volume of Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer desikan white	−0.013	−2.411	1.6E−02
Mean FA in superior fronto-occipital fasciculus (right)	Association fibres	dMRI FA	−0.013	−2.408	1.6E−02
Volume of Inferior Parietal Lobule (left)	Parietal	Freesurfer DKT	−0.013	−2.400	1.6E−02
Mean ISOVF in superior cerebellar peduncle (right)	Brainstem fibres	dMRI ISOVF	0.013	2.400	1.6E−02
Volume of Putamen (right)	Striatum	Freesurfer ASEG	0.013	2.398	1.6E−02
Grey-white contrast in Superior Frontal Gyrus (right)	Frontal	Freesurfer desikan gw	−0.011	−2.398	1.7E−02
Grey-white contrast in Parahippocampal Gyrus (left)	Temporal	Freesurfer desikan gw	−0.013	−2.396	1.7E−02
Mean ISOVF in fornix cres+stria terminalis (left)	Limbic system fibres	dMRI ISOVF	0.013	2.395	1.7E−02
Mean MD in external capsule (left)	Association fibres	dMRI diffusivity	0.012	2.392	1.7E−02
Area of SintermprimJensen (right)	Parietal	Freesurfer a2009s	−0.013	−2.391	1.7E−02
Mean ICVF in medial lemniscus (left)	Brainstem fibres	dMRI ICVF	−0.013	−2.389	1.7E−02
thickness of Cingulate Gyrus, posterior (left)	Limbic	Freesurfer DKT	−0.013	−2.386	1.7E−02
thickness of Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer DKT	−0.013	−2.386	1.7E−02
Volume of LP (left)	Thalamus	Freesurfer subsegmentation	−0.013	−2.380	1.7E−02
Mean axial diffusivity in posterior limb of internal capsule (right)	Internal capsule	dMRI diffusivity	0.013	2.373	1.8E−02
Mean OD in superior fronto-occipital fasciculus (left)	Association fibres	dMRI OD	−0.013	−2.371	1.8E−02
Area of TotalSurface (left)	NA	Freesurfer desikan pial	−0.012	−2.367	1.8E−02
Volume of Pc (left)	Thalamus	Freesurfer subsegmentation	0.012	2.367	1.8E−02
Area of Sfrontinf (left)	Frontal	Freesurfer a2009s	−0.013	−2.365	1.8E−02
Volume of Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer DKT	−0.013	−2.364	1.8E−02
Volume of SubCortGray (whole brain)	NA	Freesurfer ASEG	0.012	2.363	1.8E−02

Mean radial diffusivity in retrolenticular part of internal capsule (right)	Internal capsule	dMRI diffusivity	0.013	2.356	1.8E−02
Volume of grey matter in Temporal Fusiform Cortex, anterior division (left)	Temporal	FAST	−0.012	−2.355	1.9E−02
Volume of presubiculumhead (left)	Hippocampus	Freesurfer subsegmentation	0.012	2.348	1.9E−02
Mean radial diffusivity in medial lemniscus (left)	Brainstem fibres	dMRI diffusivity	0.013	2.348	1.9E−02
Volume of Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer desikan white	−0.013	−2.347	1.9E−02
thickness of caudalAntcingulate (left)	Limbic	Freesurfer DKT	−0.013	−2.347	1.9E−02
thickness of Gparietalsup (right)	Parietal	Freesurfer a2009s	0.012	2.342	1.9E−02
Area of SoctempmedLingual (right)	Temporal	Freesurfer a2009s	0.013	2.334	2.0E−02
Volume of Inferior Parietal Lobule (left)	Parietal	Freesurfer desikan white	−0.013	−2.330	2.0E−02
Area of Fusiform Gyrus (left)	Occipital	Freesurfer desikan pial	−0.013	−2.330	2.0E−02
Area of Inferior Parietal Lobule (left)	Parietal	Freesurfer DKT	−0.013	−2.330	2.0E−02
thickness of Lateral orbitofrontal cortex (left)	Frontal	Freesurfer desikan white	−0.013	−2.324	2.0E−02
Volume of Paracentral lobule (left)	Frontal	Freesurfer DKT	−0.012	−2.318	2.0E−02
Mean ISOVF in anterior corona radiata (left)	Thalamic radiations	dMRI ISOVF	0.013	2.316	2.1E−02
Volume of grey matter in Frontal Pole (right)	Frontal	FAST	−0.012	−2.311	2.1E−02
Mean ISOVF in sagittal stratum (left)	Association fibres	dMRI ISOVF	−0.013	−2.308	2.1E−02
thickness of Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer a2009s	−0.013	−2.308	2.1E−02
thickness of Goccipitalsup (right)	Occipital	Freesurfer a2009s	0.013	2.305	2.1E−02
thickness of Sfrontmiddle (left)	Frontal	Freesurfer a2009s	−0.012	−2.305	2.1E−02
Volume of Sorbitalmedolfact (left)	Frontal	Freesurfer a2009s	−0.013	−2.300	2.1E−02
Area of Brodmann Area 4p (left)	Frontal	Freesurfer BA exvivo	−0.013	−2.298	2.2E−02
Mean axial diffusivity in tapetum (left)	Commissural fibres	dMRI diffusivity	0.012	2.294	2.2E−02
Volume of grey matter in Pallidum (left)	Pallidum	FAST	0.012	2.289	2.2E−02
Area of Sparietooccipital (left)	Occipital	Freesurfer a2009s	−0.013	−2.287	2.2E−02
Area of Inferior Parietal Lobule (left)	Parietal	Freesurfer desikan white	−0.013	−2.286	2.2E−02
Area of Scentral (left)	Frontal	Freesurfer a2009s	−0.013	−2.286	2.2E−02
Volume of parasubiculum (left)	Hippocampus	Freesurfer subsegmentation	0.013	2.286	2.2E−02

Mean OD in external capsule (right)	Association fibres	dMRI OD	−0.012	−2.274	2.3E−02
thickness of Cingulate Gyrus, posterior (left)	Limbic	Freesurfer desikan white	−0.012	−2.274	2.3E−02
Volume of Cortamygdaloidtransitio (left)	Amygdala	Freesurfer subsegmentation	0.012	2.264	2.4E−02
Volume of 3rdVentricle (whole brain)	NA	Freesurfer ASEG	0.011	2.259	2.4E−02
Area of Spericallosal (right)	Limbic	Freesurfer a2009s	0.012	2.254	2.4E−02
Volume of Scircularinsulasup (right)	Insular	Freesurfer a2009s	−0.012	−2.248	2.5E−02
Volume of grey matter in Postcentral Gyrus (left)	Parietal	FAST	−0.012	−2.248	2.5E−02
Volume of Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer DKT	−0.012	−2.241	2.5E−02
Mean FA in cerebral peduncle (right)	Brainstem fibres	dMRI FA	−0.012	−2.239	2.5E−02
Mean MD in sagittal stratum (right)	Association fibres	dMRI diffusivity	0.012	2.239	2.5E−02
Area of Brodmann Area 1 (left)	Parietal	Freesurfer BA exvivo	−0.012	−2.234	2.5E−02
Volume of grey matter in Subcallosal Cortex (right)	Frontal	FAST	−0.012	−2.234	2.5E−02
Volume of GScingulMidPost (left)	Limbic	Freesurfer a2009s	−0.012	−2.232	2.6E−02
thickness of GScingulMidAnt (left)	Limbic	Freesurfer a2009s	−0.012	−2.232	2.6E−02
Area of GSsubcentral (right)	Frontal	Freesurfer a2009s	−0.012	−2.229	2.6E−02
Mean ISOVF in retrolenticular part of internal capsule (right)	Internal capsule	dMRI ISOVF	0.012	2.225	2.6E−02
thickness of GtempsupPlanpolar (left)	Temporal	Freesurfer a2009s	−0.012	−2.222	2.6E−02
Mean axial diffusivity in posterior limb of internal capsule (left)	Internal capsule	dMRI diffusivity	0.012	2.216	2.7E−02
Mean radial diffusivity in external capsule (right)	Association fibres	dMRI diffusivity	0.011	2.212	2.7E−02
Volume of SintermprimJensen (right)	Parietal	Freesurfer a2009s	−0.012	−2.211	2.7E−02
Volume of grey matter in Middle Frontal Gyrus (right)	Frontal	FAST	−0.012	−2.211	2.7E−02
Mean FA in fornix cres+stria terminalis (left)	Limbic system fibres	dMRI FA	−0.011	−2.208	2.7E−02
Volume of Brodmann Area 44 (right)	Frontal	Freesurfer BA exvivo	−0.012	−2.205	2.7E−02
Volume of CL (left)	Thalamus	Freesurfer subsegmentation	−0.012	−2.204	2.8E−02
Volume of Fusiform Gyrus (left)	Occipital	Freesurfer desikan white	−0.012	−2.202	2.8E−02
Grey-white contrast in rostralAntcingulate (left)	Limbic	Freesurfer desikan gw	−0.011	−2.201	2.8E−02
Mean MD in anterior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.011	2.195	2.8E−02

Volume of Pt (right)	Thalamus	Freesurfer subsegmentation	0.012	2.193	2.8E−02
Mean ISOVF in uncinate fasciculus (right)	Association fibres	dMRI ISOVF	0.012	2.189	2.9E−02
Area of Gcuneus (right)	Occipital	Freesurfer a2009s	−0.012	−2.188	2.9E−02
Volume of MGN (left)	Thalamus	Freesurfer subsegmentation	−0.012	−2.187	2.9E−02
Area of Sorbitalmedolfact (left)	Frontal	Freesurfer a2009s	−0.012	−2.186	2.9E−02
Mean FA in corticospinal tract (left)	Brainstem fibres	dMRI FA	−0.012	−2.185	2.9E−02
thickness of Frontal Pole (left)	Frontal	Freesurfer desikan white	−0.012	−2.179	2.9E−02
Volume of Gfrontmiddle (left)	Frontal	Freesurfer a2009s	−0.011	−2.175	3.0E−02
Area of Scircularinsulainf (left)	Insular	Freesurfer a2009s	0.012	2.174	3.0E−02
Mean FA in fornix cres+stria terminalis (right)	Limbic system fibres	dMRI FA	−0.011	−2.173	3.0E−02
Mean FA in superior fronto-occipital fasciculus (left)	Association fibres	dMRI FA	−0.011	−2.173	3.0E−02
Volume of choroidplexus (right)	NA	Freesurfer ASEG	0.011	2.172	3.0E−02
Volume of Brodmann Area V2 (left)	Occipital	Freesurfer BA exvivo	−0.012	−2.170	3.0E−02
Volume of CA3body (left)	Hippocampus	Freesurfer subsegmentation	−0.012	−2.169	3.0E−02
Volume of Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer DKT	−0.012	−2.167	3.0E−02
Volume of Paracentral lobule (left)	Frontal	Freesurfer desikan white	−0.012	−2.161	3.1E−02
Mean FA in anterior limb of internal capsule (right)	Internal capsule	dMRI FA	−0.012	−2.159	3.1E−02
Volume of Centralnucleus (right)	Amygdala	Freesurfer subsegmentation	0.012	2.157	3.1E−02
Volume of LGN (left)	Thalamus	Freesurfer subsegmentation	−0.011	−2.157	3.1E−02
Area of Brodmann Area 44 (left)	Frontal	Freesurfer BA exvivo	−0.012	−2.151	3.1E−02
Volume of Gcuneus (right)	Occipital	Freesurfer a2009s	−0.012	−2.148	3.2E−02
Mean intensity of Putamen (left)	Striatum	Freesurfer ASEG	−0.012	−2.147	3.2E−02
Volume of PuL (right)	Thalamus	Freesurfer subsegmentation	0.012	2.147	3.2E−02
thickness of Stemporaltransverse (right)	Temporal	Freesurfer a2009s	0.012	2.146	3.2E−02

Volume of Cuneal Cortex (right)	Occipital	Freesurfer desikan white	−0.012	−2.143	3.2E−02
Mean FA in superior corona radiata (left)	Thalamic radiations	dMRI FA	−0.011	−2.143	3.2E−02
Volume of subiculumbody (right)	Hippocampus	Freesurfer subsegmentation	0.011	2.141	3.2E−02
Volume of VAmc (right)	Thalamus	Freesurfer subsegmentation	0.011	2.141	3.2E−02
Area of GSsubcentral (left)	Frontal	Freesurfer a2009s	−0.012	−2.137	3.3E−02
Mean OD in anterior limb of internal capsule (left)	Internal capsule	dMRI OD	−0.012	−2.128	3.3E−02
Area of Gprecuneus (right)	Occipital	Freesurfer a2009s	0.012	2.126	3.4E−02
Area of Cuneal Cortex (right)	Occipital	Freesurfer DKT	−0.012	−2.125	3.4E−02
Mean MD in sagittal stratum (left)	Association fibres	dMRI diffusivity	0.011	2.123	3.4E−02
Volume of Cuneal Cortex (right)	Occipital	Freesurfer DKT	−0.012	−2.116	3.4E−02
Volume of Lateralnucleus (left)	Amygdala	Freesurfer subsegmentation	0.011	2.112	3.5E−02
Grey-white contrast in Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer desikan gw	−0.011	−2.106	3.5E−02
Mean OD in inferior cerebellar peduncle (left)	Brainstem fibres	dMRI OD	0.011	2.106	3.5E−02
Volume of Postcentral Gyrus (left)	Parietal	Freesurfer desikan white	−0.011	−2.105	3.5E−02
Volume of Brodmann Area 45 (left)	Frontal	Freesurfer BA exvivo	−0.011	−2.104	3.5E−02
Mean ISOVF in superior corona radiata (right)	Thalamic radiations	dMRI ISOVF	0.011	2.103	3.5E−02
Mean axial diffusivity in cingulum cingulate gyrus (right)	Limbic system fibres	dMRI diffusivity	0.012	2.100	3.6E−02
Volume of Postcentral Gyrus (left)	Parietal	Freesurfer DKT	−0.011	−2.092	3.6E−02
Area of LatFisantVertical (left)	NA	Freesurfer a2009s	−0.012	−2.091	3.7E−02
Volume of Sfrontinf (right)	Frontal	Freesurfer a2009s	−0.011	−2.091	3.7E−02
Area of Cingulate Gyrus, posterior (right)	Limbic	Freesurfer DKT	−0.011	−2.089	3.7E−02
Volume of Scentral (left)	Frontal	Freesurfer a2009s	−0.012	−2.089	3.7E−02
Mean intensity of Accumbensarea (right)	Striatum	Freesurfer ASEG	−0.011	−2.085	3.7E−02
Volume of molecularlayerHPhead (right)	Hippocampus	Freesurfer subsegmentation	0.011	2.080	3.8E−02
Area of GScingulAnt (left)	Limbic	Freesurfer a2009s	−0.011	−2.079	3.8E−02
Area of Superior Frontal Gyrus (right)	Frontal	Freesurfer DKT	−0.011	−2.074	3.8E−02

Volume of subiculumhead (left)	Hippocampus	Freesurfer subsegmentation	0.011	2.071	3.8E−02
Mean radial diffusivity in genu of corpus callosum on FA skeleton	Commissural fibres	dMRI diffusivity	0.011	2.070	3.8E−02
Mean FA in body of corpus callosum on FA skeleton	Commissural fibres	dMRI FA	−0.011	−2.067	3.9E−02
Volume of CSF (whole brain)	NA	Freesurfer ASEG	0.011	2.058	4.0E−02
Volume of VA (right)	Thalamus	Freesurfer subsegmentation	0.011	2.058	4.0E−02
Volume of 4thVentricle (whole brain)	NA	Freesurfer ASEG	0.011	2.055	4.0E−02
Volume of Gpostcentral (left)	Parietal	Freesurfer a2009s	−0.011	−2.054	4.0E−02
Mean FA in corticospinal tract (right)	Brainstem fibres	dMRI FA	−0.011	−2.047	4.1E−02
thickness of Scircularinsulainf (right)	Insular	Freesurfer a2009s	−0.011	−2.042	4.1E−02
Volume of Superior Frontal Gyrus (right)	Frontal	Freesurfer DKT	−0.011	−2.042	4.1E−02
thickness of Perirhinal cortex (left)	Temporal	Freesurfer BA exvivo	−0.011	−2.040	4.1E−02
Volume of grey matter in Cuneal Cortex (right)	Occipital	FAST	−0.011	−2.038	4.2E−02
Area of Medorbitofrontal (left)	Frontal	Freesurfer desikan pial	−0.011	−2.038	4.2E−02
Volume of rostralAntcingulate (left)	Limbic	Freesurfer desikan white	−0.011	−2.038	4.2E−02
Volume of Midbrain (whole brain)	NA	Freesurfer subsegmentation	0.011	2.036	4.2E−02
Volume of GSoccipitalinf (left)	Occipital	Freesurfer a2009s	0.011	2.033	4.2E−02
Volume of Cingulate Gyrus, posterior (right)	Limbic	Freesurfer DKT	−0.011	−2.031	4.2E−02
Volume of Ssubparietal (left)	Parietal	Freesurfer a2009s	0.011	2.031	4.2E−02
thickness of Scircularinsulaant (left)	Insular	Freesurfer a2009s	−0.011	−2.024	4.3E−02
thickness of GSparacentral (left)	Frontal	Freesurfer a2009s	−0.011	−2.024	4.3E−02
Area of Cuneal Cortex (right)	Occipital	Freesurfer desikan white	−0.011	−2.021	4.3E−02
Mean OD in superior longitudinal fasciculus (right)	Association fibres	dMRI OD	−0.011	−2.019	4.4E−02
Volume of grey matter in Temporal Pole (right)	Temporal	FAST	−0.011	−2.007	4.5E−02
Mean axial diffusivity in superior cerebellar peduncle (left)	Brainstem fibres	dMRI diffusivity	0.011	2.003	4.5E−02
thickness of rostralAntcingulate (right)	Limbic	Freesurfer DKT	−0.011	−1.994	4.6E−02
Mean MD in anterior limb of internal capsule (left)	Internal capsule	dMRI diffusivity	0.010	1.994	4.6E−02
thickness of SintraparietPtrans (right)	Parietal	Freesurfer a2009s	0.011	1.994	4.6E−02

Volume of grey matter	NA	FAST	−0.009	−1.991	4.6E−02
Mean OD in inferior cerebellar peduncle (right)	Brainstem fibres	dMRI OD	0.011	1.991	4.7E−02
Area of TotalSurface (right)	NA	Freesurfer desikan pial	−0.010	−1.988	4.7E−02
Volume of Precentral Gyrus (right)	Frontal	Freesurfer DKT	−0.011	−1.986	4.7E−02
thickness of Medorbitofrontal (right)	Frontal	Freesurfer desikan white	−0.011	−1.984	4.7E−02
Volume of Poletemporal (left)	Temporal	Freesurfer a2009s	−0.011	−1.984	4.7E−02
Area of Gorbital (left)	Frontal	Freesurfer a2009s	0.011	1.979	4.8E−02
Volume of grey matter in Amygdala (left)	Amygdala	FAST	0.010	1.973	4.9E−02
Volume of Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer desikan white	−0.010	−1.972	4.9E−02
Area of Cingulate Gyrus, posterior (right)	Limbic	Freesurfer desikan pial	−0.011	−1.967	4.9E−02
Area of Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer desikan pial	−0.011	−1.964	5.0E−02
Area of Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer desikan white	0.011	1.961	5.0E−02
thickness of caudalAntcingulate (left)	Limbic	Freesurfer a2009s	−0.011	−1.959	5.0E−02
thickness of Soctemplat (left)	Temporal	Freesurfer a2009s	0.011	1.958	5.0E−02
Mean ICVF in superior cerebellar peduncle (right)	Brainstem fibres	dMRI ICVF	−0.011	−1.955	5.1E−02
thickness of Scircularinsulasup (left)	Insular	Freesurfer a2009s	−0.010	−1.952	5.1E−02
Mean ISOVF in genu of corpus callosum on FA skeleton	Commissural fibres	dMRI ISOVF	0.010	1.951	5.1E−02
Volume of Precentral Gyrus (right)	Frontal	Freesurfer desikan white	−0.010	−1.944	5.2E−02
Volume of grey matter in Brain-Stem	NA	FAST	0.010	1.939	5.3E−02
Mean ICVF in genu of corpus callosum on FA skeleton	Commissural fibres	dMRI ICVF	−0.010	−1.937	5.3E−02
Area of Ssubparietal (left)	Parietal	Freesurfer a2009s	0.011	1.937	5.3E−02
Area of Poleoccipital (right)	Occipital	Freesurfer a2009s	−0.011	−1.936	5.3E−02
Volume of GfrontinfTriangul (right)	Frontal	Freesurfer a2009s	−0.011	−1.934	5.3E−02
Volume of Ginsularshort (left)	Insular	Freesurfer a2009s	−0.011	−1.933	5.3E−02
Volume of Cingulate Gyrus, posterior (right)	Limbic	Freesurfer desikan white	−0.011	−1.932	5.3E−02
Area of Cuneal Cortex (right)	Occipital	Freesurfer desikan pial	−0.011	−1.924	5.4E−02
Mean ISOVF in anterior corona radiata (right)	Thalamic radiations	dMRI ISOVF	0.011	1.923	5.5E−02

Area of GSfrontomargin (right)	Frontal	Freesurfer a2009s	0.010	1.920	5.5E−02
Area of Superior Temporal Gyrus (left)	Temporal	Freesurfer desikan pial	0.011	1.915	5.5E−02
Grey-white contrast in Supramarginal Gyrus (left)	Parietal	Freesurfer desikan gw	−0.010	−1.915	5.5E−02
thickness of Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer desikan white	−0.010	−1.914	5.6E−02
Volume of Superior Parietal Lobule (right)	Parietal	Freesurfer desikan white	0.010	1.914	5.6E−02
Mean intensity of CCCentral (whole brain)	NA	Freesurfer ASEG	−0.010	−1.911	5.6E−02
Grey-white contrast in Supramarginal Gyrus (right)	Parietal	Freesurfer desikan gw	−0.010	−1.906	5.7E−02
Volume of Gprecuneus (left)	Occipital	Freesurfer a2009s	0.010	1.904	5.7E−02
thickness of Gprecentral (left)	Frontal	Freesurfer a2009s	−0.010	−1.902	5.7E−02
thickness of LatFispost (left)	NA	Freesurfer a2009s	−0.010	−1.901	5.7E−02
Area of Cingulate Gyrus, posterior (right)	Limbic	Freesurfer desikan white	−0.010	−1.896	5.8E−02
thickness of Gorbital (left)	Frontal	Freesurfer a2009s	−0.010	−1.896	5.8E−02
Mean ISOVF in superior fronto-occipital fasciculus (right)	Association fibres	dMRI ISOVF	0.010	1.892	5.9E−02
thickness of GSoccipitalinf (left)	Occipital	Freesurfer a2009s	0.010	1.890	5.9E−02
thickness of Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer DKT	−0.010	−1.890	5.9E−02
Mean MD in cingulum cingulate gyrus (left)	Limbic system fibres	dMRI diffusivity	0.010	1.888	5.9E−02
Area of Entorhinal cortex (right)	Temporal	Freesurfer desikan pial	0.010	1.887	5.9E−02
Mean radial diffusivity in anterior limb of internal capsule (left)	Internal capsule	dMRI diffusivity	0.010	1.885	5.9E−02
Volume of GfrontinfOpercular (left)	Frontal	Freesurfer a2009s	−0.010	−1.884	6.0E−02
Mean FA in inferior cerebellar peduncle (left)	Brainstem fibres	dMRI FA	−0.010	−1.880	6.0E−02
thickness of rostralAntcingulate (right)	Limbic	Freesurfer desikan white	−0.010	−1.878	6.0E−02
Volume of pallidum (left)	Pallidum	FIRST	0.010	1.877	6.1E−02
Volume of Fusiform Gyrus (left)	Occipital	Freesurfer DKT	−0.010	−1.871	6.1E−02
Mean FA in fornix on FA skeleton	Limbic system fibres	dMRI FA	−0.009	−1.869	6.2E−02
Volume of Superior Parietal Lobule (right)	Parietal	Freesurfer DKT	0.010	1.867	6.2E−02
Area of Brodmann Area V2 (right)	Occipital	Freesurfer BA exvivo	−0.010	−1.867	6.2E−02

Volume of grey matter in V Cerebellum (right)	Cerebellum	FAST	0.010	1.867	6.2E−02
Mean axial diffusivity in anterior limb of internal capsule (left)	Internal capsule	dMRI diffusivity	0.009	1.864	6.2E−02
Volume of SCP (whole brain)	NA	Freesurfer subsegmentation	0.010	1.862	6.3E−02
Volume of Goctemplatfusifor (right)	Temporal	Freesurfer a2009s	−0.010	−1.862	6.3E−02
thickness of Brodmann Area 4a (left)	Frontal	Freesurfer BA exvivo	−0.010	−1.862	6.3E−02
Volume of presubiculumbody (right)	Hippocampus	Freesurfer subsegmentation	0.009	1.854	6.4E−02
Volume of Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer DKT	−0.010	−1.850	6.4E−02
Grey-white contrast in Lingual Gyrus (right)	Occipital	Freesurfer desikan gw	0.010	1.849	6.5E−02
thickness of Precentral Gyrus (left)	Frontal	Freesurfer desikan white	−0.010	−1.848	6.5E−02
Area of Lingual Gyrus (left)	Occipital	Freesurfer desikan pial	−0.010	−1.845	6.5E−02
Volume of Insular Cortex (right)	Insular	Freesurfer desikan white	−0.010	−1.843	6.5E−02
Mean FA in inferior cerebellar peduncle (right)	Brainstem fibres	dMRI FA	−0.010	−1.841	6.6E−02
thickness of Precentral Gyrus (left)	Frontal	Freesurfer DKT	−0.010	−1.836	6.6E−02
thickness of Sfrontmiddle (right)	Frontal	Freesurfer a2009s	−0.010	−1.835	6.6E−02
Volume of LP (right)	Thalamus	Freesurfer subsegmentation	−0.010	−1.835	6.6E−02
thickness of Sfrontinf (right)	Frontal	Freesurfer a2009s	−0.010	−1.835	6.6E−02
thickness of Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer desikan white	−0.010	−1.834	6.7E−02
Volume of grey matter in Central Opercular Cortex (right)	Insular	FAST	−0.009	−1.833	6.7E−02
Area of Inferior Temporal Gyrus (left)	Temporal	Freesurfer DKT	−0.010	−1.832	6.7E−02
Volume of grey matter in Temporal Pole (left)	Temporal	FAST	−0.010	−1.831	6.7E−02
thickness of Fusiform Gyrus (left)	Occipital	Freesurfer DKT	−0.010	−1.825	6.8E−02
Volume of grey matter in Inferior Frontal Gyrus, pars triangularis (left)	Frontal	FAST	−0.010	−1.825	6.8E−02
Area of Inferior Temporal Gyrus (left)	Temporal	Freesurfer desikan white	−0.010	−1.825	6.8E−02
Volume of Goccipitalmiddle (left)	Occipital	Freesurfer a2009s	−0.010	−1.825	6.8E−02
Area of TotalSurface (left)	NA	Freesurfer desikan white	−0.010	−1.823	6.8E−02

Volume of TotalGray (whole brain)	NA	Freesurfer ASEG	−0.009	−1.823	6.8E−02
Volume of Wholehippocampus (right)	Hippocampus	Freesurfer subsegmentation	0.009	1.822	6.8E−02
Area of Lingual Gyrus (left)	Occipital	Freesurfer DKT	−0.010	−1.818	6.9E−02
Area of GoctempmedLingual (left)	Occipital	Freesurfer a2009s	−0.010	−1.815	7.0E−02
Area of Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer DKT	0.010	1.812	7.0E−02
Mean intensity of InfLatVent (left)	NA	Freesurfer ASEG	−0.009	−1.809	7.0E−02
Area of Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer desikan white	−0.010	−1.809	7.1E−02
Area of Perirhinal cortex (right)	Temporal	Freesurfer BA exvivo	0.010	1.808	7.1E−02
Volume of OpticChiasm (whole brain)	NA	Freesurfer ASEG	0.010	1.805	7.1E−02
Volume of Sorbitalmedolfact (right)	Frontal	Freesurfer a2009s	−0.010	−1.802	7.1E−02
Volume of Scircularinsulasup (left)	Insular	Freesurfer a2009s	−0.010	−1.802	7.2E−02
Grey-white contrast in Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer desikan gw	−0.009	−1.801	7.2E−02
Volume of Goctemplatfusifor (left)	Temporal	Freesurfer a2009s	−0.010	−1.795	7.3E−02
Mean intensity of Putamen (right)	Striatum	Freesurfer ASEG	−0.010	−1.794	7.3E−02
Volume of Brodmann Area 4a (right)	Frontal	Freesurfer BA exvivo	−0.010	−1.790	7.3E−02
thickness of Fusiform Gyrus (left)	Occipital	Freesurfer a2009s	−0.010	−1.789	7.4E−02
Mean OD in posterior limb of internal capsule (left)	Internal capsule	dMRI OD	−0.010	−1.785	7.4E−02
Volume of SocmiddleLunatus (left)	Occipital	Freesurfer a2009s	−0.010	−1.785	7.4E−02
Volume of subiculumbody (left)	Hippocampus	Freesurfer subsegmentation	0.009	1.783	7.5E−02
Volume of Basalnucleus (right)	Amygdala	Freesurfer subsegmentation	0.009	1.781	7.5E−02
Volume of VLa (right)	Thalamus	Freesurfer subsegmentation	0.010	1.780	7.5E−02
Volume of PuA (right)	Thalamus	Freesurfer subsegmentation	0.010	1.774	7.6E−02
thickness of Gprecuneus (right)	Occipital	Freesurfer a2009s	0.009	1.773	7.6E−02
Mean MD in uncinate fasciculus (right)	Association fibres	dMRI diffusivity	0.009	1.772	7.6E−02
Mean ICVF in retrolenticular part of internal capsule (right)	Internal capsule	dMRI ICVF	−0.010	−1.771	7.7E−02
Area of Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer desikan white	0.010	1.766	7.7E−02

thickness of Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer desikan white	−0.009	−1.763	7.8E−02
Volume of Lingual Gyrus (left)	Occipital	Freesurfer desikan white	−0.010	−1.762	7.8E−02
Volume of grey matter in Inferior Temporal Gyrus, posterior division (right)	Temporal	FAST	−0.010	−1.762	7.8E−02
Volume of grey matter in Inferior Frontal Gyrus, pars opercularis (right)	Frontal	FAST	−0.009	−1.760	7.8E−02
Volume of GfrontinfTriangul (left)	Frontal	Freesurfer a2009s	−0.010	−1.759	7.9E−02
Area of Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer desikan white	−0.010	−1.756	7.9E−02
thickness of Poleoccipital (right)	Occipital	Freesurfer a2009s	0.010	1.755	7.9E−02
Mean FA in genu of corpus callosum on FA skeleton	Commissural fibres	dMRI FA	−0.009	−1.753	8.0E−02
Area of Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer DKT	−0.010	−1.748	8.1E−02
Area of Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer DKT	−0.010	−1.748	8.1E−02
Volume of caudalAntcingulate (left)	Limbic	Freesurfer desikan white	−0.010	−1.747	8.1E−02
thickness of Lateral Occipital Cortex (right)	Occipital	Freesurfer DKT	0.010	1.747	8.1E−02
Area of Precentral Gyrus (left)	Frontal	Freesurfer DKT	−0.010	−1.746	8.1E−02
Volume of HATA (left)	Hippocampus	Freesurfer subsegmentation	0.009	1.746	8.1E−02
Volume of grey matter in Juxtapositional Lobule Cortex (formerly Supplementary Motor Cortex) (left)	Frontal	FAST	−0.009	−1.744	8.1E−02
Volume of GSsubcentral (left)	Frontal	Freesurfer a2009s	−0.009	−1.743	8.1E−02
Volume of LatFisantHorizont (left)	NA	Freesurfer a2009s	−0.010	−1.742	8.2E−02
Area of Soctemplat (left)	Temporal	Freesurfer a2009s	−0.010	−1.741	8.2E−02
Mean ISOVF in cingulum hippocampus (right)	Limbic system fibres	dMRI ISOVF	0.010	1.736	8.3E−02
Area of Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer DKT	−0.010	−1.736	8.3E−02
thickness of GSfrontomargin (right)	Frontal	Freesurfer a2009s	−0.010	−1.732	8.3E−02
Volume of grey matter in Lingual Gyrus (left)	Occipital	FAST	0.009	1.732	8.3E−02
Volume of Putamen (left)	Striatum	Freesurfer ASEG	0.009	1.730	8.4E−02
Area of Perirhinal cortex (left)	Temporal	Freesurfer BA exvivo	0.009	1.721	8.5E−02
Mean MD in retrolenticular part of internal capsule (left)	Internal capsule	dMRI diffusivity	0.009	1.719	8.6E−02
Volume of Lingual Gyrus (left)	Occipital	Freesurfer DKT	−0.009	−1.718	8.6E−02

Mean OD in superior corona radiata (left)	Thalamic radiations	dMRI OD	−0.009	−1.717	8.6E−02
Area of GoctempmedParahip (right)	Temporal	Freesurfer a2009s	0.009	1.713	8.7E−02
Mean radial diffusivity in uncinate fasciculus (right)	Association fibres	dMRI diffusivity	0.009	1.710	8.7E−02
Mean MD in medial lemniscus (left)	Brainstem fibres	dMRI diffusivity	0.009	1.709	8.8E−02
Area of Lingual Gyrus (left)	Occipital	Freesurfer desikan white	−0.009	−1.708	8.8E−02
Mean axial diffusivity in retrolenticular part of internal capsule (left)	Internal capsule	dMRI diffusivity	0.009	1.706	8.8E−02
Volume of fimbria (left)	Hippocampus	Freesurfer subsegmentation	0.009	1.705	8.8E−02
Area of Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer desikan pial	−0.009	−1.705	8.8E−02
Mean ICVF in posterior limb of internal capsule (left)	Internal capsule	dMRI ICVF	−0.009	−1.705	8.8E−02
Volume of CA1head (left)	Hippocampus	Freesurfer subsegmentation	0.009	1.704	8.8E−02
Volume of Superior Frontal Gyrus (right)	Frontal	Freesurfer desikan white	−0.009	−1.702	8.9E−02
Mean radial diffusivity in corticospinal tract (right)	Brainstem fibres	dMRI diffusivity	0.009	1.698	8.9E−02
Volume of Middle Temporal Gyrus (left)	Temporal	Freesurfer DKT	−0.009	−1.693	9.1E−02
Volume of Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer desikan white	−0.009	−1.692	9.1E−02
Area of Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer desikan white	−0.009	−1.692	9.1E−02
Mean intensity of LateralVentricle (left)	NA	Freesurfer ASEG	−0.009	−1.691	9.1E−02
Volume of Wholehippocampus (left)	Hippocampus	Freesurfer subsegmentation	0.008	1.690	9.1E−02
thickness of Spostcentral (right)	Parietal	Freesurfer a2009s	0.009	1.689	9.1E−02
Grey-white contrast in Postcentral Gyrus (left)	Parietal	Freesurfer desikan gw	−0.009	−1.685	9.2E−02
Area of GfrontinfTriangul (right)	Frontal	Freesurfer a2009s	−0.009	−1.683	9.2E−02
Volume of AccessBasalnucleus (left)	Amygdala	Freesurfer subsegmentation	0.008	1.679	9.3E−02
Volume of Brodmann Area 6 (left)	Frontal	Freesurfer BA exvivo	−0.009	−1.674	9.4E−02
Area of Goccipitalmiddle (left)	Occipital	Freesurfer a2009s	−0.009	−1.674	9.4E−02
Grey-white contrast in Inferior Parietal Lobule (left)	Parietal	Freesurfer desikan gw	−0.008	−1.670	9.5E−02
Mean FA in cingulum hippocampus (left)	Limbic system fibres	dMRI FA	0.009	1.670	9.5E−02

thickness of Middle Temporal Gyrus (left)	Temporal	Freesurfer desikan white	−0.009	−1.669	9.5E−02
Volume of grey matter in Planum Temporale (right)	Temporal	FAST	−0.009	−1.667	9.6E−02
thickness of Brodmann Area 45 (left)	Frontal	Freesurfer BA exvivo	−0.009	−1.662	9.7E−02
thickness of GSfrontomargin (left)	Frontal	Freesurfer a2009s	−0.009	−1.660	9.7E−02
thickness of Precentral Gyrus (right)	Frontal	Freesurfer desikan white	−0.009	−1.660	9.7E−02
Area of Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer desikan pial	−0.009	−1.659	9.7E−02
Area of LatFispost (left)	NA	Freesurfer a2009s	0.009	1.658	9.7E−02
Mean MD in cingulum cingulate gyrus (right)	Limbic system fibres	dMRI diffusivity	0.009	1.658	9.7E−02
Area of Brodmann Area 44 (right)	Frontal	Freesurfer BA exvivo	−0.009	−1.657	9.7E−02
Volume of PuI (left)	Thalamus	Freesurfer subsegmentation	−0.009	−1.655	9.8E−02
Mean FA in splenium of corpus callosum on FA skeleton	Commissural fibres	dMRI FA	−0.009	−1.654	9.8E−02
Area of TotalSurface (right)	NA	Freesurfer desikan white	−0.009	−1.649	9.9E−02
Volume of grey matter in Thalamus (right)	Thalamus	FAST	0.009	1.648	9.9E−02
thickness of Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer desikan white	−0.009	−1.648	9.9E−02
Volume of Wholehippocampalhead (left)	Hippocampus	Freesurfer subsegmentation	0.008	1.647	9.9E−02
Mean OD in medial lemniscus (left)	Brainstem fibres	dMRI OD	0.009	1.646	1.0E−01
Area of Gparietalsup (right)	Parietal	Freesurfer a2009s	0.009	1.646	1.0E−01
Volume of Spericallosal (left)	Limbic	Freesurfer a2009s	−0.009	−1.646	1.0E−01
Mean OD in cingulum cingulate gyrus (left)	Limbic system fibres	dMRI OD	−0.009	−1.644	1.0E−01
Area of Gprecentral (left)	Frontal	Freesurfer a2009s	−0.009	−1.634	1.0E−01
Mean MD in corticospinal tract (right)	Brainstem fibres	dMRI diffusivity	0.009	1.633	1.0E−01
Mean ICVF in external capsule (left)	Association fibres	dMRI ICVF	−0.008	−1.629	1.0E−01
Mean ICVF in anterior limb of internal capsule (left)	Internal capsule	dMRI ICVF	−0.008	−1.628	1.0E−01
Volume of Middle Temporal Gyrus (left)	Temporal	Freesurfer desikan white	−0.009	−1.627	1.0E−01
Volume of Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer desikan white	−0.009	−1.625	1.0E−01

Area of Gfrontmiddle (left)	Frontal	Freesurfer a2009s	−0.009	−1.624	1.0E−01
Grey-white contrast in Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer desikan gw	−0.008	−1.623	1.0E−01
thickness of Insular Cortex (right)	Insular	Freesurfer DKT	−0.009	−1.619	1.1E−01
Volume of Brodmann Area 3a (left)	Parietal	Freesurfer BA exvivo	−0.009	−1.617	1.1E−01
Volume of Scollattransvant (left)	Temporal	Freesurfer a2009s	−0.009	−1.614	1.1E−01
Mean ISOVF in anterior limb of internal capsule (left)	Internal capsule	dMRI ISOVF	0.009	1.613	1.1E−01
Volume of GoctempmedLingual (left)	Occipital	Freesurfer a2009s	−0.009	−1.613	1.1E−01
Area of Sfrontinf (right)	Frontal	Freesurfer a2009s	−0.009	−1.611	1.1E−01
Volume of grey matter in Planum Polare (left)	Temporal	FAST	0.008	1.605	1.1E−01
thickness of Lateral Occipital Cortex (left)	Occipital	Freesurfer DKT	0.009	1.602	1.1E−01
Volume of Gsubcallosal (right)	Frontal	Freesurfer a2009s	−0.009	−1.600	1.1E−01
Mean axial diffusivity in fornix cres+stria terminalis (left)	Limbic system fibres	dMRI diffusivity	0.009	1.598	1.1E−01
Area of Brodmann Area 45 (left)	Frontal	Freesurfer BA exvivo	−0.009	−1.594	1.1E−01
Mean ISOVF in external capsule (left)	Association fibres	dMRI ISOVF	0.009	1.590	1.1E−01
Mean intensity of Pallidum (left)	Pallidum	Freesurfer ASEG	−0.009	−1.590	1.1E−01
thickness of Precentral Gyrus (right)	Frontal	Freesurfer DKT	−0.008	−1.587	1.1E−01
thickness of Middle Temporal Gyrus (left)	Temporal	Freesurfer DKT	−0.009	−1.585	1.1E−01
thickness of Inferior Frontal Gyrus, pars opercularis (left)	Frontal	Freesurfer DKT	−0.008	−1.585	1.1E−01
Volume of MDm (right)	Thalamus	Freesurfer subsegmentation	−0.008	−1.585	1.1E−01
Mean ISOVF in uncinate fasciculus (left)	Association fibres	dMRI ISOVF	0.009	1.585	1.1E−01
thickness of Inferior Frontal Gyrus, pars triangularis (left)	Frontal	Freesurfer desikan white	−0.008	−1.585	1.1E−01
Volume of Lateral orbitofrontal cortex (right)	Frontal	Freesurfer DKT	−0.008	−1.582	1.1E−01
thickness of Lateral Occipital Cortex (left)	Occipital	Freesurfer desikan white	0.009	1.580	1.1E−01
thickness of Lateral Occipital Cortex (right)	Occipital	Freesurfer desikan white	0.009	1.574	1.2E−01
Volume of brain stem+4th ventricle	NA	FIRST	0.009	1.574	1.2E−01
Volume of VPL (right)	Thalamus	Freesurfer subsegmentation	0.009	1.570	1.2E−01
Mean ICVF in anterior corona radiata (left)	Thalamic radiations	dMRI ICVF	−0.008	−1.568	1.2E−01

Grey-white contrast in Transverse temporal gyrus (right)	Temporal	Freesurfer desikan gw	−0.009	−1.564	1.2E−01
thickness of Entorhinal cortex (left)	Temporal	Freesurfer BA exvivo	−0.009	−1.563	1.2E−01
Area of Grectus (right)	Frontal	Freesurfer a2009s	−0.009	−1.562	1.2E−01
thickness of Stemporalsup (right)	Temporal	Freesurfer a2009s	−0.008	−1.559	1.2E−01
Area of PreCuneal Cortex (left)	Occipital	Freesurfer desikan pial	0.009	1.554	1.2E−01
Grey-white contrast in Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer desikan gw	−0.008	−1.552	1.2E−01
Area of Gtemporalinf (left)	Temporal	Freesurfer a2009s	−0.008	−1.550	1.2E−01
Volume of GSparacentral (left)	Frontal	Freesurfer a2009s	−0.008	−1.548	1.2E−01
Mean ISOVF in cingulum cingulate gyrus (right)	Limbic system fibres	dMRI ISOVF	0.009	1.548	1.2E−01
Volume of grey matter in Middle Frontal Gyrus (left)	Frontal	FAST	−0.008	−1.547	1.2E−01
Area of GoctempmedLingual (right)	Occipital	Freesurfer a2009s	−0.009	−1.546	1.2E−01
Area of Precentral Gyrus (right)	Frontal	Freesurfer desikan pial	−0.009	−1.543	1.2E−01
Volume of Parahippocampal Gyrus (right)	Temporal	Freesurfer desikan white	0.008	1.541	1.2E−01
thickness of Banks superior temporal sulcus (left)	Temporal	Freesurfer a2009s	−0.008	−1.541	1.2E−01
thickness of Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer DKT	−0.008	−1.539	1.2E−01
thickness of Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer DKT	−0.008	−1.539	1.2E−01
Area of Medorbitofrontal (left)	Frontal	Freesurfer DKT	−0.008	−1.536	1.2E−01
Volume of grey matter in Temporal Fusiform Cortex, anterior division (right)	Temporal	FAST	−0.008	−1.535	1.2E−01
Grey-white contrast in Transverse temporal gyrus (left)	Temporal	Freesurfer desikan gw	−0.008	−1.534	1.3E−01
thickness of Stemporalsup (left)	Temporal	Freesurfer a2009s	−0.008	−1.532	1.3E−01
Volume of CM (left)	Thalamus	Freesurfer subsegmentation	0.008	1.532	1.3E−01
Mean ICVF in fornix cres+stria terminalis (left)	Limbic system fibres	dMRI ICVF	−0.008	−1.531	1.3E−01
Area of Sorbitalmedolfact (right)	Frontal	Freesurfer a2009s	−0.008	−1.528	1.3E−01
Area of Lingual Gyrus (right)	Occipital	Freesurfer desikan white	−0.008	−1.524	1.3E−01
Area of Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer desikan pial	−0.008	−1.522	1.3E−01
Volume of Ssuborbital (right)	Frontal	Freesurfer a2009s	−0.008	−1.520	1.3E−01
thickness of Superior Parietal Lobule (left)	Parietal	Freesurfer DKT	0.008	1.519	1.3E−01

Area of Brodmann Area 3a (right)	Parietal	Freesurfer BA exvivo	−0.008	−1.518	1.3E−01
thickness of Scollattransvant (right)	Temporal	Freesurfer a2009s	−0.008	−1.513	1.3E−01
Area of Fusiform Gyrus (right)	Occipital	Freesurfer desikan pial	−0.008	−1.512	1.3E−01
Volume of grey matter in Vermis VIIIb Cerebellum	Cerebellum	FAST	0.008	1.507	1.3E−01
Area of GoctempmedParahip (left)	Temporal	Freesurfer a2009s	0.008	1.507	1.3E−01
thickness of Spericallosal (right)	Limbic	Freesurfer a2009s	−0.008	−1.506	1.3E−01
thickness of Brodmann Area 4a (right)	Frontal	Freesurfer BA exvivo	−0.008	−1.505	1.3E−01
Volume of Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer DKT	−0.008	−1.503	1.3E−01
Area of Precentral Gyrus (left)	Frontal	Freesurfer desikan white	−0.008	−1.503	1.3E−01
Volume of Gprecentral (right)	Frontal	Freesurfer a2009s	−0.008	−1.496	1.3E−01
Mean OD in anterior corona radiata (left)	Thalamic radiations	dMRI OD	0.008	1.496	1.3E−01
Area of Sprecentralinfpart (left)	Frontal	Freesurfer a2009s	−0.008	−1.494	1.4E−01
Area of GcingulPostventral (right)	Limbic	Freesurfer a2009s	−0.008	−1.493	1.4E−01
thickness of Gprecentral (right)	Frontal	Freesurfer a2009s	−0.008	−1.490	1.4E−01
Volume of Brodmann Area 1 (left)	Parietal	Freesurfer BA exvivo	−0.008	−1.488	1.4E−01
Grey-white contrast in Superior Parietal Lobule (left)	Parietal	Freesurfer desikan gw	−0.008	−1.488	1.4E−01
thickness of Sprecentralinfpart (right)	Frontal	Freesurfer a2009s	−0.008	−1.477	1.4E−01
thickness of Stemporalinf (left)	Temporal	Freesurfer a2009s	−0.008	−1.476	1.4E−01
Grey-white contrast in Lateral orbitofrontal cortex (left)	Frontal	Freesurfer desikan gw	−0.007	−1.474	1.4E−01
Volume of Fusiform Gyrus (right)	Occipital	Freesurfer DKT	−0.008	−1.473	1.4E−01
Volume of Scollattransvpost (right)	Temporal	Freesurfer a2009s	0.008	1.473	1.4E−01
Volume of grey matter in Parahippocampal Gyrus, anterior division (right)	Temporal	FAST	−0.008	−1.469	1.4E−01
Mean ICVF in pontine crossing tract on FA skeleton	Brainstem fibres	dMRI ICVF	−0.008	−1.468	1.4E−01
Volume of Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer DKT	−0.008	−1.467	1.4E−01
Volume of Lateral orbitofrontal cortex (right)	Frontal	Freesurfer desikan white	−0.008	−1.466	1.4E−01
Mean FA in pontine crossing tract on FA skeleton	Brainstem fibres	dMRI FA	−0.008	−1.463	1.4E−01
thickness of Scircularinsulaant (right)	Insular	Freesurfer a2009s	−0.008	−1.461	1.4E−01
Mean FA in posterior limb of internal capsule (right)	Internal capsule	dMRI FA	−0.008	−1.461	1.4E−01

Volume of grey matter in Superior Parietal Lobule (right)	Parietal	FAST	−0.008	−1.461	1.4E−01
Volume of Superior Frontal Gyrus (left)	Frontal	Freesurfer desikan white	−0.008	−1.458	1.4E−01
Area of Brodmann Area 4a (left)	Frontal	Freesurfer BA exvivo	−0.008	−1.457	1.4E−01
Mean ICVF in cerebral peduncle (left)	Brainstem fibres	dMRI ICVF	0.008	1.457	1.5E−01
thickness of Superior Temporal Gyrus (left)	Temporal	Freesurfer DKT	−0.008	−1.457	1.5E−01
Volume of GfrontinfOpercular (right)	Frontal	Freesurfer a2009s	−0.008	−1.457	1.5E−01
Volume of Gtemporalmiddle (left)	Temporal	Freesurfer a2009s	−0.008	−1.455	1.5E−01
Mean FA in posterior corona radiata (left)	Thalamic radiations	dMRI FA	−0.008	−1.453	1.5E−01
thickness of Sorbitalmedolfact (left)	Frontal	Freesurfer a2009s	−0.008	−1.453	1.5E−01
Volume of LGN (right)	Thalamus	Freesurfer subsegmentation	−0.007	−1.452	1.5E−01
Volume of Brodmann Area 3b (left)	Parietal	Freesurfer BA exvivo	−0.008	−1.451	1.5E−01
Mean ISOVF in cingulum cingulate gyrus (left)	Limbic system fibres	dMRI ISOVF	0.008	1.447	1.5E−01
Volume of HATA (right)	Hippocampus	Freesurfer subsegmentation	0.008	1.447	1.5E−01
thickness of GfrontinfTriangul (left)	Frontal	Freesurfer a2009s	−0.008	−1.446	1.5E−01
Volume of GoctempmedParahip (right)	Temporal	Freesurfer a2009s	0.008	1.446	1.5E−01
Volume of SoctempmedLingual (right)	Temporal	Freesurfer a2009s	0.008	1.445	1.5E−01
Mean ICVF in external capsule (right)	Association fibres	dMRI ICVF	−0.007	−1.445	1.5E−01
thickness of SocmiddleLunatus (right)	Occipital	Freesurfer a2009s	0.008	1.441	1.5E−01
Mean ICVF in anterior corona radiata (right)	Thalamic radiations	dMRI ICVF	−0.007	−1.440	1.5E−01
Mean ICVF in retrolenticular part of internal capsule (left)	Internal capsule	dMRI ICVF	−0.008	−1.438	1.5E−01
thickness of PreCuneal Cortex (left)	Occipital	Freesurfer desikan white	−0.008	−1.437	1.5E−01
Area of rostralAntcingulate (left)	Limbic	Freesurfer desikan pial	−0.008	−1.436	1.5E−01
thickness of Lateral orbitofrontal cortex (right)	Frontal	Freesurfer DKT	−0.008	−1.435	1.5E−01
thickness of Brodmann Area 4p (left)	Frontal	Freesurfer BA exvivo	−0.008	−1.435	1.5E−01
Mean OD in cingulum cingulate gyrus (right)	Limbic system fibres	dMRI OD	−0.008	−1.433	1.5E−01
Mean axial diffusivity in posterior thalamic radiation (right)	Thalamic radiations	dMRI diffusivity	0.008	1.432	1.5E−01

Mean OD in splenium of corpus callosum on FA skeleton	Commissural fibres	dMRI OD	−0.008	−1.432	1.5E−01
Volume of Amygdala (left)	Amygdala	Freesurfer ASEG	0.007	1.428	1.5E−01
Volume of Pons (whole brain)	NA	Freesurfer subsegmentation	0.008	1.427	1.5E−01
Grey-white contrast in Postcentral Gyrus (right)	Parietal	Freesurfer desikan gw	−0.008	−1.424	1.5E−01
Mean FA in superior longitudinal fasciculus (left)	Association fibres	dMRI FA	−0.008	−1.420	1.6E−01
thickness of Brodmann Area 44 (left)	Frontal	Freesurfer BA exvivo	−0.008	−1.414	1.6E−01
Volume of Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer DKT	0.008	1.414	1.6E−01
Grey-white contrast in Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer desikan gw	−0.007	−1.410	1.6E−01
Mean radial diffusivity in cerebral peduncle (right)	Brainstem fibres	dMRI diffusivity	0.008	1.409	1.6E−01
Area of Brodmann Area 6 (right)	Frontal	Freesurfer BA exvivo	−0.008	−1.408	1.6E−01
Volume of Cortex (right)	NA	Freesurfer ASEG	−0.007	−1.407	1.6E−01
Volume of Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer desikan white	0.007	1.406	1.6E−01
Volume of grey matter in VI Cerebellum (left)	Cerebellum	FAST	0.007	1.404	1.6E−01
Volume of Cingulate Gyrus, isthmus (left)	Limbic	Freesurfer desikan white	0.008	1.403	1.6E−01
thickness of Parahippocampal Gyrus (right)	Temporal	Freesurfer desikan white	−0.008	−1.403	1.6E−01
Volume of grey matter in Middle Temporal Gyrus, posterior division (right)	Temporal	FAST	−0.007	−1.399	1.6E−01
Volume of Inferior Temporal Gyrus (left)	Temporal	Freesurfer DKT	−0.008	−1.398	1.6E−01
Mean axial diffusivity in medial lemniscus (right)	Brainstem fibres	dMRI diffusivity	0.008	1.397	1.6E−01
Area of Paracentral lobule (left)	Frontal	Freesurfer desikan pial	−0.008	−1.397	1.6E−01
Area of Lingual Gyrus (right)	Occipital	Freesurfer DKT	−0.008	−1.395	1.6E−01
Volume of VLp (left)	Thalamus	Freesurfer subsegmentation	0.008	1.395	1.6E−01
Volume of Gtemporalinf (left)	Temporal	Freesurfer a2009s	−0.008	−1.394	1.6E−01
thickness of Cuneal Cortex (left)	Occipital	Freesurfer DKT	−0.008	−1.393	1.6E−01
Mean radial diffusivity in external capsule (left)	Association fibres	dMRI diffusivity	0.007	1.393	1.6E−01
Volume of Wholebrainstem (whole brain)	NA	Freesurfer subsegmentation	0.008	1.393	1.6E−01
Area of Brodmann Area V5 (right)	Occipital	Freesurfer BA exvivo	−0.008	−1.389	1.6E−01

Volume of Brodmann Area 4p (right)	Frontal	Freesurfer BA exvivo	−0.008	−1.388	1.7E−01
Volume of grey matter in Lateral Occipital Cortex, superior division (left)	Occipital	FAST	−0.007	−1.387	1.7E−01
thickness of Ginsularshort (right)	Insular	Freesurfer a2009s	−0.008	−1.386	1.7E−01
thickness of GfrontinfOpercular (left)	Frontal	Freesurfer a2009s	−0.007	−1.386	1.7E−01
thickness of Brodmann Area 2 (right)	Parietal	Freesurfer BA exvivo	0.007	1.384	1.7E−01
Grey-white contrast in PreCuneal Cortex (left)	Occipital	Freesurfer desikan gw	−0.007	−1.383	1.7E−01
Volume of Goccipitalsup (right)	Occipital	Freesurfer a2009s	0.008	1.381	1.7E−01
Mean ISOVF in corticospinal tract (right)	Brainstem fibres	dMRI ISOVF	0.008	1.376	1.7E−01
Area of PreCuneal Cortex (left)	Occipital	Freesurfer DKT	0.008	1.376	1.7E−01
Volume of Parahippocampal Gyrus (right)	Temporal	Freesurfer DKT	0.007	1.375	1.7E−01
Area of Entorhinal cortex (right)	Temporal	Freesurfer BA exvivo	0.008	1.374	1.7E−01
Volume of grey matter in Lateral Occipital Cortex, superior division (right)	Occipital	FAST	0.007	1.373	1.7E−01
Mean OD in medial lemniscus (right)	Brainstem fibres	dMRI OD	0.007	1.373	1.7E−01
Area of GSoccipitalinf (left)	Occipital	Freesurfer a2009s	0.008	1.371	1.7E−01
Volume of VM (left)	Thalamus	Freesurfer subsegmentation	0.008	1.371	1.7E−01
thickness of Paracentral lobule (left)	Frontal	Freesurfer desikan white	−0.007	−1.367	1.7E−01
Mean axial diffusivity in corticospinal tract (right)	Brainstem fibres	dMRI diffusivity	0.007	1.366	1.7E−01
Volume of grey matter in Middle Temporal Gyrus, anterior division (right)	Temporal	FAST	−0.007	−1.366	1.7E−01
Area of Superior Temporal Gyrus (left)	Temporal	Freesurfer desikan white	0.007	1.364	1.7E−01
Area of Fusiform Gyrus (right)	Occipital	Freesurfer DKT	−0.007	−1.355	1.8E−01
Volume of pallidum (right)	Pallidum	FIRST	0.007	1.353	1.8E−01
Volume of Sprecentralinfpart (right)	Frontal	Freesurfer a2009s	−0.007	−1.353	1.8E−01
Area of GfrontinfOpercular (left)	Frontal	Freesurfer a2009s	−0.007	−1.352	1.8E−01
Volume of Brodmann Area 45 (right)	Frontal	Freesurfer BA exvivo	−0.007	−1.351	1.8E−01
Mean axial diffusivity in posterior thalamic radiation (left)	Thalamic radiations	dMRI diffusivity	0.007	1.351	1.8E−01
thickness of Sprecentralinfpart (left)	Frontal	Freesurfer a2009s	−0.007	−1.349	1.8E−01
Mean intensity of OpticChiasm (whole brain)	NA	Freesurfer ASEG	−0.007	−1.346	1.8E−01
thickness of Brodmann Area 3a (left)	Parietal	Freesurfer BA exvivo	−0.007	−1.344	1.8E−01

Volume of Brodmann Area 6 (right)	Frontal	Freesurfer BA exvivo	−0.007	−1.344	1.8E−01
thickness of Sprecentralsuppart (right)	Frontal	Freesurfer a2009s	−0.007	−1.340	1.8E−01
Mean ICVF in anterior limb of internal capsule (right)	Internal capsule	dMRI ICVF	−0.007	−1.336	1.8E−01
thickness of GtempsupGTtransv (right)	Temporal	Freesurfer a2009s	0.007	1.329	1.8E−01
thickness of SoctempmedLingual (right)	Temporal	Freesurfer a2009s	−0.007	−1.324	1.9E−01
thickness of Brodmann Area 6 (left)	Frontal	Freesurfer BA exvivo	−0.007	−1.321	1.9E−01
thickness of Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer DKT	−0.007	−1.318	1.9E−01
Mean ISOVF in cerebral peduncle (right)	Brainstem fibres	dMRI ISOVF	0.007	1.317	1.9E−01
Area of SocmiddleLunatus (right)	Occipital	Freesurfer a2009s	−0.007	−1.317	1.9E−01
thickness of Parahippocampal Gyrus (right)	Temporal	Freesurfer DKT	−0.007	−1.316	1.9E−01
Area of caudalAntcingulate (right)	Limbic	Freesurfer desikan white	0.007	1.307	1.9E−01
Volume of VM (right)	Thalamus	Freesurfer subsegmentation	0.007	1.307	1.9E−01
Volume of SoctempmedLingual (left)	Temporal	Freesurfer a2009s	0.007	1.306	1.9E−01
thickness of Socsuptransversal (left)	Occipital	Freesurfer a2009s	0.007	1.305	1.9E−01
thickness of Paracentral lobule (left)	Frontal	Freesurfer DKT	−0.007	−1.304	1.9E−01
thickness of PreCuneal Cortex (right)	Occipital	Freesurfer DKT	0.007	1.304	1.9E−01
Volume of CCMidPosterior (whole brain)	NA	Freesurfer ASEG	−0.007	−1.303	1.9E−01
Volume of grey matter in Middle Temporal Gyrus, anterior division (left)	Temporal	FAST	−0.007	−1.300	1.9E−01
Area of Medorbitofrontal (right)	Frontal	Freesurfer desikan white	−0.007	−1.300	1.9E−01
Area of Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer DKT	0.007	1.297	1.9E−01
Volume of Lateral orbitofrontal cortex (left)	Frontal	Freesurfer DKT	−0.007	−1.291	2.0E−01
Area of Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer desikan pial	0.007	1.291	2.0E−01
Mean ISOVF in tapetum (left)	Commissural fibres	dMRI ISOVF	0.007	1.290	2.0E−01
Volume of Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer DKT	−0.007	−1.289	2.0E−01
Area of Scircularinsulasup (right)	Insular	Freesurfer a2009s	−0.007	−1.287	2.0E−01
Volume of AV (right)	Thalamus	Freesurfer subsegmentation	−0.007	−1.286	2.0E−01
Mean FA in anterior limb of internal capsule (left)	Internal capsule	dMRI FA	−0.007	−1.283	2.0E−01

Mean axial diffusivity in inferior cerebellar peduncle (left)	Brainstem fibres	dMRI diffusivity	−0.007	−1.281	2.0E−01
Volume of Gtemporalinf (right)	Temporal	Freesurfer a2009s	−0.007	−1.276	2.0E−01
thickness of Superior Frontal Gyrus (left)	Frontal	Freesurfer DKT	−0.006	−1.271	2.0E−01
Area of Socsuptransversal (left)	Occipital	Freesurfer a2009s	−0.007	−1.266	2.1E−01
thickness of Brodmann Area 4p (right)	Frontal	Freesurfer BA exvivo	−0.007	−1.264	2.1E−01
Volume of thalamus (right)	Thalamus	FIRST	−0.006	−1.259	2.1E−01
Volume of Wholeamygdala (right)	Amygdala	Freesurfer subsegment ation	0.006	1.256	2.1E−01
Volume of Cingulate Gyrus, posterior (left)	Limbic	Freesurfer DKT	−0.007	−1.254	2.1E−01
Area of Superior Frontal Gyrus (left)	Frontal	Freesurfer desikan pial	−0.007	−1.253	2.1E−01
thickness of GSsubcentral (right)	Frontal	Freesurfer a2009s	0.007	1.252	2.1E−01
Area of Brodmann Area 3a (left)	Parietal	Freesurfer BA exvivo	−0.007	−1.252	2.1E−01
Area of GcingulPostdorsal (right)	Limbic	Freesurfer a2009s	−0.007	−1.249	2.1E−01
Volume of Sprecentralinfpart (left)	Frontal	Freesurfer a2009s	−0.007	−1.249	2.1E−01
Volume of SorbitalHShaped (left)	Frontal	Freesurfer a2009s	−0.007	−1.247	2.1E−01
Mean OD in superior fronto-occipital fasciculus (right)	Association fibres	dMRI OD	−0.007	−1.247	2.1E−01
Grey-white contrast in Medorbitofrontal (left)	Frontal	Freesurfer desikan gw	−0.006	−1.247	2.1E−01
thickness of LatFispost (right)	NA	Freesurfer a2009s	−0.007	−1.247	2.1E−01
Mean radial diffusivity in posterior limb of internal capsule (left)	Internal capsule	dMRI diffusivity	0.007	1.244	2.1E−01
Mean MD in cerebral peduncle (left)	Brainstem fibres	dMRI diffusivity	−0.007	−1.243	2.1E−01
thickness of Scircularinsulasup (right)	Insular	Freesurfer a2009s	−0.007	−1.243	2.1E−01
Volume of PuL (left)	Thalamus	Freesurfer subsegment ation	0.007	1.242	2.1E−01
Area of Superior Temporal Gyrus (left)	Temporal	Freesurfer DKT	0.007	1.242	2.1E−01
Area of Lateral orbitofrontal cortex (right)	Frontal	Freesurfer desikan pial	−0.007	−1.240	2.1E−01
Volume of Stemporalsup (left)	Temporal	Freesurfer a2009s	−0.007	−1.239	2.2E−01
Volume of PreCuneal Cortex (right)	Occipital	Freesurfer desikan white	0.007	1.236	2.2E−01
Mean OD in tapetum (right)	Commissural fibres	dMRI OD	−0.007	−1.232	2.2E−01
Volume of PreCuneal Cortex (right)	Occipital	Freesurfer DKT	0.007	1.232	2.2E−01
thickness of Goctemplatfusifor (left)	Temporal	Freesurfer a2009s	−0.007	−1.231	2.2E−01

Area of GparietinfAngular (right)	Parietal	Freesurfer a2009s	−0.007	−1.231	2.2E−01
thickness of Ginsularshort (left)	Insular	Freesurfer a2009s	−0.007	−1.230	2.2E−01
thickness of GtempsupPlantempo (right)	Temporal	Freesurfer a2009s	0.007	1.229	2.2E−01
Volume of GtempsupLateral (left)	Temporal	Freesurfer a2009s	0.007	1.227	2.2E−01
Grey-white contrast in rostralAntcingulate (right)	Limbic	Freesurfer desikan gw	−0.006	−1.226	2.2E−01
thickness of Perirhinal cortex (right)	Temporal	Freesurfer BA exvivo	−0.007	−1.226	2.2E−01
Volume of grey matter in Postcentral Gyrus (right)	Parietal	FAST	−0.006	−1.225	2.2E−01
Area of SintraparietPtrans (left)	Parietal	Freesurfer a2009s	−0.007	−1.224	2.2E−01
Volume of Insular Cortex (right)	Insular	Freesurfer DKT	−0.007	−1.219	2.2E−01
thickness of Global thickness (left)	NA	Freesurfer a2009s	−0.006	−1.219	2.2E−01
Grey-white contrast in Parahippocampal Gyrus (right)	Temporal	Freesurfer desikan gw	−0.006	−1.217	2.2E−01
Area of Goctemplatfusifor (left)	Temporal	Freesurfer a2009s	−0.007	−1.217	2.2E−01
thickness of Entorhinal cortex (right)	Temporal	Freesurfer BA exvivo	−0.007	−1.215	2.2E−01
Area of caudalAntcingulate (right)	Limbic	Freesurfer DKT	0.007	1.208	2.3E−01
Area of caudalAntcingulate (right)	Limbic	Freesurfer desikan pial	0.007	1.205	2.3E−01
Area of Paracentral lobule (right)	Frontal	Freesurfer desikan pial	−0.007	−1.205	2.3E−01
thickness of GStransvfrontopol (right)	Frontal	Freesurfer a2009s	−0.006	−1.204	2.3E−01
Mean radial diffusivity in retrolenticular part of internal capsule (left)	Internal capsule	dMRI diffusivity	0.007	1.203	2.3E−01
Volume of grey matter in IX Cerebellum (right)	Cerebellum	FAST	0.006	1.200	2.3E−01
Volume of Brodmann Area V5 (right)	Occipital	Freesurfer BA exvivo	−0.007	−1.200	2.3E−01
Volume of grey matter in Superior Temporal Gyrus, anterior division (right)	Temporal	FAST	−0.006	−1.195	2.3E−01
Area of Soctemplat (right)	Temporal	Freesurfer a2009s	−0.007	−1.190	2.3E−01
Volume of caudalAntcingulate (right)	Limbic	Freesurfer desikan white	0.007	1.189	2.3E−01
Mean radial diffusivity in corticospinal tract (left)	Brainstem fibres	dMRI diffusivity	0.007	1.188	2.3E−01
Volume of Entorhinal cortex (left)	Temporal	Freesurfer DKT	0.007	1.183	2.4E−01
thickness of Postcentral Gyrus (right)	Parietal	Freesurfer DKT	0.006	1.181	2.4E−01
thickness of GoctempmedLingual (right)	Occipital	Freesurfer a2009s	0.007	1.178	2.4E−01
Volume of grey matter in Cuneal Cortex (left)	Occipital	FAST	−0.006	−1.177	2.4E−01
Area of Lateral Occipital Cortex (left)	Occipital	Freesurfer desikan pial	−0.006	−1.174	2.4E−01

thickness of Superior Frontal Gyrus (left)	Frontal	Freesurfer desikan white	−0.006	−1.172	2.4E−01
thickness of Superior Parietal Lobule (left)	Parietal	Freesurfer desikan white	0.006	1.172	2.4E−01
Volume of grey matter in Supramarginal Gyrus, posterior division (right)	Parietal	FAST	−0.006	−1.171	2.4E−01
Volume of grey matter in Central Opercular Cortex (left)	Insular	FAST	−0.006	−1.170	2.4E−01
Grey-white contrast in Cingulate Gyrus, posterior (right)	Limbic	Freesurfer desikan gw	0.006	1.166	2.4E−01
Volume of Inferior Temporal Gyrus (left)	Temporal	Freesurfer desikan white	−0.006	−1.164	2.4E−01
Volume of Fusiform Gyrus (right)	Occipital	Freesurfer desikan white	−0.006	−1.162	2.5E−01
Area of Transverse temporal gyrus (right)	Temporal	Freesurfer desikan pial	−0.006	−1.162	2.5E−01
Area of Inferior Temporal Gyrus (left)	Temporal	Freesurfer desikan pial	−0.006	−1.160	2.5E−01
Area of Gtemporalinf (right)	Temporal	Freesurfer a2009s	−0.006	−1.160	2.5E−01
Volume of Socsuptransversal (right)	Occipital	Freesurfer a2009s	0.006	1.156	2.5E−01
Mean OD in superior longitudinal fasciculus (left)	Association fibres	dMRI OD	−0.006	−1.153	2.5E−01
Volume of Hippocampaltail (right)	Hippocampus	Freesurfer subsegmentation	0.006	1.152	2.5E−01
Area of Scircularinsulasup (left)	Insular	Freesurfer a2009s	−0.006	−1.152	2.5E−01
Mean ISOVF in sagittal stratum (right)	Association fibres	dMRI ISOVF	−0.006	−1.151	2.5E−01
thickness of Stemporalinf (right)	Temporal	Freesurfer a2009s	−0.006	−1.150	2.5E−01
Volume of grey matter in Inferior Frontal Gyrus, pars opercularis (left)	Frontal	FAST	−0.006	−1.148	2.5E−01
Volume of GtempsupPlantempo (left)	Temporal	Freesurfer a2009s	0.006	1.147	2.5E−01
thickness of PreCuneal Cortex (right)	Occipital	Freesurfer desikan white	0.006	1.147	2.5E−01
Area of GSparacentral (left)	Frontal	Freesurfer a2009s	0.006	1.146	2.5E−01
Volume of grey matter in Vermis VIIIa Cerebellum	Cerebellum	FAST	0.006	1.146	2.5E−01
thickness of Stemporaltransverse (left)	Temporal	Freesurfer a2009s	−0.006	−1.145	2.5E−01
Area of PreCuneal Cortex (left)	Occipital	Freesurfer desikan white	0.006	1.145	2.5E−01
thickness of Insular Cortex (right)	Insular	Freesurfer desikan white	−0.006	−1.145	2.5E−01
thickness of PreCuneal Cortex (left)	Occipital	Freesurfer DKT	−0.006	−1.145	2.5E−01

Volume of Corticalnucleus (left)	Amygdala	Freesurfer subsegmentation	−0.006	−1.144	2.5E−01
Area of Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer desikan pial	−0.006	−1.143	2.5E−01
thickness of Lateral orbitofrontal cortex (right)	Frontal	Freesurfer desikan white	−0.006	−1.142	2.5E−01
Volume of Ginsularshort (right)	Insular	Freesurfer a2009s	−0.006	−1.140	2.5E−01
Area of GfrontinfTriangul (left)	Frontal	Freesurfer a2009s	−0.006	−1.138	2.6E−01
Area of Socsuptransversal (right)	Occipital	Freesurfer a2009s	0.006	1.135	2.6E−01
thickness of Medorbitofrontal (right)	Frontal	Freesurfer DKT	−0.006	−1.132	2.6E−01
Mean FA in uncinate fasciculus (right)	Association fibres	dMRI FA	−0.006	−1.131	2.6E−01
Mean radial diffusivity in inferior cerebellar peduncle (left)	Brainstem fibres	dMRI diffusivity	0.006	1.127	2.6E−01
thickness of GScingulAnt (left)	Limbic	Freesurfer a2009s	−0.006	−1.125	2.6E−01
Volume of grey matter in Intracalcarine Cortex (right)	Occipital	FAST	−0.006	−1.121	2.6E−01
Mean axial diffusivity in superior cerebellar peduncle (right)	Brainstem fibres	dMRI diffusivity	0.006	1.120	2.6E−01
Volume of grey matter in Thalamus (left)	Thalamus	FAST	0.006	1.120	2.6E−01
Area of Fusiform Gyrus (right)	Occipital	Freesurfer desikan white	−0.006	−1.118	2.6E−01
Volume of grey matter in Superior Frontal Gyrus (right)	Frontal	FAST	−0.006	−1.118	2.6E−01
Volume of SintraparietPtrans (left)	Parietal	Freesurfer a2009s	−0.006	−1.117	2.6E−01
Area of GSfrontomargin (left)	Frontal	Freesurfer a2009s	0.006	1.117	2.6E−01
thickness of GfrontinfOrbital (right)	Frontal	Freesurfer a2009s	0.006	1.116	2.6E−01
Volume of GparietinfAngular (left)	Parietal	Freesurfer a2009s	−0.006	−1.114	2.7E−01
thickness of GoctempmedParahip (right)	Temporal	Freesurfer a2009s	−0.006	−1.114	2.7E−01
Mean ISOVF in cingulum hippocampus (left)	Limbic system fibres	dMRI ISOVF	0.006	1.114	2.7E−01
Area of GparietinfAngular (left)	Parietal	Freesurfer a2009s	−0.006	−1.112	2.7E−01
Mean axial diffusivity in pontine crossing tract on FA skeleton	Brainstem fibres	dMRI diffusivity	0.006	1.111	2.7E−01
Volume of CCMidAnt (whole brain)	NA	Freesurfer ASEG	0.006	1.110	2.7E−01
Mean radial diffusivity in cingulum hippocampus (left)	Limbic system fibres	dMRI diffusivity	−0.006	−1.109	2.7E−01
Volume of grey matter in Pallidum (right)	Pallidum	FAST	0.006	1.106	2.7E−01
thickness of Brodmann Area V2 (right)	Occipital	Freesurfer BA exvivo	0.006	1.105	2.7E−01

Volume of Gfrontsup (left)	Frontal	Freesurfer a2009s	−0.006	−1.103	2.7E−01
thickness of Lingual Gyrus (right)	Occipital	Freesurfer desikan white	0.006	1.101	2.7E−01
Volume of grey matter in Insular Cortex (left)	Insular	FAST	−0.006	−1.100	2.7E−01
Grey-white contrast in Entorhinal cortex (right)	Temporal	Freesurfer desikan gw	−0.006	−1.100	2.7E−01
Area of ScingulMarginalis (left)	Frontal	Freesurfer a2009s	0.006	1.100	2.7E−01
Mean radial diffusivity in inferior cerebellar peduncle (right)	Brainstem fibres	dMRI diffusivity	0.006	1.097	2.7E−01
Volume of grey matter in Vermis VIIb Cerebellum	Cerebellum	FAST	0.006	1.097	2.7E−01
Volume of GSsubcentral (right)	Frontal	Freesurfer a2009s	−0.006	−1.096	2.7E−01
Mean MD in pontine crossing tract on FA skeleton	Brainstem fibres	dMRI diffusivity	0.006	1.094	2.7E−01
Volume of grey matter in Insular Cortex (right)	Insular	FAST	−0.006	−1.093	2.7E−01
Volume of grey matter in Cingulate Gyrus, posterior division (right)	Limbic	FAST	0.006	1.090	2.8E−01
Area of Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer desikan white	0.006	1.089	2.8E−01
Volume of Scircularinsulaant (left)	Insular	Freesurfer a2009s	−0.006	−1.089	2.8E−01
thickness of GtempsupLateral (right)	Temporal	Freesurfer a2009s	0.006	1.086	2.8E−01
Volume of Hippocampus (right)	Hippocampus	Freesurfer ASEG	0.005	1.082	2.8E−01
Mean axial diffusivity in anterior corona radiata (left)	Thalamic radiations	dMRI diffusivity	0.006	1.080	2.8E−01
Volume of Poletemporal (right)	Temporal	Freesurfer a2009s	0.006	1.078	2.8E−01
Mean OD in pontine crossing tract on FA skeleton	Brainstem fibres	dMRI OD	−0.006	−1.078	2.8E−01
Area of GScingulMidAnt (right)	Limbic	Freesurfer a2009s	−0.006	−1.078	2.8E−01
Mean radial diffusivity in pontine crossing tract on FA skeleton	Brainstem fibres	dMRI diffusivity	0.006	1.077	2.8E−01
thickness of GcingulPostdorsal (left)	Limbic	Freesurfer a2009s	−0.006	−1.077	2.8E−01
Grey-white contrast in Banks superior temporal sulcus (left)	Temporal	Freesurfer desikan gw	−0.006	−1.076	2.8E−01
thickness of Scentral (left)	Frontal	Freesurfer a2009s	−0.006	−1.076	2.8E−01
Volume of thalamus (left)	Thalamus	FIRST	−0.005	−1.073	2.8E−01
Area of Poletemporal (left)	Temporal	Freesurfer a2009s	−0.006	−1.073	2.8E−01
thickness of Sorbitalmedolfact (right)	Frontal	Freesurfer a2009s	−0.006	−1.072	2.8E−01
Area of Medorbitofrontal (right)	Frontal	Freesurfer DKT	−0.006	−1.071	2.8E−01
Area of Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer desikan pial	0.006	1.070	2.8E−01

Volume of CA3head (left)	Hippocampus	Freesurfer subsegmentation	−0.006	−1.069	2.9E−01
Volume of GfrontinfOrbital (right)	Frontal	Freesurfer a2009s	0.006	1.066	2.9E−01
thickness of Gsubcallosal (right)	Frontal	Freesurfer a2009s	−0.006	−1.062	2.9E−01
Volume of Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer desikan white	−0.006	−1.059	2.9E−01
Volume of AntamygdaloidareA (left)	Amygdala	Freesurfer subsegmentation	0.006	1.053	2.9E−01
Volume of GparietinfAngular (right)	Parietal	Freesurfer a2009s	−0.006	−1.053	2.9E−01
Area of Lateral Occipital Cortex (left)	Occipital	Freesurfer DKT	−0.006	−1.053	2.9E−01
Volume of Entorhinal cortex (right)	Temporal	Freesurfer DKT	0.006	1.052	2.9E−01
thickness of Lingual Gyrus (right)	Occipital	Freesurfer DKT	0.006	1.052	2.9E−01
Volume of grey matter in Heschls Gyrus (includes H1 and H2) (left)	Temporal	FAST	−0.005	−1.052	2.9E−01
thickness of Brodmann Area 44 (right)	Frontal	Freesurfer BA exvivo	−0.006	−1.050	2.9E−01
Area of Sorbitallateral (left)	Frontal	Freesurfer a2009s	0.006	1.048	2.9E−01
Volume of VLp (right)	Thalamus	Freesurfer subsegmentation	0.006	1.047	3.0E−01
Volume of Transverse temporal gyrus (left)	Temporal	Freesurfer DKT	0.006	1.047	3.0E−01
Mean ISOVF in superior longitudinal fasciculus (right)	Association fibres	dMRI ISOVF	0.006	1.043	3.0E−01
thickness of Entorhinal cortex (right)	Temporal	Freesurfer desikan white	−0.006	−1.041	3.0E−01
Volume of Wholethalamus (right)	Thalamus	Freesurfer subsegmentation	0.005	1.041	3.0E−01
thickness of Goccipitalsup (left)	Occipital	Freesurfer a2009s	0.006	1.039	3.0E−01
Area of rostralAntcingulate (right)	Limbic	Freesurfer desikan pial	0.006	1.039	3.0E−01
Grey-white contrast in Cuneal Cortex (right)	Occipital	Freesurfer desikan gw	−0.006	−1.038	3.0E−01
Volume of Soctemplat (left)	Temporal	Freesurfer a2009s	−0.006	−1.038	3.0E−01
thickness of Cuneal Cortex (right)	Occipital	Freesurfer desikan white	−0.006	−1.037	3.0E−01
Area of Gtemporalmiddle (left)	Temporal	Freesurfer a2009s	−0.006	−1.036	3.0E−01
thickness of Superior Temporal Gyrus (left)	Temporal	Freesurfer desikan white	−0.005	−1.036	3.0E−01
Mean OD in anterior corona radiata (right)	Thalamic radiations	dMRI OD	0.006	1.033	3.0E−01

Area of Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer DKT	0.006	1.033	3.0E−01
Mean axial diffusivity in inferior cerebellar peduncle (right)	Brainstem fibres	dMRI diffusivity	−0.006	−1.032	3.0E−01
Volume of Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer desikan white	−0.006	−1.030	3.0E−01
Area of Banks superior temporal sulcus (right)	Temporal	Freesurfer desikan white	−0.006	−1.028	3.0E−01
thickness of GcingulPostventral (left)	Limbic	Freesurfer a2009s	−0.006	−1.025	3.1E−01
Area of GfrontinfOpercular (right)	Frontal	Freesurfer a2009s	−0.006	−1.023	3.1E−01
Area of Supramarginal Gyrus (right)	Parietal	Freesurfer desikan pial	−0.006	−1.022	3.1E−01
Area of caudalAntcingulate (left)	Limbic	Freesurfer desikan white	−0.006	−1.022	3.1E−01
Mean intensity of InfLatVent (right)	NA	Freesurfer ASEG	0.006	1.022	3.1E−01
Area of Lateral Occipital Cortex (right)	Occipital	Freesurfer desikan white	−0.006	−1.020	3.1E−01
Area of GtempsupPlanpolar (left)	Temporal	Freesurfer a2009s	0.006	1.017	3.1E−01
Area of Precentral Gyrus (right)	Frontal	Freesurfer DKT	−0.006	−1.016	3.1E−01
Volume of Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer DKT	0.006	1.015	3.1E−01
Volume of Lateral orbitofrontal cortex (left)	Frontal	Freesurfer desikan white	−0.005	−1.013	3.1E−01
Grey-white contrast in Middle Temporal Gyrus (right)	Temporal	Freesurfer desikan gw	−0.005	−1.011	3.1E−01
Volume of Accumbensarea (right)	Striatum	Freesurfer ASEG	−0.005	−1.010	3.1E−01
Volume of CerebellumWhiteMatter (right)	Cerebellum	Freesurfer ASEG	0.005	1.009	3.1E−01
Volume of grey matter in Frontal Operculum Cortex (right)	Insular	FAST	−0.005	−1.009	3.1E−01
Grey-white contrast in Middle Temporal Gyrus (left)	Temporal	Freesurfer desikan gw	−0.005	−1.008	3.1E−01
Area of Brodmann Area 45 (right)	Frontal	Freesurfer BA exvivo	−0.006	−1.004	3.2E−01
Volume of Stemporalinf (left)	Temporal	Freesurfer a2009s	−0.005	−1.002	3.2E−01
Area of Transverse temporal gyrus (right)	Temporal	Freesurfer DKT	−0.005	−1.002	3.2E−01
Volume of Superior Frontal Gyrus (left)	Frontal	Freesurfer DKT	−0.005	−0.998	3.2E−01
thickness of Ssubparietal (right)	Parietal	Freesurfer a2009s	0.005	0.996	3.2E−01
Area of Stemporaltransverse (right)	Temporal	Freesurfer a2009s	−0.006	−0.994	3.2E−01
Area of Spericallosal (left)	Limbic	Freesurfer a2009s	0.005	0.992	3.2E−01
Area of Ssuborbital (left)	Frontal	Freesurfer a2009s	0.005	0.991	3.2E−01

Mean FA in cingulum cingulate gyrus (left)	Limbic system fibres	dMRI FA	0.005	0.989	3.2E−01
Mean FA in cerebral peduncle (left)	Brainstem fibres	dMRI FA	−0.005	−0.989	3.2E−01
thickness of Transverse temporal gyrus (right)	Temporal	Freesurfer desikan white	0.005	0.988	3.2E−01
Mean ISOVF in medial lemniscus (right)	Brainstem fibres	dMRI ISOVF	0.005	0.988	3.2E−01
Area of caudalAntcingulate (left)	Limbic	Freesurfer desikan pial	−0.005	−0.987	3.2E−01
Area of Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer desikan pial	−0.005	−0.987	3.2E−01
Volume of Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer DKT	0.005	0.985	3.2E−01
Volume of Scentral (right)	Frontal	Freesurfer a2009s	−0.005	−0.985	3.2E−01
thickness of Scollattransvpost (left)	Temporal	Freesurfer a2009s	0.005	0.981	3.3E−01
Area of Scentral (right)	Frontal	Freesurfer a2009s	−0.005	−0.980	3.3E−01
Mean OD in genu of corpus callosum on FA skeleton	Commissural fibres	dMRI OD	0.005	0.980	3.3E−01
thickness of Spostcentral (left)	Parietal	Freesurfer a2009s	0.005	0.979	3.3E−01
Area of Sprecentralinfpart (right)	Frontal	Freesurfer a2009s	−0.005	−0.978	3.3E−01
Mean axial diffusivity in anterior corona radiata (right)	Thalamic radiations	dMRI diffusivity	0.005	0.977	3.3E−01
Area of Lateral Occipital Cortex (left)	Occipital	Freesurfer desikan white	−0.005	−0.977	3.3E−01
Mean ICVF in cingulum hippocampus (left)	Limbic system fibres	dMRI ICVF	0.005	0.976	3.3E−01
Area of Entorhinal cortex (left)	Temporal	Freesurfer desikan pial	0.005	0.975	3.3E−01
Mean OD in cingulum hippocampus (right)	Limbic system fibres	dMRI OD	0.005	0.975	3.3E−01
Mean intensity of Caudate (right)	Striatum	Freesurfer ASEG	−0.005	−0.974	3.3E−01
Mean FA in cingulum cingulate gyrus (right)	Limbic system fibres	dMRI FA	0.005	0.973	3.3E−01
Area of Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer DKT	−0.005	−0.968	3.3E−01
Volume of rostralAntcingulate (right)	Limbic	Freesurfer DKT	−0.005	−0.967	3.3E−01
Mean intensity of CCMidPosterior (whole brain)	NA	Freesurfer ASEG	−0.005	−0.967	3.3E−01
thickness of Postcentral Gyrus (right)	Parietal	Freesurfer desikan white	0.005	0.966	3.3E−01
Grey-white contrast in Superior Temporal Gyrus (left)	Temporal	Freesurfer desikan gw	−0.005	−0.964	3.4E−01

Volume of Transverse temporal gyrus (left)	Temporal	Freesurfer desikan white	0.005	0.959	3.4E−01
thickness of Sfrontsup (left)	Frontal	Freesurfer a2009s	−0.005	−0.955	3.4E−01
thickness of Gfrontmiddle (left)	Frontal	Freesurfer a2009s	−0.005	−0.953	3.4E−01
Volume of Paracentral lobule (right)	Frontal	Freesurfer desikan white	−0.005	−0.949	3.4E−01
Area of Lingual Gyrus (right)	Occipital	Freesurfer desikan pial	−0.005	−0.947	3.4E−01
Volume of Cingulate Gyrus, posterior (left)	Limbic	Freesurfer desikan white	−0.005	−0.947	3.4E−01
Area of Lateral Occipital Cortex (right)	Occipital	Freesurfer DKT	−0.005	−0.945	3.4E−01
Area of Brodmann Area 2 (left)	Parietal	Freesurfer BA exvivo	−0.005	−0.945	3.4E−01
Volume of Supramarginal Gyrus (right)	Parietal	Freesurfer DKT	−0.005	−0.944	3.5E−01
Volume of ScingulMarginalis (left)	Frontal	Freesurfer a2009s	0.005	0.944	3.5E−01
Area of Brodmann Area V5 (left)	Occipital	Freesurfer BA exvivo	−0.005	−0.944	3.5E−01
Area of Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer desikan white	0.005	0.943	3.5E−01
Area of rostralAntcingulate (left)	Limbic	Freesurfer DKT	−0.005	−0.941	3.5E−01
Mean intensity of Caudate (left)	Striatum	Freesurfer ASEG	−0.005	−0.938	3.5E−01
thickness of GScingulMidPost (right)	Limbic	Freesurfer a2009s	−0.005	−0.938	3.5E−01
Area of LatFisantHorizont (left)	NA	Freesurfer a2009s	−0.005	−0.935	3.5E−01
Area of Inferior Temporal Gyrus (right)	Temporal	Freesurfer desikan white	−0.005	−0.934	3.5E−01
Volume of Brodmann Area V5 (left)	Occipital	Freesurfer BA exvivo	−0.005	−0.933	3.5E−01
Mean OD in tapetum (left)	Commissural fibres	dMRI OD	−0.005	−0.932	3.5E−01
thickness of Gtemporalmiddle (left)	Temporal	Freesurfer a2009s	−0.005	−0.932	3.5E−01
thickness of Gparietalsup (left)	Parietal	Freesurfer a2009s	0.005	0.932	3.5E−01
Volume of Scollattransvant (right)	Temporal	Freesurfer a2009s	−0.005	−0.931	3.5E−01
thickness of Transverse temporal gyrus (right)	Temporal	Freesurfer DKT	0.005	0.930	3.5E−01
Area of Ginsularshort (left)	Insular	Freesurfer a2009s	−0.005	−0.930	3.5E−01
thickness of Gorbital (right)	Frontal	Freesurfer a2009s	−0.005	−0.930	3.5E−01
Volume of Supramarginal Gyrus (right)	Parietal	Freesurfer desikan white	−0.005	−0.929	3.5E−01

Volume of caudalAntcingulate (right)	Limbic	Freesurfer DKT	0.005	0.929	3.5E−01
Volume of Sfrontmiddle (left)	Frontal	Freesurfer a2009s	−0.005	−0.928	3.5E−01
Mean ISOVF in splenium of corpus callosum on FA skeleton	Commissural fibres	dMRI ISOVF	0.005	0.927	3.5E−01
Volume of putamen (right)	Striatum	FIRST	0.005	0.926	3.5E−01
Volume of hippocampus (right)	Hippocampus	FIRST	0.005	0.925	3.6E−01
thickness of Lingual Gyrus (left)	Occipital	Freesurfer desikan white	−0.005	−0.924	3.6E−01
Mean ISOVF in posterior limb of internal capsule (left)	Internal capsule	dMRI ISOVF	0.005	0.920	3.6E−01
Mean FA in retrolenticular part of internal capsule (right)	Internal capsule	dMRI FA	−0.005	−0.918	3.6E−01
Volume of GcingulPostdorsal (left)	Limbic	Freesurfer a2009s	0.005	0.917	3.6E−01
Volume of grey matter in Occipital Pole (right)	Occipital	FAST	−0.005	−0.916	3.6E−01
Volume of BrainStem (whole brain)	NA	Freesurfer ASEG	0.005	0.916	3.6E−01
Area of Supramarginal Gyrus (right)	Parietal	Freesurfer DKT	−0.005	−0.914	3.6E−01
Volume of Banks superior temporal sulcus (left)	Temporal	Freesurfer desikan white	−0.005	−0.909	3.6E−01
Area of Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer desikan white	−0.005	−0.909	3.6E−01
thickness of Sorbitallateral (left)	Frontal	Freesurfer a2009s	−0.005	−0.908	3.6E−01
Volume of grey matter in Occipital Fusiform Gyrus (left)	Occipital	FAST	−0.005	−0.908	3.6E−01
thickness of Cuneal Cortex (left)	Occipital	Freesurfer a2009s	−0.005	−0.907	3.6E−01
Volume of GStransvfrontopol (right)	Frontal	Freesurfer a2009s	−0.005	−0.906	3.6E−01
Volume of accumbens (right)	Striatum	FIRST	−0.005	−0.905	3.7E−01
Mean FA in superior longitudinal fasciculus (right)	Association fibres	dMRI FA	−0.005	−0.904	3.7E−01
Volume of grey matter in Middle Temporal Gyrus, temporooccipital part (right)	Temporal	FAST	0.005	0.903	3.7E−01
Area of Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer DKT	−0.005	−0.902	3.7E−01
Mean radial diffusivity in middle cerebellar peduncle on FA skeleton	Brainstem fibres	dMRI diffusivity	−0.005	−0.902	3.7E−01
Area of Middle Temporal Gyrus (left)	Temporal	Freesurfer DKT	−0.005	−0.899	3.7E−01
Area of Stemporalinf (right)	Temporal	Freesurfer a2009s	0.005	0.896	3.7E−01
thickness of Superior Frontal Gyrus (right)	Frontal	Freesurfer desikan white	0.005	0.892	3.7E−01
Area of Supramarginal Gyrus (right)	Parietal	Freesurfer desikan white	−0.005	−0.891	3.7E−01

Grey-white contrast in Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer desikan gw	−0.004	−0.888	3.7E−01
Volume of grey matter in X Cerebellum (right)	Cerebellum	FAST	0.005	0.888	3.7E−01
Mean FA in posterior corona radiata (right)	Thalamic radiations	dMRI FA	−0.005	−0.888	3.7E−01
thickness of GfrontinfOrbital (left)	Frontal	Freesurfer a2009s	0.005	0.884	3.8E−01
Area of GcingulPostdorsal (left)	Limbic	Freesurfer a2009s	0.005	0.884	3.8E−01
Area of Transverse temporal gyrus (left)	Temporal	Freesurfer desikan pial	0.005	0.884	3.8E−01
Mean intensity of Pallidum (right)	Pallidum	Freesurfer ASEG	−0.005	−0.883	3.8E−01
Mean ICVF in posterior limb of internal capsule (right)	Internal capsule	dMRI ICVF	−0.005	−0.883	3.8E−01
Volume of amygdala (left)	Amygdala	FIRST	0.005	0.882	3.8E−01
Volume of Inferior Temporal Gyrus (right)	Temporal	Freesurfer desikan white	−0.005	−0.880	3.8E−01
Volume of grey matter in Superior Temporal Gyrus, posterior division (right)	Temporal	FAST	−0.005	−0.875	3.8E−01
Area of GtempsupPlantempo (left)	Temporal	Freesurfer a2009s	0.005	0.874	3.8E−01
thickness of Gfrontsup (right)	Frontal	Freesurfer a2009s	0.004	0.873	3.8E−01
Area of Superior Parietal Lobule (right)	Parietal	Freesurfer DKT	0.005	0.872	3.8E−01
thickness of ScingulMarginalis (right)	Frontal	Freesurfer a2009s	0.005	0.866	3.9E−01
thickness of GfrontinfOpercular (right)	Frontal	Freesurfer a2009s	−0.005	−0.865	3.9E−01
Area of Stemporalinf (left)	Temporal	Freesurfer a2009s	−0.005	−0.862	3.9E−01
thickness of Cingulate Gyrus, posterior (right)	Limbic	Freesurfer desikan white	−0.005	−0.859	3.9E−01
thickness of Soctemplat (right)	Temporal	Freesurfer a2009s	0.005	0.856	3.9E−01
Area of Frontal Medial Cortex, rostral (right)	Frontal	Freesurfer desikan white	−0.005	−0.855	3.9E−01
Area of Scollattransvpost (right)	Temporal	Freesurfer a2009s	0.005	0.852	3.9E−01
Volume of LatFispost (left)	NA	Freesurfer a2009s	0.005	0.851	3.9E−01
Volume of Entorhinal cortex (right)	Temporal	Freesurfer BA exvivo	0.005	0.851	3.9E−01
Area of rostralAntcingulate (right)	Limbic	Freesurfer desikan white	0.005	0.849	4.0E−01
Grey-white contrast in PreCuneal Cortex (right)	Occipital	Freesurfer desikan gw	−0.004	−0.847	4.0E−01
Volume of Lateralnucleus (right)	Amygdala	Freesurfer subsegmentation	0.004	0.847	4.0E−01
Mean OD in anterior limb of internal capsule (right)	Internal capsule	dMRI OD	−0.005	−0.846	4.0E−01

Volume of SocmiddleLunatus (right)	Occipital	Freesurfer a2009s	−0.005	−0.846	4.0E−01
thickness of Middle Temporal Gyrus (right)	Temporal	Freesurfer desikan white	−0.005	−0.844	4.0E−01
Area of Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer DKT	−0.005	−0.842	4.0E−01
Area of Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer desikan white	−0.005	−0.842	4.0E−01
Mean ICVF in uncinate fasciculus (right)	Association fibres	dMRI ICVF	−0.004	−0.841	4.0E−01
thickness of GtempsupGTtransv (left)	Temporal	Freesurfer a2009s	0.005	0.840	4.0E−01
thickness of Brodmann Area V5 (left)	Occipital	Freesurfer BA exvivo	0.005	0.839	4.0E−01
Volume of grey matter in IX Cerebellum (left)	Cerebellum	FAST	0.004	0.839	4.0E−01
thickness of Ssuborbital (left)	Frontal	Freesurfer a2009s	−0.005	−0.838	4.0E−01
Area of Insular Cortex (left)	Insular	Freesurfer desikan white	−0.005	−0.838	4.0E−01
Area of Supramarginal Gyrus (left)	Parietal	Freesurfer desikan pial	0.005	0.837	4.0E−01
Volume of grey matter in Inferior Temporal Gyrus, temporooccipital part (left)	Temporal	FAST	−0.005	−0.837	4.0E−01
thickness of GSoccipitalinf (right)	Occipital	Freesurfer a2009s	0.005	0.836	4.0E−01
Volume of Hippocampus (left)	Hippocampus	Freesurfer ASEG	0.004	0.836	4.0E−01
Area of Banks superior temporal sulcus (left)	Temporal	Freesurfer desikan white	−0.005	−0.836	4.0E−01
thickness of Cuneal Cortex (right)	Occipital	Freesurfer DKT	−0.005	−0.832	4.1E−01
Area of Precentral Gyrus (right)	Frontal	Freesurfer desikan white	−0.005	−0.831	4.1E−01
thickness of Poletemporal (left)	Temporal	Freesurfer a2009s	−0.005	−0.829	4.1E−01
Volume of grey matter in Amygdala (right)	Amygdala	FAST	0.004	0.828	4.1E−01
Volume of grey matter in Cingulate Gyrus, posterior division (left)	Limbic	FAST	0.004	0.823	4.1E−01
Volume of Amygdala (right)	Amygdala	Freesurfer ASEG	0.004	0.820	4.1E−01
Volume of Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer DKT	−0.004	−0.819	4.1E−01
Volume of Pt (left)	Thalamus	Freesurfer subsegmentation	0.004	0.816	4.1E−01
thickness of Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer DKT	−0.004	−0.814	4.2E−01
Volume of Brodmann Area 3a (right)	Parietal	Freesurfer BA exvivo	−0.004	−0.810	4.2E−01
Area of Ssuborbital (right)	Frontal	Freesurfer a2009s	−0.004	−0.809	4.2E−01

Mean MD in corticospinal tract (left)	Brainstem fibres	dMRI diffusivity	0.004	0.808	4.2E−01
Mean OD in posterior thalamic radiation (right)	Thalamic radiations	dMRI OD	0.004	0.807	4.2E−01
Area of SorbitalHShaped (left)	Frontal	Freesurfer a2009s	0.004	0.807	4.2E−01
thickness of Middle Temporal Gyrus (right)	Temporal	Freesurfer DKT	−0.004	−0.804	4.2E−01
thickness of SintraparietPtrans (left)	Parietal	Freesurfer a2009s	0.004	0.799	4.2E−01
Grey-white contrast in Fusiform Gyrus (left)	Occipital	Freesurfer desikan gw	−0.004	−0.798	4.2E−01
Grey-white contrast in Superior Temporal Gyrus (right)	Temporal	Freesurfer desikan gw	−0.004	−0.797	4.3E−01
Volume of grey matter in Temporal Occipital Fusiform Cortex (right)	Temporal	FAST	−0.004	−0.796	4.3E−01
Volume of Corticalnucleus (right)	Amygdala	Freesurfer subsegmentation	−0.004	−0.795	4.3E−01
thickness of Cingulate Gyrus, posterior (right)	Limbic	Freesurfer DKT	−0.004	−0.792	4.3E−01
Area of Supramarginal Gyrus (left)	Parietal	Freesurfer DKT	0.004	0.792	4.3E−01
Volume of Stemporalsup (right)	Temporal	Freesurfer a2009s	−0.004	−0.792	4.3E−01
Volume of VentralDC (left)	Thalamus	Freesurfer ASEG	0.004	0.788	4.3E−01
Volume of LatFispost (right)	NA	Freesurfer a2009s	−0.004	−0.788	4.3E−01
thickness of GtempsupLateral (left)	Temporal	Freesurfer a2009s	0.004	0.788	4.3E−01
thickness of Sfrontsup (right)	Frontal	Freesurfer a2009s	−0.004	−0.784	4.3E−01
Area of Medorbitofrontal (left)	Frontal	Freesurfer desikan white	−0.004	−0.778	4.4E−01
Volume of Entorhinal cortex (right)	Temporal	Freesurfer desikan white	0.004	0.777	4.4E−01
Volume of Stemporaltransverse (left)	Temporal	Freesurfer a2009s	−0.004	−0.776	4.4E−01
Area of Transverse temporal gyrus (left)	Temporal	Freesurfer DKT	0.004	0.774	4.4E−01
Mean ISOVF in posterior thalamic radiation (left)	Thalamic radiations	dMRI ISOVF	0.004	0.770	4.4E−01
Volume of Sorbitallateral (left)	Frontal	Freesurfer a2009s	0.004	0.768	4.4E−01
thickness of ScingulMarginalis (left)	Frontal	Freesurfer a2009s	−0.004	−0.768	4.4E−01
Area of Postcentral Gyrus (right)	Parietal	Freesurfer desikan pial	−0.004	−0.766	4.4E−01
Volume of Socsuptransversal (left)	Occipital	Freesurfer a2009s	−0.004	−0.765	4.4E−01
Area of Brodmann Area 6 (left)	Frontal	Freesurfer BA exvivo	−0.004	−0.763	4.5E−01
thickness of Lingual Gyrus (left)	Occipital	Freesurfer DKT	−0.004	−0.762	4.5E−01
thickness of Gfrontsup (left)	Frontal	Freesurfer a2009s	−0.004	−0.759	4.5E−01

Volume of Perirhinal cortex (right)	Temporal	Freesurfer BA exvivo	0.004	0.758	4.5E−01
Volume of Scircularinsulainf (right)	Insular	Freesurfer a2009s	−0.004	−0.752	4.5E−01
Area of Middle Temporal Gyrus (left)	Temporal	Freesurfer desikan pial	−0.004	−0.751	4.5E−01
Volume of molecularlayerHPhead (left)	Hippocampus	Freesurfer subsegmentation	0.004	0.751	4.5E−01
Area of Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer desikan pial	−0.004	−0.747	4.5E−01
Volume of AccessBasalnucleus (right)	Amygdala	Freesurfer subsegmentation	0.004	0.747	4.5E−01
Area of Lateral orbitofrontal cortex (left)	Frontal	Freesurfer DKT	0.004	0.747	4.6E−01
Area of Soccipitalant (left)	Occipital	Freesurfer a2009s	−0.004	−0.746	4.6E−01
Area of Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer desikan pial	0.004	0.746	4.6E−01
Volume of PreCuneal Cortex (left)	Occipital	Freesurfer DKT	0.004	0.746	4.6E−01
Mean intensity of CCAnt (whole brain)	NA	Freesurfer ASEG	0.004	0.743	4.6E−01
Area of Entorhinal cortex (right)	Temporal	Freesurfer DKT	0.004	0.743	4.6E−01
Volume of Superior Temporal Gyrus (left)	Temporal	Freesurfer desikan white	0.004	0.742	4.6E−01
Area of Middle Temporal Gyrus (left)	Temporal	Freesurfer desikan white	−0.004	−0.736	4.6E−01
Grey-white contrast in Insular Cortex (right)	Insular	Freesurfer desikan gw	0.004	0.736	4.6E−01
Mean OD in posterior thalamic radiation (left)	Thalamic radiations	dMRI OD	0.004	0.732	4.6E−01
Mean axial diffusivity in sagittal stratum (right)	Association fibres	dMRI diffusivity	0.004	0.732	4.6E−01
Mean axial diffusivity in uncinate fasciculus (left)	Association fibres	dMRI diffusivity	−0.004	−0.728	4.7E−01
Area of Poleoccipital (left)	Occipital	Freesurfer a2009s	−0.004	−0.728	4.7E−01
Volume of GtempsupGTransv (left)	Temporal	Freesurfer a2009s	0.004	0.723	4.7E−01
thickness of Brodmann Area 2 (left)	Parietal	Freesurfer BA exvivo	0.004	0.720	4.7E−01
Mean ISOVF in corticospinal tract (left)	Brainstem fibres	dMRI ISOVF	0.004	0.716	4.7E−01
Area of Entorhinal cortex (right)	Temporal	Freesurfer desikan white	0.004	0.715	4.7E−01
Area of Frontal Pole (right)	Frontal	Freesurfer desikan white	0.004	0.713	4.8E−01
Volume of PuA (left)	Thalamus	Freesurfer subsegmentation	−0.004	−0.713	4.8E−01
Volume of grey matter in Supramarginal Gyrus, anterior division (right)	Parietal	FAST	0.004	0.713	4.8E−01

Volume of grey matter in Inferior Temporal Gyrus, posterior division (left)	Temporal	FAST	0.004	0.712	4.8E−01
thickness of Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer desikan white	−0.004	−0.711	4.8E−01
Area of Transverse temporal gyrus (right)	Temporal	Freesurfer desikan white	−0.004	−0.709	4.8E−01
Mean ISOVF in medial lemniscus (left)	Brainstem fibres	dMRI ISOVF	0.004	0.706	4.8E−01
Volume of Paracentral lobule (right)	Frontal	Freesurfer DKT	−0.004	−0.705	4.8E−01
Area of Sfrontsup (left)	Frontal	Freesurfer a2009s	0.004	0.705	4.8E−01
Area of Gfrontsup (right)	Frontal	Freesurfer a2009s	−0.004	−0.704	4.8E−01
Volume of CL (right)	Thalamus	Freesurfer subsegmentation	−0.004	−0.703	4.8E−01
thickness of Gpostcentral (right)	Parietal	Freesurfer a2009s	0.004	0.700	4.8E−01
Volume of grey matter in Vermis Crus II Cerebellum	Cerebellum	FAST	−0.004	−0.700	4.8E−01
Volume of GScingulMidAnt (right)	Limbic	Freesurfer a2009s	−0.004	−0.700	4.8E−01
Grey-white contrast in Inferior Parietal Lobule (right)	Parietal	Freesurfer desikan gw	−0.004	−0.696	4.9E−01
Volume of ThalamusProper (left)	Thalamus	Freesurfer ASEG	−0.003	−0.695	4.9E−01
Volume of CA4body (left)	Hippocampus	Freesurfer subsegmentation	−0.004	−0.695	4.9E−01
Mean OD in uncinate fasciculus (right)	Association fibres	dMRI OD	0.004	0.694	4.9E−01
thickness of Goctemplatfusifor (right)	Temporal	Freesurfer a2009s	0.004	0.694	4.9E−01
Mean intensity of 3rdVentricle (whole brain)	NA	Freesurfer ASEG	−0.003	−0.693	4.9E−01
Volume of Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer desikan white	0.004	0.693	4.9E−01
Volume of grey matter in Parietal Operculum Cortex (right)	Insular	FAST	−0.004	−0.692	4.9E−01
Area of Stemporalsup (left)	Temporal	Freesurfer a2009s	−0.004	−0.692	4.9E−01
thickness of GSsubcentral (left)	Frontal	Freesurfer a2009s	0.004	0.692	4.9E−01
Area of PreCuneal Cortex (right)	Occipital	Freesurfer desikan pial	0.004	0.691	4.9E−01
Area of Goccipitalmiddle (right)	Occipital	Freesurfer a2009s	−0.004	−0.690	4.9E−01
Mean OD in retrolenticular part of internal capsule (left)	Internal capsule	dMRI OD	−0.004	−0.689	4.9E−01
Area of Paracentral lobule (right)	Frontal	Freesurfer desikan white	−0.004	−0.686	4.9E−01
Volume of CeM (left)	Thalamus	Freesurfer subsegmentation	0.004	0.686	4.9E−01

thickness of Brodmann Area 45 (right)	Frontal	Freesurfer BA exvivo	−0.004	−0.684	4.9E−01
Area of Entorhinal cortex (left)	Temporal	Freesurfer desikan white	−0.004	−0.683	4.9E−01
Area of Scircularinsulainf (right)	Insular	Freesurfer a2009s	0.004	0.682	5.0E−01
Volume of CA3head (right)	Hippocampus	Freesurfer subsegmentation	−0.004	−0.681	5.0E−01
Area of SintermprimJensen (left)	Parietal	Freesurfer a2009s	0.004	0.679	5.0E−01
Mean ISOVF in middle cerebellar peduncle on FA skeleton	Brainstem fibres	dMRI ISOVF	−0.004	−0.679	5.0E−01
Area of Superior Frontal Gyrus (left)	Frontal	Freesurfer desikan white	−0.004	−0.678	5.0E−01
Volume of Brodmann Area 2 (right)	Parietal	Freesurfer BA exvivo	0.004	0.677	5.0E−01
Area of SorbitalHShaped (right)	Frontal	Freesurfer a2009s	0.004	0.677	5.0E−01
Area of Inferior Temporal Gyrus (right)	Temporal	Freesurfer DKT	−0.004	−0.676	5.0E−01
Volume of Soccipitalant (left)	Occipital	Freesurfer a2009s	−0.004	−0.675	5.0E−01
Volume of Wholehippocampalbody (left)	Hippocampus	Freesurfer subsegmentation	0.003	0.672	5.0E−01
thickness of GcingulPostventral (right)	Limbic	Freesurfer a2009s	0.004	0.671	5.0E−01
thickness of Scentral (right)	Frontal	Freesurfer a2009s	−0.004	−0.670	5.0E−01
Area of Goccipitalsup (left)	Occipital	Freesurfer a2009s	−0.004	−0.667	5.0E−01
Volume of GCMLDGhead (left)	Hippocampus	Freesurfer subsegmentation	0.003	0.666	5.1E−01
Volume of Inferior Parietal Lobule (right)	Parietal	Freesurfer DKT	−0.004	−0.666	5.1E−01
thickness of Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer DKT	−0.004	−0.662	5.1E−01
thickness of Gcuneus (right)	Occipital	Freesurfer a2009s	−0.004	−0.662	5.1E−01
Volume of grey matter in Angular Gyrus (right)	Parietal	FAST	−0.004	−0.662	5.1E−01
thickness of Inferior Frontal Gyrus, pars triangularis (right)	Frontal	Freesurfer desikan white	−0.004	−0.662	5.1E−01
thickness of Scollattransvant (left)	Temporal	Freesurfer a2009s	−0.004	−0.660	5.1E−01
Mean OD in corticospinal tract (right)	Brainstem fibres	dMRI OD	0.004	0.656	5.1E−01
Volume of Gorbital (right)	Frontal	Freesurfer a2009s	−0.004	−0.656	5.1E−01
Volume of Pf (right)	Thalamus	Freesurfer subsegmentation	0.004	0.655	5.1E−01

Area of Paracentral lobule (left)	Frontal	Freesurfer desikan white	−0.004	−0.654	5.1E−01
Volume of grey matter in I-IV Cerebellum (right)	Cerebellum	FAST	0.003	0.652	5.1E−01
Volume of Inferior Temporal Gyrus (right)	Temporal	Freesurfer DKT	−0.004	−0.651	5.1E−01
Volume of SintraparietPtrans (right)	Parietal	Freesurfer a2009s	0.004	0.651	5.2E−01
Area of GtempsupPlanpolar (right)	Temporal	Freesurfer a2009s	−0.004	−0.649	5.2E−01
thickness of Socsuptransversal (right)	Occipital	Freesurfer a2009s	0.004	0.649	5.2E−01
Area of Postcentral Gyrus (right)	Parietal	Freesurfer DKT	−0.004	−0.644	5.2E−01
Area of Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer DKT	−0.004	−0.644	5.2E−01
thickness of Inferior Frontal Gyrus, pars opercularis (right)	Frontal	Freesurfer desikan white	−0.003	−0.643	5.2E−01
Volume of Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer DKT	0.003	0.641	5.2E−01
thickness of GcingulPostdorsal (right)	Limbic	Freesurfer a2009s	0.003	0.640	5.2E−01
Volume of grey matter in Lateral Occipital Cortex, inferior division (right)	Occipital	FAST	−0.003	−0.639	5.2E−01
Volume of molecularlayerHPbody (left)	Hippocampus	Freesurfer subsegmentation	0.003	0.639	5.2E−01
Volume of Soccipitalant (right)	Occipital	Freesurfer a2009s	−0.004	−0.638	5.2E−01
Grey-white contrast in Cuneal Cortex (left)	Occipital	Freesurfer desikan gw	−0.003	−0.638	5.2E−01
Mean FA in retrolenticular part of internal capsule (left)	Internal capsule	dMRI FA	−0.003	−0.634	5.3E−01
thickness of Gprecuneus (left)	Occipital	Freesurfer a2009s	−0.003	−0.631	5.3E−01
Area of GInslgScentins (left)	Insular	Freesurfer a2009s	−0.003	−0.630	5.3E−01
Area of Superior Parietal Lobule (right)	Parietal	Freesurfer desikan white	0.003	0.629	5.3E−01
Mean intensity of LateralVentricle (right)	NA	Freesurfer ASEG	−0.003	−0.626	5.3E−01
Area of Inferior Temporal Gyrus (right)	Temporal	Freesurfer desikan pial	−0.003	−0.626	5.3E−01
thickness of Poleoccipital (left)	Occipital	Freesurfer a2009s	0.003	0.624	5.3E−01
Area of Paracentral lobule (left)	Frontal	Freesurfer DKT	−0.003	−0.619	5.4E−01
Mean FA in superior corona radiata (right)	Thalamic radiations	dMRI FA	−0.003	−0.615	5.4E−01
Grey-white contrast in Fusiform Gyrus (right)	Occipital	Freesurfer desikan gw	0.003	0.614	5.4E−01
Volume of grey matter in Precuneous Cortex (left)	Parietal	FAST	−0.003	−0.609	5.4E−01
Volume of Stemporalinf (right)	Temporal	Freesurfer a2009s	0.003	0.603	5.5E−01

thickness of Pericalcarine cortex (right)	Occipital	Freesurfer DKT	−0.003	−0.602	5.5E−01
Volume of grey matter in Vermis X Cerebellum	Cerebellum	FAST	0.003	0.600	5.5E−01
Area of Supramarginal Gyrus (left)	Parietal	Freesurfer desikan white	0.003	0.600	5.5E−01
Mean ICVF in fornix on FA skeleton	Limbic system fibres	dMRI ICVF	−0.003	−0.598	5.5E−01
Area of ScingulMarginalis (right)	Frontal	Freesurfer a2009s	−0.003	−0.597	5.5E−01
Area of Postcentral Gyrus (right)	Parietal	Freesurfer desikan white	−0.003	−0.596	5.5E−01
thickness of Pericalcarine cortex (right)	Occipital	Freesurfer desikan white	−0.003	−0.596	5.5E−01
Volume of Superior Temporal Gyrus (right)	Temporal	Freesurfer DKT	0.003	0.595	5.5E−01
Volume of LatFisantVertical (right)	NA	Freesurfer a2009s	−0.003	−0.594	5.5E−01
Mean MD in cingulum hippocampus (left)	Limbic system fibres	dMRI diffusivity	−0.003	−0.594	5.5E−01
Volume of CerebellumCortex (right)	Cerebellum	Freesurfer ASEG	−0.003	−0.594	5.5E−01
Volume of MGN (right)	Thalamus	Freesurfer subsegmentation	0.003	0.592	5.5E−01
Volume of Gparietalsup (left)	Parietal	Freesurfer a2009s	0.003	0.587	5.6E−01
Grey-white contrast in Superior Parietal Lobule (right)	Parietal	Freesurfer desikan gw	−0.003	−0.587	5.6E−01
Area of GInslgScentins (right)	Insular	Freesurfer a2009s	0.003	0.584	5.6E−01
Volume of Gorbital (left)	Frontal	Freesurfer a2009s	0.003	0.584	5.6E−01
Volume of grey matter in Planum Polare (right)	Temporal	FAST	−0.003	−0.583	5.6E−01
Area of Inferior Parietal Lobule (right)	Parietal	Freesurfer desikan pial	−0.003	−0.581	5.6E−01
thickness of Scollattransvpost (right)	Temporal	Freesurfer a2009s	−0.003	−0.577	5.6E−01
Volume of Banks superior temporal sulcus (right)	Temporal	Freesurfer desikan white	−0.003	−0.577	5.6E−01
Area of Frontal Medial Cortex, rostral (left)	Frontal	Freesurfer desikan white	−0.003	−0.577	5.6E−01
Area of Grectus (left)	Frontal	Freesurfer a2009s	−0.003	−0.576	5.6E−01
Mean MD in middle cerebellar peduncle on FA skeleton	Brainstem fibres	dMRI diffusivity	−0.003	−0.575	5.7E−01
Volume of Supramarginal Gyrus (left)	Parietal	Freesurfer desikan white	0.003	0.572	5.7E−01
Volume of grey matter in Planum Temporale (left)	Temporal	FAST	−0.003	−0.571	5.7E−01

Volume of Spericallosal (right)	Limbic	Freesurfer a2009s	0.003	0.567	5.7E−01
Volume of grey matter in VIIIa Cerebellum (right)	Cerebellum	FAST	−0.003	−0.567	5.7E−01
Grey-white contrast in Entorhinal cortex (left)	Temporal	Freesurfer desikan gw	−0.003	−0.566	5.7E−01
Mean OD in uncinate fasciculus (left)	Association fibres	dMRI OD	0.003	0.566	5.7E−01
Volume of Scircularinsulaant (right)	Insular	Freesurfer a2009s	−0.003	−0.562	5.7E−01
Grey-white contrast in caudalAntcingulate (left)	Limbic	Freesurfer desikan gw	−0.003	−0.559	5.8E−01
Volume of Supramarginal Gyrus (left)	Parietal	Freesurfer DKT	0.003	0.557	5.8E−01
Area of Banks superior temporal sulcus (right)	Temporal	Freesurfer desikan pial	−0.003	−0.556	5.8E−01
Volume of Entorhinal cortex (left)	Temporal	Freesurfer desikan white	0.003	0.555	5.8E−01
Area of Sorbitallateral (right)	Frontal	Freesurfer a2009s	0.003	0.554	5.8E−01
Volume of grey matter in Superior Parietal Lobule (left)	Parietal	FAST	−0.003	−0.549	5.8E−01
Area of Scircularinsulaant (left)	Insular	Freesurfer a2009s	−0.003	−0.548	5.8E−01
Volume of Mednucleus (right)	Amygdala	Freesurfer subsegmentation	0.003	0.539	5.9E−01
Volume of SintermprimJensen (left)	Parietal	Freesurfer a2009s	0.003	0.539	5.9E−01
thickness of SintermprimJensen (right)	Parietal	Freesurfer a2009s	0.003	0.538	5.9E−01
thickness of GoctempmedLingual (left)	Occipital	Freesurfer a2009s	−0.003	−0.535	5.9E−01
Mean MD in cerebral peduncle (right)	Brainstem fibres	dMRI diffusivity	−0.003	−0.535	5.9E−01
Volume of grey matter in Crus I Cerebellum (left)	Cerebellum	FAST	−0.003	−0.535	5.9E−01
Area of Transverse temporal gyrus (left)	Temporal	Freesurfer desikan white	0.003	0.534	5.9E−01
thickness of Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer DKT	−0.003	−0.534	5.9E−01
Area of GtempsupGTtransv (right)	Temporal	Freesurfer a2009s	−0.003	−0.532	5.9E−01
Volume of grey matter in Superior Temporal Gyrus, posterior division (left)	Temporal	FAST	0.003	0.532	6.0E−01
Volume of grey matter in Precuneous Cortex (right)	Parietal	FAST	−0.003	−0.530	6.0E−01
thickness of Frontal Medial Cortex, caudal (right)	Frontal	Freesurfer desikan white	−0.003	−0.529	6.0E−01
Volume of Cortamygdaloidtransitio (right)	Amygdala	Freesurfer subsegmentation	0.003	0.528	6.0E−01
Area of Inferior Parietal Lobule (right)	Parietal	Freesurfer DKT	−0.003	−0.528	6.0E−01
Mean ISOVF in inferior cerebellar peduncle (right)	Brainstem fibres	dMRI ISOVF	0.003	0.527	6.0E−01

Volume of PreCuneal Cortex (left)	Occipital	Freesurfer desikan white	0.003	0.527	6.0E−01
thickness of Entorhinal cortex (right)	Temporal	Freesurfer DKT	−0.003	−0.525	6.0E−01
Volume of Goccipitalmiddle (right)	Occipital	Freesurfer a2009s	−0.003	−0.524	6.0E−01
Area of Fusiform Gyrus (left)	Occipital	Freesurfer desikan white	−0.003	−0.521	6.0E−01
thickness of Superior Temporal Gyrus (right)	Temporal	Freesurfer desikan white	0.003	0.520	6.0E−01
Area of Insular Cortex (left)	Insular	Freesurfer DKT	−0.003	−0.518	6.0E−01
thickness of Brodmann Area 3b (right)	Parietal	Freesurfer BA exvivo	0.003	0.518	6.0E−01
Volume of hippocampalfissure (right)	Hippocampus	Freesurfer subsegmentation	0.003	0.518	6.0E−01
Mean FA in middle cerebellar peduncle on FA skeleton	Brainstem fibres	dMRI FA	0.003	0.517	6.0E−01
Grey-white contrast in Lateral Occipital Cortex (left)	Occipital	Freesurfer desikan gw	−0.003	−0.517	6.1E−01
Volume of grey matter in Lingual Gyrus (right)	Occipital	FAST	0.003	0.516	6.1E−01
Volume of Wholehippocampalbody (right)	Hippocampus	Freesurfer subsegmentation	0.003	0.516	6.1E−01
Volume of Brodmann Area 2 (left)	Parietal	Freesurfer BA exvivo	−0.003	−0.516	6.1E−01
Mean intensity of BrainStem (whole brain)	NA	Freesurfer ASEG	−0.003	−0.515	6.1E−01
thickness of Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer DKT	0.003	0.513	6.1E−01
Area of Lateral Occipital Cortex (right)	Occipital	Freesurfer desikan pial	−0.003	−0.509	6.1E−01
Volume of Superior Parietal Lobule (left)	Parietal	Freesurfer DKT	0.003	0.504	6.1E−01
Mean FA in external capsule (left)	Association fibres	dMRI FA	0.003	0.503	6.1E−01
Volume of Inferior Parietal Lobule (right)	Parietal	Freesurfer desikan white	−0.003	−0.501	6.2E−01
Volume of CCCentral (whole brain)	NA	Freesurfer ASEG	−0.003	−0.500	6.2E−01
Area of GtempsupLateral (left)	Temporal	Freesurfer a2009s	0.003	0.498	6.2E−01
Volume of ScingulMarginalis (right)	Frontal	Freesurfer a2009s	−0.003	−0.497	6.2E−01
Area of Paracentral lobule (right)	Frontal	Freesurfer DKT	−0.003	−0.496	6.2E−01
Mean ICVF in inferior cerebellar peduncle (left)	Brainstem fibres	dMRI ICVF	0.003	0.493	6.2E−01
Volume of grey matter in Angular Gyrus (left)	Parietal	FAST	0.003	0.492	6.2E−01
thickness of Brodmann Area 3b (left)	Parietal	Freesurfer BA exvivo	0.003	0.492	6.2E−01
Grey-white contrast in Lateral orbitofrontal cortex (right)	Frontal	Freesurfer desikan gw	−0.002	−0.491	6.2E−01

thickness of Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer DKT	−0.003	−0.490	6.2E−01
Area of GfrontinfOrbital (right)	Frontal	Freesurfer a2009s	0.003	0.490	6.2E−01
thickness of LatFisantHorizont (left)	NA	Freesurfer a2009s	−0.003	−0.488	6.3E−01
thickness of LatFisantVertical (right)	NA	Freesurfer a2009s	−0.003	−0.486	6.3E−01
Mean OD in sagittal stratum (left)	Association fibres	dMRI OD	−0.003	−0.486	6.3E−01
Volume of Brodmann Area V2 (right)	Occipital	Freesurfer BA exvivo	−0.003	−0.484	6.3E−01
Volume of MV(Re) (left)	Thalamus	Freesurfer subsegmentation	−0.003	−0.483	6.3E−01
Area of Lateral orbitofrontal cortex (right)	Frontal	Freesurfer desikan white	−0.003	−0.483	6.3E−01
thickness of Scalcarine (right)	Occipital	Freesurfer a2009s	−0.003	−0.482	6.3E−01
Volume of Brodmann Area 1 (right)	Parietal	Freesurfer BA exvivo	−0.003	−0.480	6.3E−01
Mean ICVF in cingulum hippocampus (right)	Limbic system fibres	dMRI ICVF	0.003	0.479	6.3E−01
thickness of Brodmann Area 6 (right)	Frontal	Freesurfer BA exvivo	−0.002	−0.478	6.3E−01
Volume of grey matter in Heschls Gyrus (includes H1 and H2) (right)	Temporal	FAST	−0.002	−0.478	6.3E−01
Grey-white contrast in Temporal pole (right)	Temporal	Freesurfer desikan gw	0.002	0.477	6.3E−01
Mean intensity of Hippocampus (left)	Hippocampus	Freesurfer ASEG	−0.003	−0.476	6.3E−01
Volume of grey matter in VI Cerebellum (right)	Cerebellum	FAST	0.002	0.474	6.4E−01
Area of GtempsupLateral (right)	Temporal	Freesurfer a2009s	−0.003	−0.474	6.4E−01
Volume of CA4head (right)	Hippocampus	Freesurfer subsegmentation	0.002	0.470	6.4E−01
Volume of Poleoccipital (left)	Occipital	Freesurfer a2009s	−0.003	−0.468	6.4E−01
thickness of Sparietooccipital (right)	Occipital	Freesurfer a2009s	−0.003	−0.467	6.4E−01
Volume of grey matter in Parahippocampal Gyrus, posterior division (right)	Temporal	FAST	−0.002	−0.465	6.4E−01
Volume of grey matter in VIIb Cerebellum (right)	Cerebellum	FAST	−0.002	−0.465	6.4E−01
Area of Ginsularshort (right)	Insular	Freesurfer a2009s	0.003	0.461	6.4E−01
Volume of GoctempmedParahip (left)	Temporal	Freesurfer a2009s	0.003	0.461	6.4E−01
Volume of amygdala (right)	Amygdala	FIRST	0.003	0.461	6.4E−01
Mean intensity of CerebellumWhiteMatter (right)	Cerebellum	Freesurfer ASEG	−0.003	−0.461	6.5E−01
Area of Scollattransvant (left)	Temporal	Freesurfer a2009s	−0.003	−0.460	6.5E−01

Area of Superior Parietal Lobule (left)	Parietal	Freesurfer desikan pial	−0.003	−0.460	6.5E−01
Volume of grey matter in Supracalcarine Cortex (right)	Occipital	FAST	−0.002	−0.457	6.5E−01
Mean ISOVF in inferior cerebellar peduncle (left)	Brainstem fibres	dMRI ISOVF	0.002	0.455	6.5E−01
Volume of grey matter in Inferior Temporal Gyrus, anterior division (left)	Temporal	FAST	0.002	0.452	6.5E−01
Volume of Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer desikan white	0.002	0.452	6.5E−01
Area of LatFisantHorizont (right)	NA	Freesurfer a2009s	−0.002	−0.450	6.5E−01
Mean axial diffusivity in uncinate fasciculus (right)	Association fibres	dMRI diffusivity	0.002	0.447	6.5E−01
Volume of grey matter in Crus I Cerebellum (right)	Cerebellum	FAST	−0.002	−0.446	6.6E−01
Volume of Spostcentral (left)	Parietal	Freesurfer a2009s	0.002	0.441	6.6E−01
Area of GScingulMidPost (left)	Limbic	Freesurfer a2009s	−0.002	−0.441	6.6E−01
Area of Insular Cortex (right)	Insular	Freesurfer DKT	0.002	0.439	6.6E−01
Mean OD in posterior limb of internal capsule (right)	Internal capsule	dMRI OD	−0.002	−0.436	6.6E−01
thickness of GparietinfSupramar (right)	Parietal	Freesurfer a2009s	0.002	0.436	6.6E−01
Grey-white contrast in Cingulate Gyrus, posterior (left)	Limbic	Freesurfer desikan gw	−0.002	−0.435	6.6E−01
thickness of Goccipitalmiddle (left)	Occipital	Freesurfer a2009s	0.002	0.434	6.6E−01
Mean intensity of ThalamusProper (right)	Thalamus	Freesurfer ASEG	−0.002	−0.434	6.6E−01
thickness of GfrontinfTriangul (right)	Frontal	Freesurfer a2009s	−0.002	−0.434	6.6E−01
Area of Brodmann Area 1 (right)	Parietal	Freesurfer BA exvivo	−0.002	−0.433	6.6E−01
Area of Entorhinal cortex (left)	Temporal	Freesurfer BA exvivo	0.002	0.431	6.7E−01
thickness of Brodmann Area V1 (left)	Occipital	Freesurfer BA exvivo	−0.002	−0.431	6.7E−01
Area of rostralAntcingulate (left)	Limbic	Freesurfer desikan white	−0.002	−0.429	6.7E−01
Area of Brodmann Area 4p (right)	Frontal	Freesurfer BA exvivo	−0.002	−0.429	6.7E−01
thickness of Sorbitallateral (right)	Frontal	Freesurfer a2009s	−0.002	−0.424	6.7E−01
thickness of Goccipitalmiddle (right)	Occipital	Freesurfer a2009s	0.002	0.423	6.7E−01
Volume of grey matter in Supramarginal Gyrus, posterior division (left)	Parietal	FAST	0.002	0.423	6.7E−01
thickness of Soccipitalant (left)	Occipital	Freesurfer a2009s	0.002	0.422	6.7E−01
thickness of GtempsupPlanpolar (right)	Temporal	Freesurfer a2009s	−0.002	−0.421	6.7E−01
thickness of Inferior Temporal Gyrus (left)	Temporal	Freesurfer a2009s	0.002	0.420	6.7E−01

Volume of Gfrontsup (right)	Frontal	Freesurfer a2009s	−0.002	−0.419	6.8E−01
Area of Gfrontsup (left)	Frontal	Freesurfer a2009s	−0.002	−0.419	6.8E−01
Volume of PuM (right)	Thalamus	Freesurfer subsegmentation	0.002	0.419	6.8E−01
Mean axial diffusivity in cingulum hippocampus (left)	Limbic system fibres	dMRI diffusivity	0.002	0.418	6.8E−01
Volume of accumbens (left)	Striatum	FIRST	0.002	0.416	6.8E−01
Mean intensity of Amygdala (left)	Amygdala	Freesurfer ASEG	0.002	0.414	6.8E−01
Volume of Sfrontsup (left)	Frontal	Freesurfer a2009s	0.002	0.413	6.8E−01
Volume of GCMLDGbody (right)	Hippocampus	Freesurfer subsegmentation	0.002	0.413	6.8E−01
Volume of MV(Re) (right)	Thalamus	Freesurfer subsegmentation	−0.002	−0.411	6.8E−01
Area of Gparietalsup (left)	Parietal	Freesurfer a2009s	0.002	0.411	6.8E−01
Volume of grey matter in Cingulate Gyrus, anterior division (left)	Limbic	FAST	−0.002	−0.410	6.8E−01
Area of GSparacentral (right)	Frontal	Freesurfer a2009s	0.002	0.409	6.8E−01
thickness of Frontal Pole (right)	Frontal	Freesurfer desikan white	−0.002	−0.406	6.8E−01
Volume of putamen (left)	Striatum	FIRST	0.002	0.404	6.9E−01
Area of Inferior Parietal Lobule (right)	Parietal	Freesurfer desikan white	−0.002	−0.403	6.9E−01
Mean axial diffusivity in medial lemniscus (left)	Brainstem fibres	dMRI diffusivity	0.002	0.401	6.9E−01
Volume of GCMLDGhead (right)	Hippocampus	Freesurfer subsegmentation	0.002	0.398	6.9E−01
thickness of Frontal Medial Cortex, caudal (left)	Frontal	Freesurfer a2009s	−0.002	−0.396	6.9E−01
Volume of GtempsupLateral (right)	Temporal	Freesurfer a2009s	0.002	0.394	6.9E−01
Volume of CA3body (right)	Hippocampus	Freesurfer subsegmentation	−0.002	−0.391	7.0E−01
Mean axial diffusivity in sagittal stratum (left)	Association fibres	dMRI diffusivity	0.002	0.391	7.0E−01
thickness of GparietinfAngular (right)	Parietal	Freesurfer a2009s	0.002	0.389	7.0E−01
Volume of Medulla (whole brain)	NA	Freesurfer subsegmentation	−0.002	−0.388	7.0E−01
Mean ISOVF in cerebral peduncle (left)	Brainstem fibres	dMRI ISOVF	−0.002	−0.385	7.0E−01
Area of Brodmann Area 3b (right)	Parietal	Freesurfer BA exvivo	−0.002	−0.383	7.0E−01

Volume of grey matter in Parahippocampal Gyrus, anterior division (left)	Temporal	FAST	−0.002	−0.383	7.0E−01
Grey-white contrast in Cingulate Gyrus, isthmus (right)	Limbic	Freesurfer desikan gw	−0.002	−0.383	7.0E−01
Area of Sprecentralsuppart (left)	Frontal	Freesurfer a2009s	0.002	0.378	7.1E−01
Volume of grey matter in Middle Temporal Gyrus, posterior division (left)	Temporal	FAST	−0.002	−0.377	7.1E−01
Area of GStransvfrontopol (left)	Frontal	Freesurfer a2009s	−0.002	−0.375	7.1E−01
Mean intensity of CerebellumWhiteMatter (left)	Cerebellum	Freesurfer ASEG	−0.002	−0.373	7.1E−01
Volume of Transverse temporal gyrus (right)	Temporal	Freesurfer DKT	−0.002	−0.371	7.1E−01
thickness of Supramarginal Gyrus (left)	Parietal	Freesurfer DKT	−0.002	−0.369	7.1E−01
thickness of Fusiform Gyrus (right)	Occipital	Freesurfer DKT	−0.002	−0.368	7.1E−01
Volume of GtempsupPlanpolar (right)	Temporal	Freesurfer a2009s	−0.002	−0.367	7.1E−01
Mean FA in uncinate fasciculus (left)	Association fibres	dMRI FA	−0.002	−0.366	7.1E−01
Area of GcingulPostventral (left)	Limbic	Freesurfer a2009s	−0.002	−0.366	7.1E−01
Volume of grey matter in I-IV Cerebellum (left)	Cerebellum	FAST	−0.002	−0.365	7.2E−01
thickness of Fusiform Gyrus (right)	Occipital	Freesurfer desikan white	−0.002	−0.364	7.2E−01
thickness of Entorhinal cortex (left)	Temporal	Freesurfer DKT	0.002	0.363	7.2E−01
Volume of GSfrontomargin (right)	Frontal	Freesurfer a2009s	0.002	0.362	7.2E−01
Volume of Superior Temporal Gyrus (right)	Temporal	Freesurfer desikan white	0.002	0.361	7.2E−01
Area of Gsubcallosal (right)	Frontal	Freesurfer a2009s	−0.002	−0.360	7.2E−01
Volume of CA4head (left)	Hippocampus	Freesurfer subsegmentation	0.002	0.360	7.2E−01
Volume of Pf (left)	Thalamus	Freesurfer subsegmentation	0.002	0.357	7.2E−01
Volume of MDl (left)	Thalamus	Freesurfer subsegmentation	0.002	0.357	7.2E−01
Mean OD in superior cerebellar peduncle (left)	Brainstem fibres	dMRI OD	−0.002	−0.353	7.2E−01
thickness of Brodmann Area V5 (right)	Occipital	Freesurfer BA exvivo	0.002	0.352	7.2E−01
Volume of grey matter in Supramarginal Gyrus, anterior division (left)	Parietal	FAST	−0.002	−0.350	7.3E−01
Area of Fusiform Gyrus (left)	Occipital	Freesurfer DKT	−0.002	−0.350	7.3E−01
Grey-white contrast in Pericalcarine cortex (left)	Occipital	Freesurfer desikan gw	0.002	0.348	7.3E−01
Volume of Middle Temporal Gyrus (right)	Temporal	Freesurfer DKT	−0.002	−0.346	7.3E−01

Volume of rostralAntcingulate (right)	Limbic	Freesurfer desikan white	0.002	0.345	7.3E−01
Area of Superior Temporal Gyrus (right)	Temporal	Freesurfer desikan pial	0.002	0.345	7.3E−01
Area of Cingulate Gyrus, posterior (left)	Limbic	Freesurfer desikan white	0.002	0.342	7.3E−01
Mean OD in fornix cres+stria terminalis (left)	Limbic system fibres	dMRI OD	0.002	0.339	7.3E−01
Area of Insular Cortex (right)	Insular	Freesurfer desikan white	−0.002	−0.338	7.4E−01
thickness of Pericalcarine cortex (left)	Occipital	Freesurfer DKT	−0.002	−0.337	7.4E−01
Volume of grey matter in Superior Temporal Gyrus, anterior division (left)	Temporal	FAST	0.002	0.337	7.4E−01
Volume of Postcentral Gyrus (right)	Parietal	Freesurfer DKT	0.002	0.337	7.4E−01
Volume of Stemporaltransverse (right)	Temporal	Freesurfer a2009s	0.002	0.335	7.4E−01
Volume of Sfrontmiddle (right)	Frontal	Freesurfer a2009s	−0.002	−0.335	7.4E−01
Volume of Soctemplat (right)	Temporal	Freesurfer a2009s	−0.002	−0.335	7.4E−01
Volume of Goccipitalsup (left)	Occipital	Freesurfer a2009s	−0.002	−0.334	7.4E−01
Mean ISOVF in pontine crossing tract on FA skeleton	Brainstem fibres	dMRI ISOVF	0.002	0.333	7.4E−01
Mean OD in superior cerebellar peduncle (right)	Brainstem fibres	dMRI OD	0.002	0.332	7.4E−01
Area of Banks superior temporal sulcus (left)	Temporal	Freesurfer desikan pial	0.002	0.331	7.4E−01
Mean OD in cingulum hippocampus (left)	Limbic system fibres	dMRI OD	−0.002	−0.329	7.4E−01
Mean radial diffusivity in cerebral peduncle (left)	Brainstem fibres	dMRI diffusivity	0.002	0.326	7.4E−01
Mean MD in inferior cerebellar peduncle (right)	Brainstem fibres	dMRI diffusivity	0.002	0.325	7.4E−01
Volume of grey matter in V Cerebellum (left)	Cerebellum	FAST	0.002	0.323	7.5E−01
thickness of Soccipitalant (right)	Occipital	Freesurfer a2009s	−0.002	−0.322	7.5E−01
thickness of Sfrontinf (left)	Frontal	Freesurfer a2009s	−0.002	−0.321	7.5E−01
Area of Sfrontsup (right)	Frontal	Freesurfer a2009s	−0.002	−0.316	7.5E−01
Area of Superior Parietal Lobule (left)	Parietal	Freesurfer desikan white	−0.002	−0.316	7.5E−01
Volume of Superior Temporal Gyrus (left)	Temporal	Freesurfer DKT	0.002	0.310	7.6E−01
Mean OD in corticospinal tract (left)	Brainstem fibres	dMRI OD	0.002	0.310	7.6E−01
Area of Gorbital (right)	Frontal	Freesurfer a2009s	0.002	0.307	7.6E−01

Volume of grey matter in X Cerebellum (left)	Cerebellum	FAST	0.002	0.307	7.6E−01
Grey-white contrast in Lateral Occipital Cortex (right)	Occipital	Freesurfer desikan gw	0.002	0.301	7.6E−01
Volume of CeM (right)	Thalamus	Freesurfer subsegmentation	0.002	0.298	7.7E−01
Mean intensity of CerebellumCortex (left)	Cerebellum	Freesurfer ASEG	−0.002	−0.296	7.7E−01
Area of Entorhinal cortex (left)	Temporal	Freesurfer DKT	−0.002	−0.295	7.7E−01
Area of GfrontinfOrbital (left)	Frontal	Freesurfer a2009s	−0.002	−0.295	7.7E−01
thickness of Gcuneus (left)	Occipital	Freesurfer a2009s	−0.002	−0.294	7.7E−01
thickness of Pericalcarine cortex (left)	Occipital	Freesurfer desikan white	−0.002	−0.293	7.7E−01
Volume of grey matter in Cingulate Gyrus, anterior division (right)	Limbic	FAST	0.002	0.292	7.7E−01
Volume of Accumbensarea (left)	Striatum	Freesurfer ASEG	0.001	0.292	7.7E−01
thickness of Superior Temporal Gyrus (right)	Temporal	Freesurfer DKT	0.002	0.290	7.7E−01
Volume of GSoccipitalinf (right)	Occipital	Freesurfer a2009s	0.002	0.290	7.7E−01
Grey-white contrast in Inferior Temporal Gyrus (left)	Temporal	Freesurfer desikan gw	−0.001	−0.290	7.7E−01
thickness of Transverse temporal gyrus (left)	Temporal	Freesurfer DKT	0.002	0.288	7.7E−01
Area of Superior Parietal Lobule (right)	Parietal	Freesurfer desikan pial	0.002	0.286	7.8E−01
thickness of Postcentral Gyrus (left)	Parietal	Freesurfer desikan white	0.002	0.284	7.8E−01
thickness of Postcentral Gyrus (left)	Parietal	Freesurfer DKT	0.002	0.283	7.8E−01
thickness of Inferior Temporal Gyrus (right)	Temporal	Freesurfer DKT	−0.002	−0.283	7.8E−01
Area of Superior Temporal Gyrus (right)	Temporal	Freesurfer DKT	−0.002	−0.283	7.8E−01
Area of Gtemporalmiddle (right)	Temporal	Freesurfer a2009s	0.002	0.281	7.8E−01
Area of Stemporaltransverse (left)	Temporal	Freesurfer a2009s	−0.002	−0.281	7.8E−01
thickness of Transverse temporal gyrus (left)	Temporal	Freesurfer desikan white	0.002	0.280	7.8E−01
Mean radial diffusivity in cingulum cingulate gyrus (left)	Limbic system fibres	dMRI diffusivity	0.001	0.280	7.8E−01
Grey-white contrast in Frontal Pole (right)	Frontal	Freesurfer desikan gw	0.001	0.278	7.8E−01
Mean ICVF in uncinate fasciculus (left)	Association fibres	dMRI ICVF	0.001	0.276	7.8E−01
Mean ICVF in corticospinal tract (left)	Brainstem fibres	dMRI ICVF	0.002	0.275	7.8E−01
Mean axial diffusivity in corticospinal tract (left)	Brainstem fibres	dMRI diffusivity	0.002	0.275	7.8E−01

Mean MD in inferior cerebellar peduncle (left)	Brainstem fibres	dMRI diffusivity	0.001	0.274	7.8E−01
Area of Lateral orbitofrontal cortex (left)	Frontal	Freesurfer desikan pial	0.001	0.273	7.8E−01
Volume of MDl (right)	Thalamus	Freesurfer subsegmentation	−0.001	−0.272	7.9E−01
Volume of fimbria (right)	Hippocampus	Freesurfer subsegmentation	0.001	0.272	7.9E−01
Mean MD in uncinate fasciculus (left)	Association fibres	dMRI diffusivity	−0.001	−0.270	7.9E−01
thickness of SorbitalHShaped (right)	Frontal	Freesurfer a2009s	−0.001	−0.270	7.9E−01
Volume of grey matter in VIIIb Cerebellum (left)	Cerebellum	FAST	−0.001	−0.270	7.9E−01
Area of Frontal Pole (left)	Frontal	Freesurfer desikan white	0.001	0.269	7.9E−01
thickness of Inferior Temporal Gyrus (left)	Temporal	Freesurfer DKT	0.001	0.269	7.9E−01
Volume of Middle Temporal Gyrus (right)	Temporal	Freesurfer desikan white	−0.001	−0.268	7.9E−01
Volume of SorbitalHShaped (right)	Frontal	Freesurfer a2009s	−0.001	−0.268	7.9E−01
thickness of Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer DKT	0.001	0.267	7.9E−01
thickness of Gtemporalinf (left)	Temporal	Freesurfer a2009s	0.001	0.266	7.9E−01
Volume of GcingulPostventral (left)	Limbic	Freesurfer a2009s	−0.001	−0.265	7.9E−01
Mean ICVF in middle cerebellar peduncle on FA skeleton	Brainstem fibres	dMRI ICVF	0.001	0.265	7.9E−01
Volume of GcingulPostdorsal (right)	Limbic	Freesurfer a2009s	−0.001	−0.264	7.9E−01
Mean ICVF in fornix cres+stria terminalis (right)	Limbic system fibres	dMRI ICVF	−0.001	−0.262	7.9E−01
Area of SintraparietPtrans (right)	Parietal	Freesurfer a2009s	−0.001	−0.262	7.9E−01
thickness of Ssubparietal (left)	Parietal	Freesurfer a2009s	−0.001	−0.259	8.0E−01
Volume of GparietinfSupramar (left)	Parietal	Freesurfer a2009s	−0.001	−0.258	8.0E−01
Volume of grey matter in Inferior Temporal Gyrus, anterior division (right)	Temporal	FAST	0.001	0.256	8.0E−01
Volume of Lingual Gyrus (right)	Occipital	Freesurfer desikan white	−0.001	−0.256	8.0E−01
Area of Middle Temporal Gyrus (right)	Temporal	Freesurfer desikan pial	0.001	0.256	8.0E−01
Volume of grey matter in Middle Temporal Gyrus, temporooccipital part (left)	Temporal	FAST	−0.001	−0.255	8.0E−01
Volume of CCPosterior (whole brain)	NA	Freesurfer ASEG	−0.001	−0.255	8.0E−01
Area of Sfrontmiddle (left)	Frontal	Freesurfer a2009s	−0.001	−0.255	8.0E−01

Volume of hippocampalfissure (left)	Hippocampus	Freesurfer subsegmentation	−0.001	−0.254	8.0E−01
Volume of Lateral Occipital Cortex (right)	Occipital	Freesurfer DKT	0.001	0.252	8.0E−01
Mean ICVF in cingulum cingulate gyrus (right)	Limbic system fibres	dMRI ICVF	−0.001	−0.252	8.0E−01
Volume of Lateral Occipital Cortex (left)	Occipital	Freesurfer DKT	−0.001	−0.250	8.0E−01
Volume of GoctempmedLingual (right)	Occipital	Freesurfer a2009s	−0.001	−0.249	8.0E−01
thickness of Inferior Temporal Gyrus (right)	Temporal	Freesurfer desikan white	−0.001	−0.248	8.0E−01
Volume of Sprecentralsuppart (right)	Frontal	Freesurfer a2009s	−0.001	−0.244	8.1E−01
Area of Goccipitalsup (right)	Occipital	Freesurfer a2009s	0.001	0.243	8.1E−01
Volume of VPL (left)	Thalamus	Freesurfer subsegmentation	0.001	0.242	8.1E−01
Volume of CCAnt (whole brain)	NA	Freesurfer ASEG	−0.001	−0.242	8.1E−01
thickness of Sprecentralsuppart (left)	Frontal	Freesurfer a2009s	−0.001	−0.241	8.1E−01
Volume of Sorbitallateral (right)	Frontal	Freesurfer a2009s	−0.001	−0.239	8.1E−01
thickness of GScingulAnt (right)	Limbic	Freesurfer a2009s	−0.001	−0.238	8.1E−01
Volume of grey matter in Frontal Orbital Cortex (left)	Frontal	FAST	−0.001	−0.238	8.1E−01
Mean ISOVF in retrolenticular part of internal capsule (left)	Internal capsule	dMRI ISOVF	0.001	0.238	8.1E−01
Volume of GInslgScentins (right)	Insular	Freesurfer a2009s	0.001	0.237	8.1E−01
thickness of Inferior Parietal Lobule (left)	Parietal	Freesurfer a2009s	0.001	0.237	8.1E−01
Area of Lateral orbitofrontal cortex (right)	Frontal	Freesurfer DKT	−0.001	−0.237	8.1E−01
Area of Stemporalsup (right)	Temporal	Freesurfer a2009s	−0.001	−0.235	8.1E−01
Volume of Lateral Occipital Cortex (left)	Occipital	Freesurfer desikan white	−0.001	−0.235	8.1E−01
thickness of Paracentral lobule (right)	Frontal	Freesurfer DKT	0.001	0.233	8.2E−01
Volume of GtempsupPlantempo (right)	Temporal	Freesurfer a2009s	0.001	0.231	8.2E−01
Volume of Pc (right)	Thalamus	Freesurfer subsegmentation	0.001	0.231	8.2E−01
Area of Scircularinsulaant (right)	Insular	Freesurfer a2009s	−0.001	−0.230	8.2E−01
Volume of Gpostcentral (right)	Parietal	Freesurfer a2009s	0.001	0.229	8.2E−01
thickness of Supramarginal Gyrus (right)	Parietal	Freesurfer desikan white	0.001	0.229	8.2E−01

Grey-white contrast in Insular Cortex (left)	Insular	Freesurfer desikan gw	−0.001	−0.228	8.2E−01
thickness of Gtemporalinf (right)	Temporal	Freesurfer a2009s	−0.001	−0.226	8.2E−01
Volume of molecularlayerHPbody (right)	Hippocampus	Freesurfer subsegmentation	0.001	0.224	8.2E−01
Volume of VentralDC (right)	Thalamus	Freesurfer ASEG	0.001	0.224	8.2E−01
Area of rostralAntcingulate (right)	Limbic	Freesurfer DKT	−0.001	−0.224	8.2E−01
Mean ICVF in cingulum cingulate gyrus (left)	Limbic system fibres	dMRI ICVF	−0.001	−0.221	8.3E−01
Area of Cingulate Gyrus, posterior (left)	Limbic	Freesurfer DKT	0.001	0.220	8.3E−01
Volume of Parahippocampal Gyrus (left)	Temporal	Freesurfer DKT	0.001	0.218	8.3E−01
Volume of Mednucleus (left)	Amygdala	Freesurfer subsegmentation	−0.001	−0.218	8.3E−01
Area of Soccipitalant (right)	Occipital	Freesurfer a2009s	−0.001	−0.215	8.3E−01
Area of Middle Temporal Gyrus (right)	Temporal	Freesurfer desikan white	0.001	0.215	8.3E−01
Mean intensity of choroidplexus (right)	NA	Freesurfer ASEG	−0.001	−0.214	8.3E−01
Area of Scollattransvpost (left)	Temporal	Freesurfer a2009s	0.001	0.213	8.3E−01
Volume of Perirhinal cortex (left)	Temporal	Freesurfer BA exvivo	0.001	0.213	8.3E−01
Mean ISOVF in superior longitudinal fasciculus (left)	Association fibres	dMRI ISOVF	0.001	0.213	8.3E−01
thickness of Superior Frontal Gyrus (right)	Frontal	Freesurfer DKT	0.001	0.212	8.3E−01
Mean axial diffusivity in cingulum hippocampus (right)	Limbic system fibres	dMRI diffusivity	−0.001	−0.208	8.4E−01
Volume of GSfrontomargin (left)	Frontal	Freesurfer a2009s	−0.001	−0.206	8.4E−01
Area of Superior Frontal Gyrus (left)	Frontal	Freesurfer DKT	−0.001	−0.206	8.4E−01
Mean intensity of 4thVentricle (whole brain)	NA	Freesurfer ASEG	−0.001	−0.205	8.4E−01
Volume of Sprecentralsuppart (left)	Frontal	Freesurfer a2009s	0.001	0.205	8.4E−01
Volume of GtempsupPlanpolar (left)	Temporal	Freesurfer a2009s	−0.001	−0.204	8.4E−01
Mean ICVF in inferior cerebellar peduncle (right)	Brainstem fibres	dMRI ICVF	0.001	0.204	8.4E−01
Volume of Lingual Gyrus (right)	Occipital	Freesurfer DKT	−0.001	−0.203	8.4E−01
Mean FA in cingulum hippocampus (right)	Limbic system fibres	dMRI FA	0.001	0.202	8.4E−01
thickness of Paracentral lobule (right)	Frontal	Freesurfer desikan white	0.001	0.199	8.4E−01

Area of Inferior Frontal Gyrus, pars orbitalis (left)	Frontal	Freesurfer DKT	0.001	0.199	8.4E−01
Area of LatFispost (right)	NA	Freesurfer a2009s	−0.001	−0.198	8.4E−01
thickness of Supramarginal Gyrus (left)	Parietal	Freesurfer desikan white	−0.001	−0.195	8.5E−01
thickness of GScingulMidAnt (right)	Limbic	Freesurfer a2009s	−0.001	−0.193	8.5E−01
Grey-white contrast in caudalAntcingulate (right)	Limbic	Freesurfer desikan gw	−0.001	−0.193	8.5E−01
Mean intensity of CSF (whole brain)	NA	Freesurfer ASEG	−0.001	−0.193	8.5E−01
Volume of grey matter in Superior Frontal Gyrus (left)	Frontal	FAST	−0.001	−0.188	8.5E−01
Mean radial diffusivity in cingulum cingulate gyrus (right)	Limbic system fibres	dMRI diffusivity	0.001	0.185	8.5E−01
thickness of Gpostcentral (left)	Parietal	Freesurfer a2009s	0.001	0.184	8.5E−01
Volume of AntamygdaloidareA (right)	Amygdala	Freesurfer subsegmentation	0.001	0.181	8.6E−01
Volume of Brodmann Area 3b (right)	Parietal	Freesurfer BA exvivo	0.001	0.181	8.6E−01
Volume of Parahippocampal Gyrus (left)	Temporal	Freesurfer desikan white	−0.001	−0.180	8.6E−01
thickness of Poletemporal (right)	Temporal	Freesurfer a2009s	0.001	0.180	8.6E−01
Mean ISOVF in posterior thalamic radiation (right)	Thalamic radiations	dMRI ISOVF	−0.001	−0.179	8.6E−01
Grey-white contrast in Lingual Gyrus (left)	Occipital	Freesurfer desikan gw	−0.001	−0.178	8.6E−01
Area of Sprecentralsuppart (right)	Frontal	Freesurfer a2009s	−0.001	−0.178	8.6E−01
Volume of Transverse temporal gyrus (right)	Temporal	Freesurfer desikan white	−0.001	−0.178	8.6E−01
Area of PreCuneal Cortex (right)	Occipital	Freesurfer desikan white	0.001	0.176	8.6E−01
Volume of Wholethalamus (left)	Thalamus	Freesurfer subsegmentation	−0.001	−0.176	8.6E−01
Area of Cingulate Gyrus, posterior (left)	Limbic	Freesurfer desikan pial	0.001	0.176	8.6E−01
Area of Spostcentral (left)	Parietal	Freesurfer a2009s	−0.001	−0.173	8.6E−01
thickness of Brodmann Area 1 (right)	Parietal	Freesurfer BA exvivo	0.001	0.173	8.6E−01
thickness of Gfrontmiddle (right)	Frontal	Freesurfer a2009s	−0.001	−0.169	8.7E−01
Mean FA in posterior limb of internal capsule (left)	Internal capsule	dMRI FA	−0.001	−0.169	8.7E−01
thickness of Entorhinal cortex (left)	Temporal	Freesurfer a2009s	0.001	0.169	8.7E−01
Mean ICVF in corticospinal tract (right)	Brainstem fibres	dMRI ICVF	0.001	0.166	8.7E−01

Volume of grey matter in VIIb Cerebellum (left)	Cerebellum	FAST	−0.001	−0.165	8.7E−01
Mean OD in middle cerebellar peduncle on FA skeleton	Brainstem fibres	dMRI OD	0.001	0.165	8.7E−01
Area of Spostcentral (right)	Parietal	Freesurfer a2009s	−0.001	−0.161	8.7E−01
Volume of grey matter in Temporal Fusiform Cortex, posterior division (right)	Temporal	FAST	−0.001	−0.161	8.7E−01
Volume of Postcentral Gyrus (right)	Parietal	Freesurfer desikan white	0.001	0.161	8.7E−01
Mean OD in fornix cres+stria terminalis (right)	Limbic system fibres	dMRI OD	0.001	0.160	8.7E−01
thickness of Global thickness (right)	NA	Freesurfer desikan white	0.001	0.159	8.7E−01
Area of GtempsupGTtransv (left)	Temporal	Freesurfer a2009s	0.001	0.158	8.7E−01
Area of PreCuneal Cortex (right)	Occipital	Freesurfer DKT	0.001	0.152	8.8E−01
Volume of grey matter in Temporal Fusiform Cortex, posterior division (left)	Temporal	FAST	0.001	0.149	8.8E−01
Area of Gpostcentral (right)	Parietal	Freesurfer a2009s	−0.001	−0.148	8.8E−01
Volume of GparietinfSupramar (right)	Parietal	Freesurfer a2009s	0.001	0.148	8.8E−01
thickness of caudalAntcingulate (right)	Limbic	Freesurfer DKT	−0.001	−0.147	8.8E−01
thickness of Brodmann Area 1 (left)	Parietal	Freesurfer BA exvivo	0.001	0.147	8.8E−01
Area of Brodmann Area 4a (right)	Frontal	Freesurfer BA exvivo	0.001	0.146	8.8E−01
Mean OD in body of corpus callosum on FA skeleton	Commissural fibres	dMRI OD	−0.001	−0.146	8.8E−01
Mean MD in cingulum hippocampus (right)	Limbic system fibres	dMRI diffusivity	−0.001	−0.145	8.8E−01
thickness of caudalAntcingulate (right)	Limbic	Freesurfer desikan white	−0.001	−0.145	8.8E−01
thickness of Supramarginal Gyrus (right)	Parietal	Freesurfer DKT	0.001	0.142	8.9E−01
thickness of GSparacentral (right)	Frontal	Freesurfer a2009s	−0.001	−0.141	8.9E−01
Mean intensity of VentralDC (right)	Thalamus	Freesurfer ASEG	0.001	0.140	8.9E−01
Volume of grey matter in Inferior Frontal Gyrus, pars triangularis (right)	Frontal	FAST	0.001	0.139	8.9E−01
Area of Lateral orbitofrontal cortex (left)	Frontal	Freesurfer desikan white	0.001	0.139	8.9E−01
Area of Gsubcallosal (left)	Frontal	Freesurfer a2009s	−0.001	−0.138	8.9E−01
Volume of Poleoccipital (right)	Occipital	Freesurfer a2009s	−0.001	−0.138	8.9E−01
thickness of Ssuborbital (right)	Frontal	Freesurfer a2009s	0.001	0.137	8.9E−01

Volume of Frontal Pole (right)	Frontal	Freesurfer desikan white	−0.001	−0.137	8.9E−01
Area of Gprecentral (right)	Frontal	Freesurfer a2009s	−0.001	−0.135	8.9E−01
Volume of grey matter in Parietal Operculum Cortex (left)	Insular	FAST	−0.001	−0.131	9.0E−01
Volume of Ssuborbital (left)	Frontal	Freesurfer a2009s	0.001	0.131	9.0E−01
thickness of Scalcarine (left)	Occipital	Freesurfer a2009s	−0.001	−0.130	9.0E−01
Mean radial diffusivity in uncinate fasciculus (left)	Association fibres	dMRI diffusivity	0.001	0.129	9.0E−01
Volume of grey matter in VIIIb Cerebellum (right)	Cerebellum	FAST	−0.001	−0.129	9.0E−01
Volume of Entorhinal cortex (left)	Temporal	Freesurfer BA exvivo	0.001	0.129	9.0E−01
Area of Middle Temporal Gyrus (right)	Temporal	Freesurfer DKT	0.001	0.128	9.0E−01
Volume of InfLatVent (right)	NA	Freesurfer ASEG	0.001	0.127	9.0E−01
Grey-white contrast in Frontal Pole (left)	Frontal	Freesurfer desikan gw	−0.001	−0.127	9.0E−01
Area of Poletemporal (right)	Temporal	Freesurfer a2009s	0.001	0.127	9.0E−01
Volume of grey matter in VIIIa Cerebellum (left)	Cerebellum	FAST	−0.001	−0.127	9.0E−01
Area of GSoccipitalinf (right)	Occipital	Freesurfer a2009s	−0.001	−0.126	9.0E−01
Volume of GcingulPostventral (right)	Limbic	Freesurfer a2009s	−0.001	−0.126	9.0E−01
Mean FA in external capsule (right)	Association fibres	dMRI FA	−0.001	−0.124	9.0E−01
Area of GparietinfSupramar (right)	Parietal	Freesurfer a2009s	0.001	0.122	9.0E−01
Volume of Spostcentral (right)	Parietal	Freesurfer a2009s	0.001	0.121	9.0E−01
Mean intensity of CerebellumCortex (right)	Cerebellum	Freesurfer ASEG	−0.001	−0.120	9.0E−01
Volume of Scircularinsulainf (left)	Insular	Freesurfer a2009s	0.001	0.116	9.1E−01
thickness of GparietinfSupramar (left)	Parietal	Freesurfer a2009s	0.001	0.112	9.1E−01
Volume of GtempsupGTtransv (right)	Temporal	Freesurfer a2009s	0.001	0.108	9.1E−01
Volume of GSparacentral (right)	Frontal	Freesurfer a2009s	0.001	0.106	9.2E−01
Mean axial diffusivity in middle cerebellar peduncle on FA skeleton	Brainstem fibres	dMRI diffusivity	0.001	0.105	9.2E−01
Volume of grey matter in Vermis Crus I Cerebellum	Cerebellum	FAST	−0.001	−0.105	9.2E−01
Volume of AV (left)	Thalamus	Freesurfer subsegmentation	−0.001	−0.104	9.2E−01
Mean OD in sagittal stratum (right)	Association fibres	dMRI OD	0.001	0.103	9.2E−01
Mean radial diffusivity in cingulum hippocampus (right)	Limbic system fibres	dMRI diffusivity	−0.001	−0.100	9.2E−01

Volume of CA4body (right)	Hippocampus	Freesurfer subsegmentation	0.001	0.098	9.2E−01
thickness of LatFisantHorizont (right)	NA	Freesurfer a2009s	−0.001	−0.097	9.2E−01
thickness of Inferior Parietal Lobule (left)	Parietal	Freesurfer DKT	0.001	0.097	9.2E−01
Volume of Scollattransvpost (left)	Temporal	Freesurfer a2009s	−0.001	−0.097	9.2E−01
Volume of grey matter in Vermis VI Cerebellum	Cerebellum	FAST	0.000	0.094	9.2E−01
Volume of CerebellumWhiteMatter (left)	Cerebellum	Freesurfer ASEG	0.000	−0.088	9.3E−01
thickness of Banks superior temporal sulcus (right)	Temporal	Freesurfer desikan white	0.000	−0.086	9.3E−01
thickness of Inferior Parietal Lobule (right)	Parietal	Freesurfer DKT	0.000	−0.083	9.3E−01
Volume of Gtemporalmiddle (right)	Temporal	Freesurfer a2009s	0.000	−0.081	9.4E−01
Area of GStransvfrontopol (right)	Frontal	Freesurfer a2009s	0.000	0.077	9.4E−01
Grey-white contrast in Temporal pole (left)	Temporal	Freesurfer desikan gw	0.000	−0.069	9.4E−01
thickness of Brodmann Area 3a (right)	Parietal	Freesurfer BA exvivo	0.000	0.064	9.5E−01
Area of GparietinfSupramar (left)	Parietal	Freesurfer a2009s	0.000	−0.063	9.5E−01
Volume of Superior Parietal Lobule (left)	Parietal	Freesurfer desikan white	0.000	0.063	9.5E−01
Volume of grey matter in Lateral Occipital Cortex, inferior division (left)	Occipital	FAST	0.000	0.059	9.5E−01
Volume of GCMLDGbody (left)	Hippocampus	Freesurfer subsegmentation	0.000	−0.057	9.5E−01
Volume of Sfrontsup (right)	Frontal	Freesurfer a2009s	0.000	−0.057	9.5E−01
Volume of Lateral Occipital Cortex (right)	Occipital	Freesurfer desikan white	0.000	0.057	9.5E−01
Volume of grey matter in Crus II Cerebellum (right)	Cerebellum	FAST	0.000	−0.056	9.6E−01
thickness of GtempsupPlantempo (left)	Temporal	Freesurfer a2009s	0.000	−0.055	9.6E−01
Area of Superior Temporal Gyrus (right)	Temporal	Freesurfer desikan white	0.000	−0.053	9.6E−01
thickness of GInslgScentins (right)	Insular	Freesurfer a2009s	0.000	−0.051	9.6E−01
Grey-white contrast in Medorbitofrontal (right)	Frontal	Freesurfer desikan gw	0.000	0.043	9.7E−01
Area of Scollattransvant (right)	Temporal	Freesurfer a2009s	0.000	−0.042	9.7E−01
Volume of CerebellumCortex (left)	Cerebellum	Freesurfer ASEG	0.000	0.041	9.7E−01
Volume of grey matter in Parahippocampal Gyrus, posterior division (left)	Temporal	FAST	0.000	−0.040	9.7E−01

thickness of Brodmann Area V1 (right)	Occipital	Freesurfer BA exvivo	0.000	−0.040	9.7E−01
Area of LatFisantVertical (right)	NA	Freesurfer a2009s	0.000	−0.039	9.7E−01
Volume of PuI (right)	Thalamus	Freesurfer subsegmentation	0.000	0.039	9.7E−01
Volume of LatFisantHorizont (right)	NA	Freesurfer a2009s	0.000	−0.038	9.7E−01
thickness of Gtemporalmiddle (right)	Temporal	Freesurfer a2009s	0.000	−0.037	9.7E−01
Grey-white contrast in Inferior Temporal Gyrus (right)	Temporal	Freesurfer desikan gw	0.000	0.037	9.7E−01
Volume of grey matter in Inferior Temporal Gyrus, temporooccipital part (right)	Temporal	FAST	0.000	0.037	9.7E−01
Volume of ThalamusProper (right)	Thalamus	Freesurfer ASEG	0.000	0.037	9.7E−01
Grey-white contrast in Banks superior temporal sulcus (right)	Temporal	Freesurfer desikan gw	0.000	0.036	9.7E−01
Volume of grey matter in Supracalcarine Cortex (left)	Occipital	FAST	0.000	−0.034	9.7E−01
thickness of GparietinfAngular (left)	Parietal	Freesurfer a2009s	0.000	−0.032	9.7E−01
Volume of GfrontinfOrbital (left)	Frontal	Freesurfer a2009s	0.000	0.029	9.8E−01
Volume of grey matter in Crus II Cerebellum (left)	Cerebellum	FAST	0.000	−0.021	9.8E−01
Area of Brodmann Area 2 (right)	Parietal	Freesurfer BA exvivo	0.000	0.019	9.9E−01
Area of GtempsupPlantempo (right)	Temporal	Freesurfer a2009s	0.000	−0.015	9.9E−01
Volume of hippocampus (left)	Hippocampus	FIRST	0.000	−0.012	9.9E−01
thickness of Inferior Parietal Lobule (right)	Parietal	Freesurfer desikan white	0.000	0.011	9.9E−01
Volume of grey matter in Occipital Fusiform Gyrus (right)	Occipital	FAST	0.000	−0.011	9.9E−01
Mean intensity of ThalamusProper (left)	Thalamus	Freesurfer ASEG	0.000	−0.009	9.9E−01
Volume of grey matter in Frontal Orbital Cortex (right)	Frontal	FAST	0.000	−0.008	9.9E−01
thickness of SintermprimJensen (left)	Parietal	Freesurfer a2009s	0.000	−0.007	9.9E−01
Mean intensity of VentralDC (left)	Thalamus	Freesurfer ASEG	0.000	−0.007	9.9E−01
Area of Sfrontmiddle (right)	Frontal	Freesurfer a2009s	0.000	−0.006	1.0E+00
Area of Superior Parietal Lobule (left)	Parietal	Freesurfer DKT	0.000	0.006	1.0E+00
Area of Frontal Pole (right)	Frontal	Freesurfer desikan pial	0.000	−0.005	1.0E+00
thickness of Brodmann Area V2 (left)	Occipital	Freesurfer BA exvivo	0.000	0.003	1.0E+00
thickness of Inferior Frontal Gyrus, pars orbitalis (right)	Frontal	Freesurfer desikan white	0.000	−0.001	1.0E+00

Linear regression models estimated the association between neuroticism z-scores and each IDP, adjusting for sex, age and polynomial age terms, age×sex, ethnicity, Townsend deprivation index, education, smoking status, alcohol consumption, and body mass index.

Appendix 6.2: Mediation analyses

Model/atlas	Description	Mediator	Parameter	Estimate	p
FAST	Volume of grey matter in Left Caudate	anxiety and stress related disorders	ACME	0.004	<0.001
FAST	Volume of grey matter in Left Caudate	anxiety and stress related disorders	ADE	0.021	<0.001
FAST	Volume of grey matter in Left Caudate	anxiety and stress related disorders	Total Effect	0.025	<0.001
FAST	Volume of grey matter in Left Caudate	anxiety and stress related disorders	Prop. Mediated	0.153	<0.001
FAST	Volume of grey matter in Right Caudate	anxiety and stress related disorders	ACME	0.005	<0.001
FAST	Volume of grey matter in Right Caudate	anxiety and stress related disorders	ADE	0.019	<0.001
FAST	Volume of grey matter in Right Caudate	anxiety and stress related disorders	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Caudate	anxiety and stress related disorders	Prop. Mediated	0.192	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	anxiety and stress related disorders	ACME	−0.001	0.274
FAST	Volume of grey matter in Left Frontal Medial Cortex	anxiety and stress related disorders	ADE	−0.026	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	anxiety and stress related disorders	Total Effect	−0.027	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	anxiety and stress related disorders	Prop. Mediated	0.046	0.274
FAST	Volume of grey matter in Left Putamen	anxiety and stress related disorders	ACME	0.003	<0.001
FAST	Volume of grey matter in Left Putamen	anxiety and stress related disorders	ADE	0.021	<0.001
FAST	Volume of grey matter in Left Putamen	anxiety and stress related disorders	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Left Putamen	anxiety and stress related disorders	Prop. Mediated	0.135	<0.001
FAST	Volume of grey matter in Right Putamen	anxiety and stress related disorders	ACME	0.003	0.01
FAST	Volume of grey matter in Right Putamen	anxiety and stress related disorders	ADE	0.021	<0.001
FAST	Volume of grey matter in Right Putamen	anxiety and stress related disorders	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Putamen	anxiety and stress related disorders	Prop. Mediated	0.121	0.01
FAST	Volume of grey matter in Left Subcallosal Cortex	anxiety and stress related disorders	ACME	−0.001	0.186
FAST	Volume of grey matter in Left Subcallosal Cortex	anxiety and stress related disorders	ADE	−0.022	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	anxiety and stress related disorders	Total Effect	−0.024	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	anxiety and stress related disorders	Prop. Mediated	0.061	0.186
FAST	Volume of grey matter in Left Ventral Striatum	anxiety and stress related disorders	ACME	0.002	0.068
FAST	Volume of grey matter in Left Ventral Striatum	anxiety and stress related disorders	ADE	0.019	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	anxiety and stress related disorders	Total Effect	0.021	<0.001

FAST	Volume of grey matter in Left Ventral Striatum	anxiety and stress related disorders	Prop. Mediated	0.089	0.068
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	anxiety and stress related disorders	ACME	0.003	0.002
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	anxiety and stress related disorders	ADE	0.020	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	anxiety and stress related disorders	Total Effect	0.022	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	anxiety and stress related disorders	Prop. Mediated	0.127	0.002
dMRI	Mean axial diffusivity in external capsule (right)	anxiety and stress related disorders	ACME	0.005	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	anxiety and stress related disorders	ADE	0.017	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	anxiety and stress related disorders	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	anxiety and stress related disorders	Prop. Mediated	0.240	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	anxiety and stress related disorders	ACME	0.001	0.194
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	anxiety and stress related disorders	ADE	0.022	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	anxiety and stress related disorders	Total Effect	0.023	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	anxiety and stress related disorders	Prop. Mediated	0.059	0.194
dMRI	Mean MD in fornix cres+stria terminalis (right)	anxiety and stress related disorders	ACME	0.002	0.016
dMRI	Mean MD in fornix cres+stria terminalis (right)	anxiety and stress related disorders	ADE	0.020	0.002
dMRI	Mean MD in fornix cres+stria terminalis (right)	anxiety and stress related disorders	Total Effect	0.023	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	anxiety and stress related disorders	Prop. Mediated	0.108	0.016
dMRI	Mean axial diffusivity in posterior corona radiata (left)	anxiety and stress related disorders	ACME	0.004	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	anxiety and stress related disorders	ADE	0.023	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	anxiety and stress related disorders	Total Effect	0.026	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	anxiety and stress related disorders	Prop. Mediated	0.146	<0.001
dMRI	Mean MD in posterior corona radiata (left)	anxiety and stress related disorders	ACME	0.004	<0.001
dMRI	Mean MD in posterior corona radiata (left)	anxiety and stress related disorders	ADE	0.019	<0.001
dMRI	Mean MD in posterior corona radiata (left)	anxiety and stress related disorders	Total Effect	0.023	<0.001
dMRI	Mean MD in posterior corona radiata (left)	anxiety and stress related disorders	Prop. Mediated	0.187	<0.001
dMRI	Mean OD in posterior corona radiata (left)	anxiety and stress related disorders	ACME	−0.002	0.086
dMRI	Mean OD in posterior corona radiata (left)	anxiety and stress related disorders	ADE	−0.022	<0.001

dMRI	Mean OD in posterior corona radiata (left)	anxiety and stress related disorders	Total Effect	−0.024	<0.001
dMRI	Mean OD in posterior corona radiata (left)	anxiety and stress related disorders	Prop. Mediated	0.078	0.086
dMRI	Mean axial diffusivity in posterior corona radiata (right)	anxiety and stress related disorders	ACME	0.004	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	anxiety and stress related disorders	ADE	0.019	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	anxiety and stress related disorders	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	anxiety and stress related disorders	Prop. Mediated	0.177	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	anxiety and stress related disorders	ACME	−0.003	0.004
dMRI	Mean FA in posterior thalamic radiation (left)	anxiety and stress related disorders	ADE	−0.023	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	anxiety and stress related disorders	Total Effect	−0.026	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	anxiety and stress related disorders	Prop. Mediated	0.118	0.004
dMRI	Mean ICVF in posterior thalamic radiation (left)	anxiety and stress related disorders	ACME	−0.003	0.022
dMRI	Mean ICVF in posterior thalamic radiation (left)	anxiety and stress related disorders	ADE	−0.021	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	anxiety and stress related disorders	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	anxiety and stress related disorders	Prop. Mediated	0.109	0.022
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	anxiety and stress related disorders	ACME	0.003	0.002
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	anxiety and stress related disorders	ADE	0.022	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	anxiety and stress related disorders	Total Effect	0.025	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	anxiety and stress related disorders	Prop. Mediated	0.123	0.002
dMRI	Mean FA in posterior thalamic radiation (right)	anxiety and stress related disorders	ACME	−0.003	0.01
dMRI	Mean FA in posterior thalamic radiation (right)	anxiety and stress related disorders	ADE	−0.026	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	anxiety and stress related disorders	Total Effect	−0.028	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	anxiety and stress related disorders	Prop. Mediated	0.093	0.01
dMRI	Mean ICVF in posterior thalamic radiation (right)	anxiety and stress related disorders	ACME	−0.003	0.006
dMRI	Mean ICVF in posterior thalamic radiation (right)	anxiety and stress related disorders	ADE	−0.023	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	anxiety and stress related disorders	Total Effect	−0.026	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	anxiety and stress related disorders	Prop. Mediated	0.130	0.006
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	anxiety and stress related disorders	ACME	0.003	0.002
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	anxiety and stress related disorders	ADE	0.025	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	anxiety and stress related disorders	Total Effect	0.028	<0.001

dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	anxiety and stress related disorders	Prop. Mediated	0.118	0.002
dMRI	Mean MD in posterior thalamic radiation (right)	anxiety and stress related disorders	ACME	0.003	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	anxiety and stress related disorders	ADE	0.021	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	anxiety and stress related disorders	Total Effect	0.024	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	anxiety and stress related disorders	Prop. Mediated	0.132	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	anxiety and stress related disorders	ACME	0.004	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	anxiety and stress related disorders	ADE	0.019	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	anxiety and stress related disorders	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	anxiety and stress related disorders	Prop. Mediated	0.160	<0.001
dMRI	Mean MD in superior corona radiata (right)	anxiety and stress related disorders	ACME	0.005	<0.001
dMRI	Mean MD in superior corona radiata (right)	anxiety and stress related disorders	ADE	0.017	0.002
dMRI	Mean MD in superior corona radiata (right)	anxiety and stress related disorders	Total Effect	0.021	<0.001
dMRI	Mean MD in superior corona radiata (right)	anxiety and stress related disorders	Prop. Mediated	0.221	<0.001
dMRI	Mean ICVF in tapetum (right)	anxiety and stress related disorders	ACME	−0.002	0.018
dMRI	Mean ICVF in tapetum (right)	anxiety and stress related disorders	ADE	−0.021	<0.001
dMRI	Mean ICVF in tapetum (right)	anxiety and stress related disorders	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in tapetum (right)	anxiety and stress related disorders	Prop. Mediated	0.103	0.018
dMRI	Mean axial diffusivity in tapetum (right)	anxiety and stress related disorders	ACME	0.001	0.364
dMRI	Mean axial diffusivity in tapetum (right)	anxiety and stress related disorders	ADE	0.021	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	anxiety and stress related disorders	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	anxiety and stress related disorders	Prop. Mediated	0.042	0.364
dMRI	Mean MD in tapetum (right)	anxiety and stress related disorders	ACME	0.002	0.074
dMRI	Mean MD in tapetum (right)	anxiety and stress related disorders	ADE	0.021	<0.001
dMRI	Mean MD in tapetum (right)	anxiety and stress related disorders	Total Effect	0.023	<0.001
dMRI	Mean MD in tapetum (right)	anxiety and stress related disorders	Prop. Mediated	0.083	0.074
Freesurfer a2009s	Area of Calcarine sulcus (left)	anxiety and stress related disorders	ACME	−0.002	0.08
Freesurfer a2009s	Area of Calcarine sulcus (left)	anxiety and stress related disorders	ADE	−0.022	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	anxiety and stress related disorders	Total Effect	−0.024	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	anxiety and stress related disorders	Prop. Mediated	0.082	0.08

Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	anxiety and stress related disorders	ACME	−0.002	0.032
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	anxiety and stress related disorders	ADE	−0.021	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	anxiety and stress related disorders	Total Effect	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	anxiety and stress related disorders	Prop. Mediated	0.097	0.032
Freesurfer ASEG	Volume of WM-hypointensities	anxiety and stress related disorders	ACME	0.003	0.006
Freesurfer ASEG	Volume of WM-hypointensities	anxiety and stress related disorders	ADE	0.020	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	anxiety and stress related disorders	Total Effect	0.023	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	anxiety and stress related disorders	Prop. Mediated	0.133	0.006
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ACME	−0.001	0.598
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ADE	0.028	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Total Effect	0.028	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Prop. Mediated	−0.021	0.598
Freesurfer DKT	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	ACME	−0.002	0.09
Freesurfer DKT	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	ADE	−0.021	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	Total Effect	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	Prop. Mediated	0.087	0.09
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ACME	−0.001	0.536
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ADE	−0.024	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Total Effect	−0.025	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Prop. Mediated	0.029	0.536
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	anxiety and stress related disorders	ACME	−0.002	0.184
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	anxiety and stress related disorders	ADE	−0.022	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	anxiety and stress related disorders	Total Effect	−0.024	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	anxiety and stress related disorders	Prop. Mediated	0.063	0.184
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	anxiety and stress related disorders	ACME	0.000	0.722
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	anxiety and stress related disorders	ADE	−0.022	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	anxiety and stress related disorders	Total Effect	−0.023	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	anxiety and stress related disorders	Prop. Mediated	0.016	0.722
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ACME	0.000	0.916

Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ADE	0.024	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Total Effect	0.024	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Prop. Mediated	0.004	0.916
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	ACME	−0.002	0.126
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	ADE	−0.022	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	Total Effect	−0.024	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	Prop. Mediated	0.074	0.126
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ACME	−0.001	0.52
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ADE	0.025	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Total Effect	0.024	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Prop. Mediated	−0.025	0.52
Freesurfer desikan white	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	ACME	−0.002	0.09
Freesurfer desikan white	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	ADE	−0.022	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	Total Effect	−0.023	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	anxiety and stress related disorders	Prop. Mediated	0.083	0.09
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ACME	−0.001	0.496
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	ADE	−0.024	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Total Effect	−0.025	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	anxiety and stress related disorders	Prop. Mediated	0.032	0.496
FAST	Volume of grey matter in Left Caudate	depression	ACME	0.004	0.006
FAST	Volume of grey matter in Left Caudate	depression	ADE	0.020	<0.001
FAST	Volume of grey matter in Left Caudate	depression	Total Effect	0.025	<0.001
FAST	Volume of grey matter in Left Caudate	depression	Prop. Mediated	0.177	0.006
FAST	Volume of grey matter in Right Caudate	depression	ACME	0.004	0.004
FAST	Volume of grey matter in Right Caudate	depression	ADE	0.020	<0.001
FAST	Volume of grey matter in Right Caudate	depression	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Caudate	depression	Prop. Mediated	0.175	0.004
FAST	Volume of grey matter in Left Frontal Medial Cortex	depression	ACME	−0.003	0.012
FAST	Volume of grey matter in Left Frontal Medial Cortex	depression	ADE	−0.024	<0.001

FAST	Volume of grey matter in Left Frontal Medial Cortex	depression	Total Effect	−0.027	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	depression	Prop. Mediated	0.116	0.012
FAST	Volume of grey matter in Left Putamen	depression	ACME	0.003	0.05
FAST	Volume of grey matter in Left Putamen	depression	ADE	0.022	<0.001
FAST	Volume of grey matter in Left Putamen	depression	Total Effect	0.025	<0.001
FAST	Volume of grey matter in Left Putamen	depression	Prop. Mediated	0.113	0.05
FAST	Volume of grey matter in Right Putamen	depression	ACME	0.002	0.12
FAST	Volume of grey matter in Right Putamen	depression	ADE	0.022	<0.001
FAST	Volume of grey matter in Right Putamen	depression	Total Effect	0.025	<0.001
FAST	Volume of grey matter in Right Putamen	depression	Prop. Mediated	0.091	0.12
FAST	Volume of grey matter in Left Subcallosal Cortex	depression	ACME	−0.002	0.168
FAST	Volume of grey matter in Left Subcallosal Cortex	depression	ADE	−0.022	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	depression	Total Effect	−0.024	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	depression	Prop. Mediated	0.079	0.168
FAST	Volume of grey matter in Left Ventral Striatum	depression	ACME	−0.001	0.322
FAST	Volume of grey matter in Left Ventral Striatum	depression	ADE	0.023	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	depression	Total Effect	0.021	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	depression	Prop. Mediated	−0.068	0.322
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	depression	ACME	0.004	0.006
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	depression	ADE	0.019	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	depression	Total Effect	0.022	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	depression	Prop. Mediated	0.161	0.006
dMRI	Mean axial diffusivity in external capsule (right)	depression	ACME	0.006	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	depression	ADE	0.016	0.002
dMRI	Mean axial diffusivity in external capsule (right)	depression	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	depression	Prop. Mediated	0.285	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	depression	ACME	0.004	0.016

dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	depression	ADE	0.020	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	depression	Total Effect	0.023	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	depression	Prop. Mediated	0.150	0.016
dMRI	Mean MD in fornix cres+stria terminalis (right)	depression	ACME	0.007	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	depression	ADE	0.016	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	depression	Total Effect	0.023	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	depression	Prop. Mediated	0.294	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	depression	ACME	0.006	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	depression	ADE	0.021	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	depression	Total Effect	0.027	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	depression	Prop. Mediated	0.227	<0.001
dMRI	Mean MD in posterior corona radiata (left)	depression	ACME	0.007	<0.001
dMRI	Mean MD in posterior corona radiata (left)	depression	ADE	0.015	0.002
dMRI	Mean MD in posterior corona radiata (left)	depression	Total Effect	0.022	<0.001
dMRI	Mean MD in posterior corona radiata (left)	depression	Prop. Mediated	0.318	<0.001
dMRI	Mean OD in posterior corona radiata (left)	depression	ACME	−0.002	0.192
dMRI	Mean OD in posterior corona radiata (left)	depression	ADE	−0.022	<0.001
dMRI	Mean OD in posterior corona radiata (left)	depression	Total Effect	−0.024	<0.001
dMRI	Mean OD in posterior corona radiata (left)	depression	Prop. Mediated	0.077	0.192
dMRI	Mean axial diffusivity in posterior corona radiata (right)	depression	ACME	0.006	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	depression	ADE	0.017	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	depression	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	depression	Prop. Mediated	0.278	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	depression	ACME	−0.007	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	depression	ADE	−0.019	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	depression	Total Effect	−0.026	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	depression	Prop. Mediated	0.256	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	depression	ACME	−0.005	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	depression	ADE	−0.019	<0.001

dMRI	Mean ICVF in posterior thalamic radiation (left)	depression	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	depression	Prop. Mediated	0.205	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	depression	ACME	0.006	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	depression	ADE	0.019	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	depression	Total Effect	0.025	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	depression	Prop. Mediated	0.251	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	depression	ACME	−0.007	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	depression	ADE	−0.021	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	depression	Total Effect	−0.028	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	depression	Prop. Mediated	0.253	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	depression	ACME	−0.006	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	depression	ADE	−0.020	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	depression	Total Effect	−0.026	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	depression	Prop. Mediated	0.231	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	depression	ACME	0.007	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	depression	ADE	0.021	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	depression	Total Effect	0.028	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	depression	Prop. Mediated	0.265	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	depression	ACME	0.006	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	depression	ADE	0.018	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	depression	Total Effect	0.024	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	depression	Prop. Mediated	0.260	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	depression	ACME	0.007	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	depression	ADE	0.016	0.004
dMRI	Mean axial diffusivity in superior corona radiata (right)	depression	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	depression	Prop. Mediated	0.304	<0.001
dMRI	Mean MD in superior corona radiata (right)	depression	ACME	0.011	<0.001
dMRI	Mean MD in superior corona radiata (right)	depression	ADE	0.011	0.036
dMRI	Mean MD in superior corona radiata (right)	depression	Total Effect	0.021	<0.001

dMRI	Mean MD in superior corona radiata (right)	depression	Prop. Mediated	0.510	<0.001
dMRI	Mean ICVF in tapetum (right)	depression	ACME	−0.003	0.028
dMRI	Mean ICVF in tapetum (right)	depression	ADE	−0.021	<0.001
dMRI	Mean ICVF in tapetum (right)	depression	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in tapetum (right)	depression	Prop. Mediated	0.135	0.028
dMRI	Mean axial diffusivity in tapetum (right)	depression	ACME	0.002	0.138
dMRI	Mean axial diffusivity in tapetum (right)	depression	ADE	0.021	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	depression	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	depression	Prop. Mediated	0.091	0.138
dMRI	Mean MD in tapetum (right)	depression	ACME	0.003	0.034
dMRI	Mean MD in tapetum (right)	depression	ADE	0.021	<0.001
dMRI	Mean MD in tapetum (right)	depression	Total Effect	0.023	<0.001
dMRI	Mean MD in tapetum (right)	depression	Prop. Mediated	0.121	0.034
Freesurfer a2009s	Area of Calcarine sulcus (left)	depression	ACME	0.000	0.984
Freesurfer a2009s	Area of Calcarine sulcus (left)	depression	ADE	−0.023	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	depression	Total Effect	−0.023	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	depression	Prop. Mediated	0.002	0.984
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	depression	ACME	0.000	0.884
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	depression	ADE	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	depression	Total Effect	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	depression	Prop. Mediated	0.010	0.884
Freesurfer ASEG	Volume of WM-hypointensities	depression	ACME	0.005	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	depression	ADE	0.018	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	depression	Total Effect	0.023	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	depression	Prop. Mediated	0.208	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	depression	ACME	−0.005	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	depression	ADE	0.033	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	depression	Total Effect	0.028	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	depression	Prop. Mediated	−0.194	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	depression	ACME	0.000	0.7

Freesurfer DKT	Area of Pericalcarine cortex (left)	depression	ADE	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	depression	Total Effect	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	depression	Prop. Mediated	0.020	0.7
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	depression	ACME	0.001	0.702
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	depression	ADE	−0.025	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	depression	Total Effect	−0.024	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	depression	Prop. Mediated	−0.024	0.702
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	depression	ACME	0.000	0.744
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	depression	ADE	−0.024	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	depression	Total Effect	−0.024	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	depression	Prop. Mediated	−0.023	0.744
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	depression	ACME	−0.003	0.032
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	depression	ADE	−0.020	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	depression	Total Effect	−0.023	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	depression	Prop. Mediated	0.124	0.032
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	depression	ACME	−0.003	0.028
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	depression	ADE	0.028	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	depression	Total Effect	0.024	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	depression	Prop. Mediated	−0.124	0.028
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	depression	ACME	0.000	0.968
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	depression	ADE	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	depression	Total Effect	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	depression	Prop. Mediated	−0.002	0.968
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	depression	ACME	−0.005	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	depression	ADE	0.029	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	depression	Total Effect	0.024	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	depression	Prop. Mediated	−0.192	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	depression	ACME	−0.001	0.756
Freesurfer desikan white	Area of Pericalcarine cortex (left)	depression	ADE	−0.023	<0.001

Freesurfer desikan white	Area of Pericalcarine cortex (left)	depression	Total Effect	−0.024	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	depression	Prop. Mediated	0.022	0.756
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	depression	ACME	0.001	0.684
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	depression	ADE	−0.026	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	depression	Total Effect	−0.025	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	depression	Prop. Mediated	−0.027	0.684
FAST	Volume of grey matter in Left Caudate	diabetes	ACME	0.000	0.384
FAST	Volume of grey matter in Left Caudate	diabetes	ADE	0.025	<0.001
FAST	Volume of grey matter in Left Caudate	diabetes	Total Effect	0.025	<0.001
FAST	Volume of grey matter in Left Caudate	diabetes	Prop. Mediated	0.003	0.384
FAST	Volume of grey matter in Right Caudate	diabetes	ACME	0.000	0.288
FAST	Volume of grey matter in Right Caudate	diabetes	ADE	0.024	<0.001
FAST	Volume of grey matter in Right Caudate	diabetes	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Caudate	diabetes	Prop. Mediated	0.003	0.288
FAST	Volume of grey matter in Left Frontal Medial Cortex	diabetes	ACME	0.000	0.002
FAST	Volume of grey matter in Left Frontal Medial Cortex	diabetes	ADE	−0.026	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	diabetes	Total Effect	−0.027	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	diabetes	Prop. Mediated	0.015	0.002
FAST	Volume of grey matter in Left Putamen	diabetes	ACME	−0.001	0.002
FAST	Volume of grey matter in Left Putamen	diabetes	ADE	0.025	<0.001
FAST	Volume of grey matter in Left Putamen	diabetes	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Left Putamen	diabetes	Prop. Mediated	−0.029	0.002
FAST	Volume of grey matter in Right Putamen	diabetes	ACME	−0.001	<0.001
FAST	Volume of grey matter in Right Putamen	diabetes	ADE	0.025	<0.001
FAST	Volume of grey matter in Right Putamen	diabetes	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Putamen	diabetes	Prop. Mediated	−0.031	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	diabetes	ACME	−0.001	0.004
FAST	Volume of grey matter in Left Subcallosal Cortex	diabetes	ADE	−0.023	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	diabetes	Total Effect	−0.024	<0.001

FAST	Volume of grey matter in Left Subcallosal Cortex	diabetes	Prop. Mediated	0.024	0.004
FAST	Volume of grey matter in Left Ventral Striatum	diabetes	ACME	−0.001	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	diabetes	ADE	0.022	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	diabetes	Total Effect	0.021	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	diabetes	Prop. Mediated	−0.048	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	diabetes	ACME	0.001	0.002
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	diabetes	ADE	0.021	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	diabetes	Total Effect	0.022	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	diabetes	Prop. Mediated	0.034	0.002
dMRI	Mean axial diffusivity in external capsule (right)	diabetes	ACME	0.001	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	diabetes	ADE	0.022	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	diabetes	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	diabetes	Prop. Mediated	0.023	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	diabetes	ACME	0.001	0.006
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	diabetes	ADE	0.022	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	diabetes	Total Effect	0.023	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	diabetes	Prop. Mediated	0.035	0.006
dMRI	Mean MD in fornix cres+stria terminalis (right)	diabetes	ACME	0.001	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	diabetes	ADE	0.022	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	diabetes	Total Effect	0.023	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	diabetes	Prop. Mediated	0.038	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	diabetes	ACME	0.001	0.004
dMRI	Mean axial diffusivity in posterior corona radiata (left)	diabetes	ADE	0.026	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	diabetes	Total Effect	0.027	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	diabetes	Prop. Mediated	0.023	0.004
dMRI	Mean MD in posterior corona radiata (left)	diabetes	ACME	0.001	0.004
dMRI	Mean MD in posterior corona radiata (left)	diabetes	ADE	0.022	<0.001

dMRI	Mean MD in posterior corona radiata (left)	diabetes	Total Effect	0.022	<0.001
dMRI	Mean MD in posterior corona radiata (left)	diabetes	Prop. Mediated	0.027	0.004
dMRI	Mean OD in posterior corona radiata (left)	diabetes	ACME	0.000	0.004
dMRI	Mean OD in posterior corona radiata (left)	diabetes	ADE	−0.024	<0.001
dMRI	Mean OD in posterior corona radiata (left)	diabetes	Total Effect	−0.024	<0.001
dMRI	Mean OD in posterior corona radiata (left)	diabetes	Prop. Mediated	0.013	0.004
dMRI	Mean axial diffusivity in posterior corona radiata (right)	diabetes	ACME	0.001	0.002
dMRI	Mean axial diffusivity in posterior corona radiata (right)	diabetes	ADE	0.023	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	diabetes	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	diabetes	Prop. Mediated	0.029	0.002
dMRI	Mean FA in posterior thalamic radiation (left)	diabetes	ACME	−0.001	0.01
dMRI	Mean FA in posterior thalamic radiation (left)	diabetes	ADE	−0.025	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	diabetes	Total Effect	−0.026	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	diabetes	Prop. Mediated	0.032	0.01
dMRI	Mean ICVF in posterior thalamic radiation (left)	diabetes	ACME	−0.001	0.004
dMRI	Mean ICVF in posterior thalamic radiation (left)	diabetes	ADE	−0.024	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	diabetes	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	diabetes	Prop. Mediated	0.023	0.004
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	diabetes	ACME	0.001	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	diabetes	ADE	0.025	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	diabetes	Total Effect	0.026	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	diabetes	Prop. Mediated	0.026	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	diabetes	ACME	−0.001	0.004
dMRI	Mean FA in posterior thalamic radiation (right)	diabetes	ADE	−0.027	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	diabetes	Total Effect	−0.028	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	diabetes	Prop. Mediated	0.032	0.004
dMRI	Mean ICVF in posterior thalamic radiation (right)	diabetes	ACME	−0.001	0.002
dMRI	Mean ICVF in posterior thalamic radiation (right)	diabetes	ADE	−0.026	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	diabetes	Total Effect	−0.027	<0.001

dMRI	Mean ICVF in posterior thalamic radiation (right)	diabetes	Prop. Mediated	0.020	0.002
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	diabetes	ACME	0.001	0.002
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	diabetes	ADE	0.027	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	diabetes	Total Effect	0.028	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	diabetes	Prop. Mediated	0.025	0.002
dMRI	Mean MD in posterior thalamic radiation (right)	diabetes	ACME	0.000	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	diabetes	ADE	0.023	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	diabetes	Total Effect	0.024	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	diabetes	Prop. Mediated	0.015	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	diabetes	ACME	0.001	0.002
dMRI	Mean axial diffusivity in superior corona radiata (right)	diabetes	ADE	0.022	0.002
dMRI	Mean axial diffusivity in superior corona radiata (right)	diabetes	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	diabetes	Prop. Mediated	0.028	0.002
dMRI	Mean MD in superior corona radiata (right)	diabetes	ACME	0.001	0.004
dMRI	Mean MD in superior corona radiata (right)	diabetes	ADE	0.021	<0.001
dMRI	Mean MD in superior corona radiata (right)	diabetes	Total Effect	0.021	<0.001
dMRI	Mean MD in superior corona radiata (right)	diabetes	Prop. Mediated	0.033	0.004
dMRI	Mean ICVF in tapetum (right)	diabetes	ACME	0.000	<0.001
dMRI	Mean ICVF in tapetum (right)	diabetes	ADE	−0.023	<0.001
dMRI	Mean ICVF in tapetum (right)	diabetes	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in tapetum (right)	diabetes	Prop. Mediated	0.017	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	diabetes	ACME	0.001	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	diabetes	ADE	0.022	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	diabetes	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	diabetes	Prop. Mediated	0.027	<0.001
dMRI	Mean MD in tapetum (right)	diabetes	ACME	0.001	0.002
dMRI	Mean MD in tapetum (right)	diabetes	ADE	0.023	<0.001
dMRI	Mean MD in tapetum (right)	diabetes	Total Effect	0.023	<0.001
dMRI	Mean MD in tapetum (right)	diabetes	Prop. Mediated	0.027	0.002
Freesurfer a2009s	Area of Calcarine sulcus (left)	diabetes	ACME	0.000	0.412

Freesurfer a2009s	Area of Calcarine sulcus (left)	diabetes	ADE	−0.024	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	diabetes	Total Effect	−0.024	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	diabetes	Prop. Mediated	0.003	0.412
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	diabetes	ACME	0.000	0.05
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	diabetes	ADE	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	diabetes	Total Effect	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	diabetes	Prop. Mediated	0.006	0.05
Freesurfer ASEG	Volume of WM-hypointensities	diabetes	ACME	0.001	0.004
Freesurfer ASEG	Volume of WM-hypointensities	diabetes	ADE	0.022	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	diabetes	Total Effect	0.023	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	diabetes	Prop. Mediated	0.034	0.004
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	diabetes	ACME	0.000	0.05
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	diabetes	ADE	0.028	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	diabetes	Total Effect	0.028	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	diabetes	Prop. Mediated	−0.005	0.05
Freesurfer DKT	Area of Pericalcarine cortex (left)	diabetes	ACME	0.000	0.056
Freesurfer DKT	Area of Pericalcarine cortex (left)	diabetes	ADE	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	diabetes	Total Effect	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	diabetes	Prop. Mediated	0.006	0.056
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	diabetes	ACME	0.000	0.114
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	diabetes	ADE	−0.024	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	diabetes	Total Effect	−0.024	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	diabetes	Prop. Mediated	0.005	0.114
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	diabetes	ACME	0.000	0.56
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	diabetes	ADE	−0.023	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	diabetes	Total Effect	−0.023	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	diabetes	Prop. Mediated	0.002	0.56
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	diabetes	ACME	0.000	0.006
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	diabetes	ADE	−0.022	<0.001

Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	diabetes	Total Effect	−0.023	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	diabetes	Prop. Mediated	0.021	0.006
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	diabetes	ACME	0.000	0.144
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	diabetes	ADE	0.025	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	diabetes	Total Effect	0.025	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	diabetes	Prop. Mediated	−0.005	0.144
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	diabetes	ACME	0.000	0.622
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	diabetes	ADE	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	diabetes	Total Effect	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	diabetes	Prop. Mediated	0.002	0.622
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	diabetes	ACME	0.000	0.078
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	diabetes	ADE	0.025	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	diabetes	Total Effect	0.025	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	diabetes	Prop. Mediated	−0.006	0.078
Freesurfer desikan white	Area of Pericalcarine cortex (left)	diabetes	ACME	0.000	0.136
Freesurfer desikan white	Area of Pericalcarine cortex (left)	diabetes	ADE	−0.023	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	diabetes	Total Effect	−0.023	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	diabetes	Prop. Mediated	0.005	0.136
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	diabetes	ACME	0.000	0.1
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	diabetes	ADE	−0.024	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	diabetes	Total Effect	−0.025	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	diabetes	Prop. Mediated	0.005	0.1
FAST	Volume of grey matter in Left Caudate	hypertension	ACME	0.006	<0.001
FAST	Volume of grey matter in Left Caudate	hypertension	ADE	0.019	<0.001
FAST	Volume of grey matter in Left Caudate	hypertension	Total Effect	0.025	<0.001
FAST	Volume of grey matter in Left Caudate	hypertension	Prop. Mediated	0.223	<0.001
FAST	Volume of grey matter in Right Caudate	hypertension	ACME	0.006	<0.001
FAST	Volume of grey matter in Right Caudate	hypertension	ADE	0.018	<0.001
FAST	Volume of grey matter in Right Caudate	hypertension	Total Effect	0.024	<0.001

FAST	Volume of grey matter in Right Caudate	hypertension	Prop. Mediated	0.246	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	hypertension	ACME	−0.002	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	hypertension	ADE	−0.025	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	hypertension	Total Effect	−0.027	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	hypertension	Prop. Mediated	0.077	<0.001
FAST	Volume of grey matter in Left Putamen	hypertension	ACME	0.003	<0.001
FAST	Volume of grey matter in Left Putamen	hypertension	ADE	0.022	<0.001
FAST	Volume of grey matter in Left Putamen	hypertension	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Left Putamen	hypertension	Prop. Mediated	0.113	<0.001
FAST	Volume of grey matter in Right Putamen	hypertension	ACME	0.002	<0.001
FAST	Volume of grey matter in Right Putamen	hypertension	ADE	0.022	<0.001
FAST	Volume of grey matter in Right Putamen	hypertension	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Putamen	hypertension	Prop. Mediated	0.078	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	hypertension	ACME	−0.002	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	hypertension	ADE	−0.021	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	hypertension	Total Effect	−0.024	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	hypertension	Prop. Mediated	0.101	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	hypertension	ACME	−0.002	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	hypertension	ADE	0.024	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	hypertension	Total Effect	0.021	0.002
FAST	Volume of grey matter in Left Ventral Striatum	hypertension	Prop. Mediated	−0.112	0.002
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	hypertension	ACME	0.007	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	hypertension	ADE	0.015	0.002
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	hypertension	Total Effect	0.022	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	hypertension	Prop. Mediated	0.309	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	hypertension	ACME	0.008	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	hypertension	ADE	0.014	0.002

dMRI	Mean axial diffusivity in external capsule (right)	hypertension	Total Effect	0.022	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	hypertension	Prop. Mediated	0.364	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	hypertension	ACME	0.003	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	hypertension	ADE	0.020	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	hypertension	Total Effect	0.023	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	hypertension	Prop. Mediated	0.140	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	hypertension	ACME	0.004	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	hypertension	ADE	0.019	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	hypertension	Total Effect	0.023	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	hypertension	Prop. Mediated	0.183	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	hypertension	ACME	0.006	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	hypertension	ADE	0.020	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	hypertension	Total Effect	0.027	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	hypertension	Prop. Mediated	0.236	<0.001
dMRI	Mean MD in posterior corona radiata (left)	hypertension	ACME	0.007	<0.001
dMRI	Mean MD in posterior corona radiata (left)	hypertension	ADE	0.016	0.006
dMRI	Mean MD in posterior corona radiata (left)	hypertension	Total Effect	0.023	<0.001
dMRI	Mean MD in posterior corona radiata (left)	hypertension	Prop. Mediated	0.287	<0.001
dMRI	Mean OD in posterior corona radiata (left)	hypertension	ACME	−0.003	<0.001
dMRI	Mean OD in posterior corona radiata (left)	hypertension	ADE	−0.020	<0.001
dMRI	Mean OD in posterior corona radiata (left)	hypertension	Total Effect	−0.024	<0.001
dMRI	Mean OD in posterior corona radiata (left)	hypertension	Prop. Mediated	0.145	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	hypertension	ACME	0.006	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	hypertension	ADE	0.017	0.002
dMRI	Mean axial diffusivity in posterior corona radiata (right)	hypertension	Total Effect	0.024	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	hypertension	Prop. Mediated	0.262	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	hypertension	ACME	−0.006	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	hypertension	ADE	−0.020	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	hypertension	Total Effect	−0.026	<0.001

dMRI	Mean FA in posterior thalamic radiation (left)	hypertension	Prop. Mediated	0.235	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	hypertension	ACME	−0.005	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	hypertension	ADE	−0.019	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	hypertension	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	hypertension	Prop. Mediated	0.201	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	hypertension	ACME	0.006	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	hypertension	ADE	0.019	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	hypertension	Total Effect	0.026	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	hypertension	Prop. Mediated	0.255	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	hypertension	ACME	−0.006	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	hypertension	ADE	−0.022	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	hypertension	Total Effect	−0.028	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	hypertension	Prop. Mediated	0.207	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	hypertension	ACME	−0.004	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	hypertension	ADE	−0.022	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	hypertension	Total Effect	−0.026	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	hypertension	Prop. Mediated	0.168	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	hypertension	ACME	0.006	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	hypertension	ADE	0.022	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	hypertension	Total Effect	0.028	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	hypertension	Prop. Mediated	0.222	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	hypertension	ACME	0.006	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	hypertension	ADE	0.018	0.002
dMRI	Mean MD in posterior thalamic radiation (right)	hypertension	Total Effect	0.024	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	hypertension	Prop. Mediated	0.248	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	hypertension	ACME	0.006	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	hypertension	ADE	0.017	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	hypertension	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	hypertension	Prop. Mediated	0.268	<0.001

dMRI	Mean MD in superior corona radiata (right)	hypertension	ACME	0.008	<0.001
dMRI	Mean MD in superior corona radiata (right)	hypertension	ADE	0.014	0.018
dMRI	Mean MD in superior corona radiata (right)	hypertension	Total Effect	0.022	<0.001
dMRI	Mean MD in superior corona radiata (right)	hypertension	Prop. Mediated	0.354	<0.001
dMRI	Mean ICVF in tapetum (right)	hypertension	ACME	−0.004	<0.001
dMRI	Mean ICVF in tapetum (right)	hypertension	ADE	−0.020	<0.001
dMRI	Mean ICVF in tapetum (right)	hypertension	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in tapetum (right)	hypertension	Prop. Mediated	0.161	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	hypertension	ACME	0.005	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	hypertension	ADE	0.018	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	hypertension	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	hypertension	Prop. Mediated	0.201	<0.001
dMRI	Mean MD in tapetum (right)	hypertension	ACME	0.005	<0.001
dMRI	Mean MD in tapetum (right)	hypertension	ADE	0.018	<0.001
dMRI	Mean MD in tapetum (right)	hypertension	Total Effect	0.023	<0.001
dMRI	Mean MD in tapetum (right)	hypertension	Prop. Mediated	0.212	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	hypertension	ACME	−0.001	0.02
Freesurfer a2009s	Area of Calcarine sulcus (left)	hypertension	ADE	−0.023	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	hypertension	Total Effect	−0.023	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	hypertension	Prop. Mediated	0.037	0.02
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	hypertension	ACME	−0.002	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	hypertension	ADE	−0.021	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	hypertension	Total Effect	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	hypertension	Prop. Mediated	0.067	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	hypertension	ACME	0.007	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	hypertension	ADE	0.015	0.002
Freesurfer ASEG	Volume of WM-hypointensities	hypertension	Total Effect	0.023	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	hypertension	Prop. Mediated	0.314	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	hypertension	ACME	−0.001	0.082
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	hypertension	ADE	0.028	<0.001

Freesurfer DKT	Area of Parahippocampal Gyrus (left)	hypertension	Total Effect	0.027	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	hypertension	Prop. Mediated	−0.021	0.082
Freesurfer DKT	Area of Pericalcarine cortex (left)	hypertension	ACME	−0.001	0.016
Freesurfer DKT	Area of Pericalcarine cortex (left)	hypertension	ADE	−0.022	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	hypertension	Total Effect	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	hypertension	Prop. Mediated	0.037	0.016
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	hypertension	ACME	−0.001	0.014
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	hypertension	ADE	−0.024	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	hypertension	Total Effect	−0.025	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	hypertension	Prop. Mediated	0.037	0.014
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	hypertension	ACME	0.000	0.242
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	hypertension	ADE	−0.023	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	hypertension	Total Effect	−0.024	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	hypertension	Prop. Mediated	0.018	0.242
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	hypertension	ACME	−0.002	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	hypertension	ADE	−0.020	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	hypertension	Total Effect	−0.023	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	hypertension	Prop. Mediated	0.102	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	hypertension	ACME	0.000	0.778
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	hypertension	ADE	0.025	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	hypertension	Total Effect	0.025	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	hypertension	Prop. Mediated	−0.004	0.778
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	hypertension	ACME	−0.001	0.08
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	hypertension	ADE	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	hypertension	Total Effect	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	hypertension	Prop. Mediated	0.028	0.08
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	hypertension	ACME	−0.001	0.09
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	hypertension	ADE	0.025	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	hypertension	Total Effect	0.024	<0.001

Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	hypertension	Prop. Mediated	−0.024	0.09
Freesurfer desikan white	Area of Pericalcarine cortex (left)	hypertension	ACME	−0.001	0.016
Freesurfer desikan white	Area of Pericalcarine cortex (left)	hypertension	ADE	−0.022	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	hypertension	Total Effect	−0.023	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	hypertension	Prop. Mediated	0.037	0.016
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	hypertension	ACME	−0.001	0.01
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	hypertension	ADE	−0.024	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	hypertension	Total Effect	−0.025	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	hypertension	Prop. Mediated	0.037	0.01
FAST	Volume of grey matter in Left Caudate	ischaemic heart disease	ACME	0.000	0.17
FAST	Volume of grey matter in Left Caudate	ischaemic heart disease	ADE	0.025	<0.001
FAST	Volume of grey matter in Left Caudate	ischaemic heart disease	Total Effect	0.025	<0.001
FAST	Volume of grey matter in Left Caudate	ischaemic heart disease	Prop. Mediated	0.008	0.17
FAST	Volume of grey matter in Right Caudate	ischaemic heart disease	ACME	0.000	0.232
FAST	Volume of grey matter in Right Caudate	ischaemic heart disease	ADE	0.024	<0.001
FAST	Volume of grey matter in Right Caudate	ischaemic heart disease	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Caudate	ischaemic heart disease	Prop. Mediated	0.007	0.232
FAST	Volume of grey matter in Left Frontal Medial Cortex	ischaemic heart disease	ACME	0.000	0.52
FAST	Volume of grey matter in Left Frontal Medial Cortex	ischaemic heart disease	ADE	−0.027	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	ischaemic heart disease	Total Effect	−0.027	<0.001
FAST	Volume of grey matter in Left Frontal Medial Cortex	ischaemic heart disease	Prop. Mediated	0.004	0.52
FAST	Volume of grey matter in Left Putamen	ischaemic heart disease	ACME	0.000	0.554
FAST	Volume of grey matter in Left Putamen	ischaemic heart disease	ADE	0.024	<0.001
FAST	Volume of grey matter in Left Putamen	ischaemic heart disease	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Left Putamen	ischaemic heart disease	Prop. Mediated	0.004	0.554
FAST	Volume of grey matter in Right Putamen	ischaemic heart disease	ACME	0.000	0.308
FAST	Volume of grey matter in Right Putamen	ischaemic heart disease	ADE	0.024	<0.001
FAST	Volume of grey matter in Right Putamen	ischaemic heart disease	Total Effect	0.024	<0.001
FAST	Volume of grey matter in Right Putamen	ischaemic heart disease	Prop. Mediated	0.006	0.308

FAST	Volume of grey matter in Left Subcallosal Cortex	ischaemic heart disease	ACME	0.000	0.042
FAST	Volume of grey matter in Left Subcallosal Cortex	ischaemic heart disease	ADE	−0.024	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	ischaemic heart disease	Total Effect	−0.024	<0.001
FAST	Volume of grey matter in Left Subcallosal Cortex	ischaemic heart disease	Prop. Mediated	0.012	0.042
FAST	Volume of grey matter in Left Ventral Striatum	ischaemic heart disease	ACME	0.000	0.286
FAST	Volume of grey matter in Left Ventral Striatum	ischaemic heart disease	ADE	0.021	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	ischaemic heart disease	Total Effect	0.021	<0.001
FAST	Volume of grey matter in Left Ventral Striatum	ischaemic heart disease	Prop. Mediated	−0.007	0.286
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	ischaemic heart disease	ACME	0.000	0.006
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	ischaemic heart disease	ADE	0.022	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	ischaemic heart disease	Total Effect	0.022	<0.001
FLAIR	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	ischaemic heart disease	Prop. Mediated	0.018	0.006
dMRI	Mean axial diffusivity in external capsule (right)	ischaemic heart disease	ACME	0.000	0.018
dMRI	Mean axial diffusivity in external capsule (right)	ischaemic heart disease	ADE	0.022	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in external capsule (right)	ischaemic heart disease	Prop. Mediated	0.016	0.018
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	ischaemic heart disease	ACME	0.000	0.014
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	ischaemic heart disease	ADE	0.023	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean ISOVF in fornix cres+stria terminalis (right)	ischaemic heart disease	Prop. Mediated	0.016	0.014
dMRI	Mean MD in fornix cres+stria terminalis (right)	ischaemic heart disease	ACME	0.000	0.002
dMRI	Mean MD in fornix cres+stria terminalis (right)	ischaemic heart disease	ADE	0.022	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean MD in fornix cres+stria terminalis (right)	ischaemic heart disease	Prop. Mediated	0.018	0.002
dMRI	Mean axial diffusivity in posterior corona radiata (left)	ischaemic heart disease	ACME	0.000	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	ischaemic heart disease	ADE	0.026	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (left)	ischaemic heart disease	Total Effect	0.026	<0.001

dMRI	Mean axial diffusivity in posterior corona radiata (left)	ischaemic heart disease	Prop. Mediated	0.017	<0.001
dMRI	Mean MD in posterior corona radiata (left)	ischaemic heart disease	ACME	0.000	0.01
dMRI	Mean MD in posterior corona radiata (left)	ischaemic heart disease	ADE	0.022	<0.001
dMRI	Mean MD in posterior corona radiata (left)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean MD in posterior corona radiata (left)	ischaemic heart disease	Prop. Mediated	0.017	0.01
dMRI	Mean OD in posterior corona radiata (left)	ischaemic heart disease	ACME	0.000	0.046
dMRI	Mean OD in posterior corona radiata (left)	ischaemic heart disease	ADE	−0.024	<0.001
dMRI	Mean OD in posterior corona radiata (left)	ischaemic heart disease	Total Effect	−0.024	<0.001
dMRI	Mean OD in posterior corona radiata (left)	ischaemic heart disease	Prop. Mediated	0.013	0.046
dMRI	Mean axial diffusivity in posterior corona radiata (right)	ischaemic heart disease	ACME	0.001	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	ischaemic heart disease	ADE	0.023	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in posterior corona radiata (right)	ischaemic heart disease	Prop. Mediated	0.024	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	ischaemic heart disease	ACME	0.000	0.074
dMRI	Mean FA in posterior thalamic radiation (left)	ischaemic heart disease	ADE	−0.025	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	ischaemic heart disease	Total Effect	−0.026	<0.001
dMRI	Mean FA in posterior thalamic radiation (left)	ischaemic heart disease	Prop. Mediated	0.011	0.074
dMRI	Mean ICVF in posterior thalamic radiation (left)	ischaemic heart disease	ACME	0.000	0.36
dMRI	Mean ICVF in posterior thalamic radiation (left)	ischaemic heart disease	ADE	−0.024	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	ischaemic heart disease	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (left)	ischaemic heart disease	Prop. Mediated	0.005	0.36
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	ischaemic heart disease	ACME	0.000	0.042
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	ischaemic heart disease	ADE	0.025	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	ischaemic heart disease	Total Effect	0.025	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (left)	ischaemic heart disease	Prop. Mediated	0.011	0.042
dMRI	Mean FA in posterior thalamic radiation (right)	ischaemic heart disease	ACME	0.000	0.016
dMRI	Mean FA in posterior thalamic radiation (right)	ischaemic heart disease	ADE	−0.028	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	ischaemic heart disease	Total Effect	−0.028	<0.001
dMRI	Mean FA in posterior thalamic radiation (right)	ischaemic heart disease	Prop. Mediated	0.013	0.016

dMRI	Mean ICVF in posterior thalamic radiation (right)	ischaemic heart disease	ACME	0.000	0.156
dMRI	Mean ICVF in posterior thalamic radiation (right)	ischaemic heart disease	ADE	−0.026	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	ischaemic heart disease	Total Effect	−0.026	<0.001
dMRI	Mean ICVF in posterior thalamic radiation (right)	ischaemic heart disease	Prop. Mediated	0.008	0.156
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	ischaemic heart disease	ACME	0.000	0.038
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	ischaemic heart disease	ADE	0.028	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	ischaemic heart disease	Total Effect	0.028	<0.001
dMRI	Mean radial diffusivity in posterior thalamic radiation (right)	ischaemic heart disease	Prop. Mediated	0.012	0.038
dMRI	Mean MD in posterior thalamic radiation (right)	ischaemic heart disease	ACME	0.000	0.2
dMRI	Mean MD in posterior thalamic radiation (right)	ischaemic heart disease	ADE	0.024	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	ischaemic heart disease	Total Effect	0.024	<0.001
dMRI	Mean MD in posterior thalamic radiation (right)	ischaemic heart disease	Prop. Mediated	0.008	0.2
dMRI	Mean axial diffusivity in superior corona radiata (right)	ischaemic heart disease	ACME	0.000	0.002
dMRI	Mean axial diffusivity in superior corona radiata (right)	ischaemic heart disease	ADE	0.022	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in superior corona radiata (right)	ischaemic heart disease	Prop. Mediated	0.019	0.002
dMRI	Mean MD in superior corona radiata (right)	ischaemic heart disease	ACME	0.001	<0.001
dMRI	Mean MD in superior corona radiata (right)	ischaemic heart disease	ADE	0.021	<0.001
dMRI	Mean MD in superior corona radiata (right)	ischaemic heart disease	Total Effect	0.022	<0.001
dMRI	Mean MD in superior corona radiata (right)	ischaemic heart disease	Prop. Mediated	0.024	<0.001
dMRI	Mean ICVF in tapetum (right)	ischaemic heart disease	ACME	0.000	0.262
dMRI	Mean ICVF in tapetum (right)	ischaemic heart disease	ADE	−0.023	<0.001
dMRI	Mean ICVF in tapetum (right)	ischaemic heart disease	Total Effect	−0.024	<0.001
dMRI	Mean ICVF in tapetum (right)	ischaemic heart disease	Prop. Mediated	0.007	0.262
dMRI	Mean axial diffusivity in tapetum (right)	ischaemic heart disease	ACME	0.001	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	ischaemic heart disease	ADE	0.022	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean axial diffusivity in tapetum (right)	ischaemic heart disease	Prop. Mediated	0.022	<0.001
dMRI	Mean MD in tapetum (right)	ischaemic heart disease	ACME	0.001	<0.001

dMRI	Mean MD in tapetum (right)	ischaemic heart disease	ADE	0.023	<0.001
dMRI	Mean MD in tapetum (right)	ischaemic heart disease	Total Effect	0.023	<0.001
dMRI	Mean MD in tapetum (right)	ischaemic heart disease	Prop. Mediated	0.022	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	ischaemic heart disease	ACME	0.000	0.05
Freesurfer a2009s	Area of Calcarine sulcus (left)	ischaemic heart disease	ADE	−0.023	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	ischaemic heart disease	Total Effect	−0.024	<0.001
Freesurfer a2009s	Area of Calcarine sulcus (left)	ischaemic heart disease	Prop. Mediated	0.012	0.05
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	ischaemic heart disease	ACME	0.000	0.478
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	ischaemic heart disease	ADE	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	ischaemic heart disease	Total Effect	−0.023	<0.001
Freesurfer a2009s	Volume of Cingulate Cortex, anterior (right)	ischaemic heart disease	Prop. Mediated	0.004	0.478
Freesurfer ASEG	Volume of WM-hypointensities	ischaemic heart disease	ACME	0.000	0.002
Freesurfer ASEG	Volume of WM-hypointensities	ischaemic heart disease	ADE	0.022	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	ischaemic heart disease	Total Effect	0.022	<0.001
Freesurfer ASEG	Volume of WM-hypointensities	ischaemic heart disease	Prop. Mediated	0.016	0.002
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	ACME	0.000	0.192
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	ADE	0.028	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	Total Effect	0.028	<0.001
Freesurfer DKT	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	Prop. Mediated	0.007	0.192
Freesurfer DKT	Area of Pericalcarine cortex (left)	ischaemic heart disease	ACME	0.000	0.088
Freesurfer DKT	Area of Pericalcarine cortex (left)	ischaemic heart disease	ADE	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	ischaemic heart disease	Total Effect	−0.023	<0.001
Freesurfer DKT	Area of Pericalcarine cortex (left)	ischaemic heart disease	Prop. Mediated	0.011	0.088
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	ACME	0.000	0.218
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	ADE	−0.024	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	Total Effect	−0.025	<0.001
Freesurfer DKT	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	Prop. Mediated	0.007	0.218
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	ischaemic heart disease	ACME	0.000	0.894
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	ischaemic heart disease	ADE	−0.024	<0.001

Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	ischaemic heart disease	Total Effect	−0.024	<0.001
Freesurfer DKT	Volume of Cingulate Gyrus, caudal anterior (left)	ischaemic heart disease	Prop. Mediated	0.001	0.894
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	ischaemic heart disease	ACME	0.000	0.556
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	ischaemic heart disease	ADE	−0.023	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	ischaemic heart disease	Total Effect	−0.023	<0.001
Freesurfer DKT	Volume of Medial Orbitofrontal Cortex (left)	ischaemic heart disease	Prop. Mediated	−0.004	0.556
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	ACME	0.000	0.2
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	ADE	0.024	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	Total Effect	0.024	<0.001
Freesurfer desikan pial	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	Prop. Mediated	0.007	0.2
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	ischaemic heart disease	ACME	0.000	0.114
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	ischaemic heart disease	ADE	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	ischaemic heart disease	Total Effect	−0.023	<0.001
Freesurfer desikan pial	Area of Pericalcarine cortex (left)	ischaemic heart disease	Prop. Mediated	0.009	0.114
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	ACME	0.000	0.084
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	ADE	0.024	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	Total Effect	0.024	<0.001
Freesurfer desikan white	Area of Parahippocampal Gyrus (left)	ischaemic heart disease	Prop. Mediated	0.010	0.084
Freesurfer desikan white	Area of Pericalcarine cortex (left)	ischaemic heart disease	ACME	0.000	0.058
Freesurfer desikan white	Area of Pericalcarine cortex (left)	ischaemic heart disease	ADE	−0.023	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	ischaemic heart disease	Total Effect	−0.024	<0.001
Freesurfer desikan white	Area of Pericalcarine cortex (left)	ischaemic heart disease	Prop. Mediated	0.011	0.058
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	ACME	0.000	0.158
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	ADE	−0.024	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	Total Effect	−0.025	<0.001
Freesurfer a2009s	Mean thickness of Parahippocampal Gyrus (left)	ischaemic heart disease	Prop. Mediated	0.008	0.158

ACME, average causal mediation effect; ADE, average direct effect. Causal mediation analyses decomposed the total effect of neuroticism on each significant IDP into: the average causal mediation effect (ACME), the average direct effect (ADE), the total effect, and the proportion mediated. Models were adjusted sex, age and age polynomials, age×sex, ethnicity, Townsend deprivation index, education, smoking, alcohol consumption, and body mass index. P-values were derived using quasi-Bayesian Monte Carlo approach with 1000 simulations.

Appendix 6.3: Summary of genetic instruments for phenotypes used in Mendelian Randomisation analyses

Phenotype	Model/atlas	GWAS source	GWAS dataset	GWAS sample size	N_{snp}	R^2
Neuroticism		Gupta et al., 2024	MVP, UKB, GPC	623,482	132	0.014
Mean ICVF in posterior thalamic radiation (left)	dMRI	Smith et al., 2021	UKB	20859	21	0.052
Mean ICVF in posterior thalamic radiation (right)	dMRI	Smith et al., 2021	UKB	20859	20	0.052
Area of Pericalcarine cortex (left)	Freesurfer DKT	Smith et al., 2021	UKB	21282	24	0.049
Volume of grey matter in Putamen (left)	FAST	Smith et al., 2021	UKB	22133	14	0.048
Area of Pericalcarine cortex (left)	Freesurfer desikan white	Smith et al., 2021	UKB	21282	23	0.048
Volume of grey matter in Ventral Striatum (left)	FAST	Smith et al., 2021	UKB	22133	14	0.046
Volume of grey matter in Putamen (right)	FAST	Smith et al., 2021	UKB	22133	14	0.045
Area of Scalcarine (left)	Freesurfer a2009s	Smith et al., 2021	UKB	21282	21	0.041
Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	FLAIR	Smith et al., 2021	UKB	21381	15	0.037
Area of Pericalcarine cortex (left)	Freesurfer desikan pial	Smith et al., 2021	UKB	21282	17	0.036
Mean MD in superior corona radiata (right)	dMRI	Smith et al., 2021	UKB	20860	11	0.024
Mean MD in posterior thalamic radiation (right)	dMRI	Smith et al., 2021	UKB	20860	9	0.022
Volume of grey matter in Caudate (left)	FAST	Smith et al., 2021	UKB	22133	12	0.021
Mean ICVF in tapetum (right)	dMRI	Smith et al., 2021	UKB	20859	9	0.020
Volume of grey matter in Caudate (right)	FAST	Smith et al., 2021	UKB	22133	10	0.020
Mean MD in posterior corona radiata (left)	dMRI	Smith et al., 2021	UKB	20860	8	0.020
Volume of WMhypointensities (whole brain)	Freesurfer ASEG	Smith et al., 2021	UKB	21282	8	0.019
Mean axial diffusivity in posterior corona radiata (left)	dMRI	Smith et al., 2021	UKB	20860	10	0.018
Mean axial diffusivity in external capsule (right)	dMRI	Smith et al., 2021	UKB	20860	8	0.016

Volume of grey matter in Subcallosal Cortex (left)	FAST	Smith et al., 2021	UKB	22133	6	0.012
Mean radial diffusivity in posterior thalamic radiation (right)	dMRI	Smith et al., 2021	UKB	20860	4	0.012
Mean radial diffusivity in posterior thalamic radiation (left)	dMRI	Smith et al., 2021	UKB	20860	4	0.012
Mean FA in posterior thalamic radiation (right)	dMRI	Smith et al., 2021	UKB	20860	4	0.011
Mean axial diffusivity in posterior corona radiata (right)	dMRI	Smith et al., 2021	UKB	20860	5	0.011
Mean FA in posterior thalamic radiation (left)	dMRI	Smith et al., 2021	UKB	20860	4	0.010
Mean axial diffusivity in superior corona radiata (right)	dMRI	Smith et al., 2021	UKB	20860	6	0.010
Mean MD in tapetum (right)	dMRI	Smith et al., 2021	UKB	20860	6	0.010
Mean axial diffusivity in tapetum (right)	dMRI	Smith et al., 2021	UKB	20860	4	0.007
Mean OD in posterior corona radiata (left)	dMRI	Smith et al., 2021	UKB	20859	3	0.005
Volume of caudalAntcingulate (left)	Freesurfer DKT	Smith et al., 2021	UKB	21282	3	0.004
Area of Parahippocampal Gyrus (left)	Freesurfer DKT	Smith et al., 2021	UKB	21282	3	0.004
Volume of grey matter in Frontal Medial Cortex (left)	FAST	Smith et al., 2021	UKB	22133	2	0.003
Mean MD in fornix cres+stria terminalis (right)	dMRI	Smith et al., 2021	UKB	20860	2	0.003
Area of Parahippocampal Gyrus (left)	Freesurfer desikan white	Smith et al., 2021	UKB	21282	2	0.003
Area of Parahippocampal Gyrus (left)	Freesurfer desikan pial	Smith et al., 2021	UKB	21282	2	0.003
Volume of Medorbitofrontal (left)	Freesurfer DKT	Smith et al., 2021	UKB	21282	1	0.002
Volume of GScingulAnt (right)	Freesurfer a2009s	Smith et al., 2021	UKB	21282	1	0.002
thickness of Parahippocampal Gyrus (left)	Freesurfer desikan white	Smith et al., 2021	UKB	21282	1	0.001
thickness of Parahippocampal Gyrus (left)	Freesurfer DKT	Smith et al., 2021	UKB	21282	1	0.001
Mean ISOVF in fornix cres+stria terminalis (right)	dMRI	Smith et al., 2021	UKB	20859	2	<0.001

GWAS, genome-wide association studies; MVP, Million Veteran Program; UKB, UK Biobank; GPC, Genetics of Personality Consortium; SNP, single nucleotide polymorphism; N_{SNP}, number of genetic variants used as instrumental variables; R^2, proportion of variance explained.

Appendix 6.4: Primary (inverse-variance weighted) analyses for forward Mendelian randomisation

Outcome	Model/atlas	β	SE	p
Volume of grey matter in Left Caudate	FAST	0.162	0.069	0.018
Volume of grey matter in Right Caudate	FAST	0.133	0.072	0.065
Volume of grey matter in Left Frontal Medial Cortex	FAST	−0.017	0.069	0.804
Volume of grey matter in Left Putamen	FAST	0.118	0.072	0.104
Volume of grey matter in Right Putamen	FAST	0.110	0.075	0.145
Volume of grey matter in Left Subcallosal Cortex	FAST	−0.123	0.071	0.084
Volume of grey matter in Left Ventral Striatum	FAST	−0.007	0.067	0.912
Total volume of white matter hyperintensities (from T1 and T2 FLAIR images)	FLAIR	0.205	0.067	0.002
Mean axial diffusivity in external capsule (right)	dMRI	0.206	0.078	0.008
Mean ISOVF in fornix cres+stria terminalis (right)	dMRI	0.122	0.065	0.062
Mean MD in fornix cres+stria terminalis (right)	dMRI	0.105	0.071	0.138
Mean axial diffusivity in posterior corona radiata (left)	dMRI	0.154	0.073	0.034
Mean MD in posterior corona radiata (left)	dMRI	0.154	0.068	0.024
Mean OD in posterior corona radiata (left)	dMRI	−0.150	0.081	0.065
Mean axial diffusivity in posterior corona radiata (right)	dMRI	0.143	0.079	0.069
Mean FA in posterior thalamic radiation (left)	dMRI	−0.092	0.062	0.142
Mean ICVF in posterior thalamic radiation (left)	dMRI	−0.169	0.069	0.014
Mean radial diffusivity in posterior thalamic radiation (left)	dMRI	0.115	0.062	0.064
Mean FA in posterior thalamic radiation (right)	dMRI	−0.062	0.065	0.342
Mean ICVF in posterior thalamic radiation (right)	dMRI	−0.164	0.072	0.023
Mean radial diffusivity in posterior thalamic radiation (right)	dMRI	0.098	0.063	0.123
Mean MD in posterior thalamic radiation (right)	dMRI	0.162	0.066	0.013
Mean axial diffusivity in superior corona radiata (right)	dMRI	0.129	0.074	0.082
Mean MD in superior corona radiata (right)	dMRI	0.173	0.071	0.015
Mean ICVF in tapetum (right)	dMRI	−0.184	0.075	0.014
Mean axial diffusivity in tapetum (right)	dMRI	0.097	0.074	0.188
Mean MD in tapetum (right)	dMRI	0.106	0.079	0.181
Area of Calcarine sulcus (left)	Freesurfer a2009s	−0.059	0.085	0.488
Volume of Cingulate Cortex, anterior (right)	Freesurfer a2009s	−0.084	0.076	0.270
Volume of WM-hypointensities	Freesurfer ASEG	0.101	0.073	0.163
Area of Parahippocampal Gyrus (left)	Freesurfer DKT	0.010	0.075	0.895

Area of Pericalcarine cortex (left)	Freesurfer DKT	−0.022	0.084	0.795
Mean thickness of Parahippocampal Gyrus (left)	Freesurfer DKT	−0.033	0.070	0.637
Volume of Cingulate Gyrus, caudal anterior (left)	Freesurfer DKT	−0.188	0.077	0.014
Volume of Medial Orbitofrontal Cortex (left)	Freesurfer DKT	−0.102	0.073	0.166
Area of Parahippocampal Gyrus (left)	Freesurfer desikan pial	0.034	0.076	0.655
Area of Pericalcarine cortex (left)	Freesurfer desikan pial	−0.009	0.083	0.915
Area of Parahippocampal Gyrus (left)	Freesurfer desikan white	0.013	0.074	0.864
Area of Pericalcarine cortex (left)	Freesurfer desikan white	−0.026	0.084	0.760
Mean thickness of Parahippocampal Gyrus (left)	Freesurfer a2009s	−0.034	0.070	0.628

SE, standard error. Estimates reflect the association between genetically predicted neuroticism and each imaging-derived phenotype, obtained using the inverse-variance weighted method.

Appendix 6.5: Robust Mendelian randomisation methods applied to associations significant in inverse-variance weighted analyses

Exposure	Outcome	Model/atlas	Method	N_{snp}	β	SE	p
Volume of grey matter in Left Caudate	neuroticism	FAST	Inverse-variance weighted	8	0.061	0.018	0.001
Volume of grey matter in Left Caudate	neuroticism	FAST	MR-Egger	8	0.189	0.049	0.008
Volume of grey matter in Left Caudate	neuroticism	FAST	Weighted median	8	0.045	0.020	0.024
Volume of grey matter in Left Caudate	neuroticism	FAST	MRlap	11	0.044	0.024	0.065
Volume of grey matter in Right Caudate	neuroticism	FAST	Inverse-variance weighted	7	0.057	0.021	0.007
Volume of grey matter in Right Caudate	neuroticism	FAST	MR-Egger	7	0.130	0.071	0.125
Volume of grey matter in Right Caudate	neuroticism	FAST	Weighted median	7	0.050	0.020	0.011
Volume of grey matter in Right Caudate	neuroticism	FAST	MRlap	11	0.037	0.026	0.162
Volume of grey matter in Left Subcallosal Cortex	neuroticism	FAST	Inverse-variance weighted	5	−0.062	0.031	0.045
Volume of grey matter in Left Subcallosal Cortex	neuroticism	FAST	MR-Egger	5	−0.305	0.798	0.728
Volume of grey matter in Left Subcallosal Cortex	neuroticism	FAST	Weighted median	5	−0.053	0.023	0.020
Volume of grey matter in Left Subcallosal Cortex	neuroticism	FAST	MRlap	6	−0.065	0.043	0.130
neuroticism	Volume of grey matter in Left Caudate	FAST	Inverse-variance weighted	119	0.162	0.069	0.018

neuroticism	Volume of grey matter in Left Caudate	FAST	MR-Egger	119	0.758	0.296	0.012
neuroticism	Volume of grey matter in Left Caudate	FAST	Weighted median	119	0.175	0.091	0.055
neuroticism	Volume of grey matter in Left Caudate	FAST	MRlap	102	0.264	0.115	0.022
neuroticism	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	FLAIR	Inverse-variance weighted	119	0.205	0.067	0.002
neuroticism	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	FLAIR	MR-Egger	119	0.503	0.295	0.090
neuroticism	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	FLAIR	Weighted median	119	0.107	0.092	0.244
neuroticism	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	FLAIR	MRlap	102	0.303	0.111	0.006
neuroticism	Mean axial diffusivity in external capsule (right)	dMRI	Inverse-variance weighted	119	0.206	0.078	0.008
neuroticism	Mean axial diffusivity in external capsule (right)	dMRI	MR-Egger	119	1.027	0.335	0.003
neuroticism	Mean axial diffusivity in external capsule (right)	dMRI	Weighted median	119	0.068	0.092	0.464
neuroticism	Mean axial diffusivity in external capsule (right)	dMRI	MRlap	102	0.349	0.119	0.003
neuroticism	Mean axial diffusivity in posterior corona radiata (left)	dMRI	MR-Egger	119	0.853	0.313	0.008
neuroticism	Mean axial diffusivity in posterior corona radiata (left)	dMRI	Weighted median	119	0.087	0.094	0.353
neuroticism	Mean axial diffusivity in posterior corona radiata (left)	dMRI	Inverse-variance weighted	119	0.154	0.073	0.034
neuroticism	Mean axial diffusivity in posterior corona radiata (left)	dMRI	MRlap	102	0.288	0.117	0.014
neuroticism	Mean MD in posterior corona radiata (left)	dMRI	Inverse-variance weighted	119	0.154	0.068	0.024
neuroticism	Mean MD in posterior corona radiata (left)	dMRI	MR-Egger	119	0.934	0.290	0.002
neuroticism	Mean MD in posterior corona radiata (left)	dMRI	Weighted median	119	0.180	0.092	0.051
neuroticism	Mean MD in posterior corona radiata (left)	dMRI	MRlap	102	0.241	0.110	0.029
neuroticism	Mean ICVF in posterior thalamic radiation (left)	dMRI	Inverse-variance weighted	119	−0.169	0.069	0.014
neuroticism	Mean ICVF in posterior thalamic radiation (left)	dMRI	MR-Egger	119	−0.992	0.293	0.001
neuroticism	Mean ICVF in posterior thalamic radiation (left)	dMRI	Weighted median	119	−0.186	0.099	0.061
neuroticism	Mean ICVF in posterior thalamic radiation (left)	dMRI	MRlap	102	−0.155	0.115	0.176
neuroticism	Mean ICVF in posterior thalamic radiation (right)	dMRI	MR-Egger	119	−1.050	0.307	0.001
neuroticism	Mean ICVF in posterior thalamic radiation (right)	dMRI	Weighted median	119	−0.124	0.096	0.196
neuroticism	Mean ICVF in posterior thalamic radiation (right)	dMRI	Inverse-variance weighted	119	−0.164	0.072	0.023
neuroticism	Mean ICVF in posterior thalamic radiation (right)	dMRI	MRlap	102	−0.156	0.118	0.184

neuroticism	Mean MD in posterior thalamic radiation (right)	dMRI	Inverse-variance weighted	119	0.162	0.066	0.013
neuroticism	Mean MD in posterior thalamic radiation (right)	dMRI	MR-Egger	119	0.969	0.278	0.001
neuroticism	Mean MD in posterior thalamic radiation (right)	dMRI	Weighted median	119	0.107	0.095	0.258
neuroticism	Mean MD in posterior thalamic radiation (right)	dMRI	MRlap	102	0.197	0.111	0.075
neuroticism	Mean MD in superior corona radiata (right)	dMRI	Inverse-variance weighted	119	0.173	0.071	0.015
neuroticism	Mean MD in superior corona radiata (right)	dMRI	MR-Egger	119	0.859	0.306	0.006
neuroticism	Mean MD in superior corona radiata (right)	dMRI	Weighted median	119	0.120	0.092	0.191
neuroticism	Mean MD in superior corona radiata (right)	dMRI	MRlap	102	0.180	0.104	0.085
neuroticism	Mean ICVF in tapetum (right)	dMRI	Inverse-variance weighted	119	−0.184	0.075	0.014
neuroticism	Mean ICVF in tapetum (right)	dMRI	MR-Egger	119	−0.964	0.322	0.003
neuroticism	Mean ICVF in tapetum (right)	dMRI	Weighted median	119	−0.089	0.095	0.345
neuroticism	Mean ICVF in tapetum (right)	dMRI	MRlap	102	−0.206	0.114	0.072
neuroticism	Volume of Cingulate Gyrus, caudal anterior (left)	Freesurfer DKT	MR-Egger	119	−0.452	0.336	0.181
neuroticism	Volume of Cingulate Gyrus, caudal anterior (left)	Freesurfer DKT	Weighted median	119	−0.117	0.092	0.204
neuroticism	Volume of Cingulate Gyrus, caudal anterior (left)	Freesurfer DKT	Inverse-variance weighted	119	−0.188	0.077	0.014
neuroticism	Volume of Cingulate Gyrus, caudal anterior (left)	Freesurfer DKT	MRlap	102	−0.235	0.109	0.031

N_{snp}, number of single nucleotide polymorphisms used as genetic instruments; SE, standard error. Sensitivity analyses were conducted for all neuroticism-IDP associations that reached nominal significance in the primary inverse-variance weighted analyses.

Appendix 6.6: Sensitivity analyses for Mendelian randomisation

Exposure	Outcome	Model/atlas	p for Q IVW	p for Q MR-Egger	p for Egger intercept	R^2 exposure	R^2 outcome	p for Steiger
Volume of grey matter in Left Caudate	neuroticism	FAST	0.071	0.465	0.035	0.014	<0.001	<0.001
Volume of grey matter in Right Caudate	neuroticism	FAST	0.013	0.023	0.331	0.014	<0.001	<0.001
Volume of grey matter in Left Subcallosal Cortex	neuroticism	FAST	0.004	0.002	0.780	0.010	<0.001	<0.001
neuroticism	Volume of grey matter in Left Caudate	FAST	0.022	0.037	0.041	0.009	0.007	0.152
neuroticism	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	FLAIR	0.080	0.082	0.302	0.009	0.007	0.142
neuroticism	Mean axial diffusivity in external capsule (right)	dMRI	<0.001	<0.001	0.013	0.009	0.009	0.708
neuroticism	Mean axial diffusivity in posterior corona radiata (left)	dMRI	0.006	0.014	0.024	0.009	0.008	0.478
neuroticism	Mean MD in posterior corona radiata (left)	dMRI	0.079	0.167	0.007	0.009	0.007	0.133
neuroticism	Mean ICVF in posterior thalamic radiation (left)	dMRI	0.057	0.138	0.005	0.009	0.007	0.184
neuroticism	Mean ICVF in posterior thalamic radiation (right)	dMRI	0.008	0.031	0.004	0.009	0.008	0.451
neuroticism	Mean MD in posterior thalamic radiation (right)	dMRI	0.208	0.379	0.004	0.009	0.007	0.059
neuroticism	Mean MD in superior corona radiata (right)	dMRI	0.017	0.035	0.023	0.009	0.008	0.347
neuroticism	Mean ICVF in tapetum (right)	dMRI	0.001	0.004	0.014	0.009	0.009	0.820
neuroticism	Volume of Cingulate Gyrus, caudal anterior (left)	Freesurfer DKT	<0.001	<0.001	0.422	0.009	0.009	0.967

IVW, inverse-variance weighted; Q, Cochran's Q-statistic for heterogeneity; R^2, proportion of variance explained; Steiger, Steiger directionality test. Sensitivity analyses were conducted for all neuroticism-IDP associations that reached nominal significance in the primary inverse-variance weighted analyses.

Appendix 6.7: Primary (inverse-variance weighted) analyses for reverse Mendelian randomisation

Exposure	Model/atlas	β	SE	p
Volume of grey matter in Left Caudate	FAST	0.061	0.018	0.001
Volume of grey matter in Right Caudate	FAST	0.057	0.021	0.007
Volume of grey matter in Left Putamen	FAST	0.023	0.017	0.169
Volume of grey matter in Right Putamen	FAST	0.012	0.016	0.428
Volume of grey matter in Left Subcallosal Cortex	FAST	−0.062	0.031	0.045
Volume of grey matter in Left Ventral Striatum	FAST	0.015	0.011	0.152
Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)	FLAIR	0.000	0.015	0.991
Mean axial diffusivity in external capsule (right)	dMRI	−0.006	0.031	0.845
Mean MD in fornix cres+stria terminalis (right)	dMRI	0.040	0.086	0.644
Mean axial diffusivity in posterior corona radiata (left)	dMRI	0.003	0.044	0.944
Mean MD in posterior corona radiata (left)	dMRI	−0.002	0.019	0.913
Mean OD in posterior corona radiata (left)	dMRI	−0.114	0.162	0.482
Mean axial diffusivity in posterior corona radiata (right)	dMRI	0.009	0.059	0.880
Mean FA in posterior thalamic radiation (left)	dMRI	−0.002	0.016	0.917
Mean ICVF in posterior thalamic radiation (left)	dMRI	−0.003	0.011	0.823
Mean radial diffusivity in posterior thalamic radiation (left)	dMRI	−0.007	0.029	0.819
Mean FA in posterior thalamic radiation (right)	dMRI	−0.003	0.018	0.852
Mean ICVF in posterior thalamic radiation (right)	dMRI	−0.002	0.010	0.842
Mean radial diffusivity in posterior thalamic radiation (right)	dMRI	0.001	0.022	0.961
Mean MD in posterior thalamic radiation (right)	dMRI	0.013	0.030	0.666
Mean axial diffusivity in superior corona radiata (right)	dMRI	−0.010	0.029	0.732
Mean MD in superior corona radiata (right)	dMRI	0.017	0.016	0.299
Mean ICVF in tapetum (right)	dMRI	0.005	0.016	0.768
Mean axial diffusivity in tapetum (right)	dMRI	0.013	0.062	0.832
Mean MD in tapetum (right)	dMRI	0.006	0.017	0.716
Volume of grey matter in Left Subcallosal Cortex	FAST	−0.062	0.031	0.045
Area of Calcarine sulcus (left)	Freesurfer a2009s	0.002	0.008	0.788

Volume of WM-hypointensities	Freesurfer ASEG	0.021	0.027	0.441
Area of Parahippocampal Gyrus (left)	Freesurfer DKT	−0.064	0.045	0.157
Area of Pericalcarine cortex (left)	Freesurfer DKT	0.001	0.009	0.946
Volume of Cingulate Gyrus, caudal anterior (left)	Freesurfer DKT	−0.055	0.168	0.742
Area of Parahippocampal Gyrus (left)	Freesurfer desikan pial	−0.075	0.052	0.144
Area of Pericalcarine cortex (left)	Freesurfer desikan pial	0.000	0.010	0.980
Area of Parahippocampal Gyrus (left)	Freesurfer desikan white	−0.072	0.054	0.179
Area of Pericalcarine cortex (left)	Freesurfer desikan white	−0.001	0.009	0.871
Mean thickness of Parahippocampal Gyrus (left)	Freesurfer a2009s	0.190	0.040	<0.001

SE, standard error. Estimates reflect the association between each genetically predicted imaging-derived phenotype and neuroticism, obtained using the inverse-variance weighted method.