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# Association between brain similarity to severe mental illnesses and comorbid cerebral, physical, and cognitive impairments

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## Abstract

Severe mental illnesses (SMIs) are often associated with compromised brain health, physical comorbidities, and cognitive deficits, but it is incompletely understood whether these comorbidities are intrinsic to SMI pathophysiology or secondary to having SMIs. We tested the hypothesis that cerebral, cardiometabolic, and cognitive impairments commonly observed in SMIs can be observed in non-psychiatric individuals with SMI-like brain patterns of deviation as seen on magnetic resonance imaging. 22,883 participants free of common neuropsychiatric conditions from the UK Biobank (age = 63.4 ± 7.5 years, range = 45–82 years, 50.9% female) were split into discovery and replication samples. The regional vulnerability index (RVI) was used to quantify each participant's respective brain similarity to meta-analytical patterns of schizophrenia spectrum



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Declaration of interest

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Code availability

Associated Code are available upon reasonable request from the corresponding author.

Supplementary materials

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disorder, bipolar disorder, and major depressive disorder in gray matter thickness, subcortical gray matter volume, and white matter integrity. Cluster analysis revealed five clusters with distinct RVI profiles. Compared with a cluster with no RVI elevation, a cluster with RVI elevation across all SMIs and brain structures showed significantly higher volume of white matter hyperintensities (Cohen's $d = 0.59$, $p_{FDR} < 10^{-16}$), poorer cardiovascular (Cohen's $d = 0.30$, $p_{FDR} < 10^{-16}$) and metabolic (Cohen's $d = 0.12$, $p_{FDR} = 1.3 \times 10^{-4}$) health, and slower speed of information processing (|Cohen's $d$| = 0.11–0.17, $p_{FDR} = 1.6 \times 10^{-3}$-$4.6 \times 10^{-8}$). This cluster also had significantly higher level of C-reactive protein and alcohol use (Cohen's $d = 0.11$ and 0.28, $p_{FDR} = 4.1 \times 10^{-3}$ and $1.1 \times 10^{-11}$). Three other clusters with respective RVI elevation in gray matter thickness, subcortical gray matter volume, and white matter integrity showed intermediate level of white matter hyperintensities, cardiometabolic health, and alcohol use. Our results suggest that cerebral, physical, and cognitive impairments in SMIs may be partly intrinsic via shared pathophysiological pathways with SMI-related brain anatomical changes.

### Keywords

Severe mental illnesses; regional vulnerability index; white matter hyperintensities; cardiometabolic health; processing speed

## Introduction

Individuals with severe mental illnesses (SMIs), including schizophrenia spectrum disorder (SSD), bipolar disorder (BD), and major depressive disorder (MDD), often suffer from compromised brain health, physical comorbidities, and cognitive deficits (Felker et al., 1996; Firth et al., 2019; Gold and Harvey, 1993; Herrmann et al., 2008; Lee et al., 2012; Pillai et al., 2002; Ribe et al., 2015; Robinson et al., 2006; Sachdev and Brodaty, 1999; Schmaal et al., 2020). Understanding the nature of these comorbidities is important to improve the quality and span of life in SMIs. However, whether these co-occurring impairments are intrinsic to SMI pathophysiology or consequences of having SMIs (e.g., medication use, lifestyle and socioeconomic changes, and inadequate healthcare) is unknown. Here, we posited that comorbidities and reduced functionalities commonly reported in SMIs may be observed in individuals without SMIs but whose brains share similarity with established SMI brain deficit patterns. We tested this hypothesis in a large epidemiological sample ($N$ = 22,883) of non-psychiatric participants.

SMIs have complex genetic and environmental underpinnings and their pathophysiological processes likely act throughout the human body, leading to cerebral, physical, and cognitive impairments in addition to psychiatric symptoms. Researchers have examined the intrinsicality of SMI co-occurring health impairments by studying non-SMI individuals with SMI genetic liability. For example, individuals in the general population with elevated polygenic risk score (PRS) for schizophrenia show increased rates of respiratory and digestive disorders, and deficits in attention, learning, and executive functioning (Liebers et al., 2016; Zhang et al., 2021) suggesting pleiotropic effects of schizophrenia risk genes. However, this approach does not account for co-occurring impairments that are inherent to SMIs through non-genetic pathways, such as epigenetic, environment, gene-by-

environment and more complex interactions that dysregulate vital cellular pathways leading to impairments across the body. To this end, examining the association between SMI co-occurring impairments and phenotypic patterns for SMIs may offer additional insight by capturing these complex effects in SMI etiopathology.

We developed a regional vulnerability index (RVI) to quantify the brain phenotypic liability for three major SMIs (Kochunov et al., 2020b). The RVI capitalizes on outcomes of the large and inclusive meta-analyses by the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium, which demonstrated that regional brain deficit patterns are distinct and replicable neurobiological signatures of SSD, BD, and MDD (Favre et al., 2019; Hibar et al., 2018, 2016; Kelly et al., 2018; Schmaal et al., 2017, 2016; van Erp et al., 2018, 2016; van Velzen et al., 2020). The RVI acts as a phenotypic counterpart of the PRS and translates these patterns in large-scale datasets to the individual level by correlating normalized individual regional brain measures with the illness-specific regional brain effect sizes from the ENIGMA consortium. Like the PRS, the RVI for SSD, BD and MDD can be calculated for any individual and shows specificity for separating patients with SSD, BD and MDD from controls and from each other (Kochunov et al., 2019, 2020a, 2021c). The RVI outperformed any single regional brain measure in explaining symptom severity, illness duration, and cognitive deficits in patients with SMIs (Kochunov et al., 2019, 2020a, 2021c). Sensitivity, specificity, and association with cognition were on par with or exceeded that of PRS in patients (Kochunov et al., 2021b). Moreover, the RVI for SSD explained variance in cognitive performance among healthy controls, suggesting that the RVI may be applicable to the general population and capture the continuum of subclinical and clinical variation (Kochunov et al., 2019).

In this study, we examined the association between SMI-RVI and brain health, physical health, and cognitive performance in 22,883 non-psychiatric participants from the UK Biobank (UKBB). Participants without a history of diagnoses of psychiatric, neurological, and medical disorders with neurological complications were randomly split into discovery and replication samples equivalent in sex, age, and other demographic characteristics. Cluster analysis was used to group participants based on their RVI for SSD, BD, and MDD in cortical gray matter thickness (GMT), subcortical gray matter volume (SV) and white matter (WM) fractional anisotropy. Based on common co-occurring impairments in SMIs (Firth et al., 2019; Gold and Harvey, 1993; Herrmann et al., 2008; Lee et al., 2012; Pillai et al., 2002; Robinson et al., 2006; Sachdev and Brodaty, 1999), we hypothesized that clusters characterized with elevated RVI would show significantly higher volume of white matter hyperintensities, poorer cardiometabolic health, and worse cognitive performance than clusters with no RVI elevation.

## Methods

### Participants

22,883 participants (age = 63.4 ± 7.5 years, range = 45–82 years, 50.9% female, 84.6% white) in the UKBB's neuroimaging data release version 1.7, Application Number 34077 (Jan 2020) were included. We chose participants who were free of common neuropsychiatric conditions, including: 1) psychiatric disorders, 2) neurological conditions (traumatic brain

injury, stroke, meningitis, etc.), and 3) medical disorders often associated with neurological complications (human immunodeficiency virus infection, diabetes, etc.). We also excluded participants who were diagnosed with any type of cancer. Medical history was based on available hospital records, self-report at site visits, online follow-up, and death registries. See Supplementary Table 1 for a complete list of excluded conditions.

The UKBB was approved by the North West Multi-centre Research Ethics Committee. All participants provided written informed consent. We received approval from the UKBB to access and analyze the data.

## Imaging and Behavioral Assessment

Participants underwent the standard UKBB behavioral and neuroimaging protocol (Miller et al., 2016; Sudlow et al., 2015) during the UKBB's imaging visit that started in 2014. Participants were randomly split into discovery ($N$ = 11,442) and replication ($N$ = 11,441) samples. No significant differences were found between the two groups on age, sex, race/ethnicity, college education, household income, and scanning site (all $p$'s >.05). We conducted all the following analyses independently in the discovery and replication samples.

## Subclinical depressive symptoms

To characterize subclinical depressive symptoms in this non-psychiatric sample, participants rated the following over the past two weeks from "not at all" to "nearly every day" (0–3): "felt down, depressed, or hopeless"; "had little interest or pleasure in doing things"; "felt tense, fidgety, or restless"; and "felt tired or had little energy." Depressive symptoms were the sum of the answers, transformed to a 4-point scale to correct for right skewness (0 = 0, 1 = 1–2; 2 = 3–5, 3 = 6 or more).

## Regional vulnerability index (RVI)

Steps for deriving RVI were described in a previous paper (Kochunov et al., 2020a) and implemented in the 'RVIpkg' package (version 0.3.0) (Kochunov et al., 2021a) in R (R Core Team, 2019). Briefly, we used imaging-derived phenotypes generated by the UKBB (Alfaro-Almagro et al., 2018; Miller et al., 2016) (see Supplementary Table 2 for a complete list). Quality control was described in (Alfaro-Almagro et al., 2018) and we did not implement additional quality control steps. The cortical gray matter thickness (GMT) and subcortical gray matter volume (SV) measures were derived from the UKBB's T1 pipeline (Alfaro-Almagro et al., 2018) and generated with the Desikan-Killiany parcellation in FreeSurfer (Desikan et al., 2006; Fischl et al., 2004) and FSL's FIRST tool (Patenaude et al., 2011), respectively. The white matter (WM) fractional anisotropy (FA) measures were derived from the UKBB's dMRI pipeline (Alfaro-Almagro et al., 2018) and generated with FSL's TBSS tool (Smith et al., 2006). We derived 33 GMT, 8 SV, and 24 WM FA measures whose effect sizes for SSD, BD, and MDD were reported by the ENIGMA consortium (Favre et al., 2019; Hibar et al., 2018, 2016; Kelly et al., 2018; Schmaal et al., 2017, 2016; van Erp et al., 2018, 2016; van Velzen et al., 2020). We regressed out the effects of age, sex, intracranial volume, and scanning site from all measures. To quantify an individual's similarity to SSD in the WM (i.e., $RVI_{WM,SSD}$), we correlated the individual's standardized FA scores across WM tracts with the corresponding ENIGMA effect sizes (Cohen's $d$s). Other RVI values

were derived similarly, resulting in 9 RVIs for 3 SMIs (SSD, BD, MDD) × 3 tissue types (GMT, SV, WM). All RVIs were transformed to Fisher's z values to enhance normality. The ENIGMA effect sizes used in this study are included in Supplementary Tables 3–5.

## Brain health

We used the total volume of white matter hyperintensities as an index of overall brain health. Hyperintense white matter regions observed on T2 weighted FLAIR images reflect accumulation of interstitial fluid and are associated with areas of localized demyelination and white matter damage. Total volume of white matter hyperintensities is a sensitive but non-specific index of brain health that has strong associations with cardiovascular risks, trauma, neurodegeneration, and aging (Debette and Markus, 2010; van Dijk et al., 2004). We used the total volume of white matter hyperintensities data from the UKBB (Field ID 25781), which were automatically estimated with T1 and T2_FLAIR data using the Brain Intensity Abnormality Classification Algorithm in FSL (Griffanti et al., 2016).

## Physical health

We evaluated cardiovascular and metabolic health as diseases in these two systems are the most reported physical comorbidities in SMIs (Firth et al., 2019). We measured cardiovascular and metabolic health continuously with the biological health scores (Chadeau-Hyam et al., 2020; Karimi et al., 2019). Biomarkers used in the cardiovascular health score included systolic and diastolic blood pressure (averaged across two consecutive readings, either manual or automated) and pulse rate. Biomarkers used in the metabolic health score included blood glycated haemoglobin, high-density lipoprotein, low-density lipoprotein, and triglycerides (Supplementary Table 6). Computation was previously described in full detail (Chadeau-Hyam et al., 2020; Karimi et al., 2019). Briefly, we binarized each biomarker by assigning 1 to individuals within the extreme quartile of their age and sex group. We then adjusted for medication management by assigning 1 to relevant biomarkers for individuals taking blood pressure, cholesterol lowering, and insulin medication (Supplementary Table 6). We averaged the binarized biomarker values within the respective systems to derive cardiovascular and metabolic health scores. The biological health scores were computed in the entire UKBB sample, rather than the relatively healthy 22,883 participants included in the cluster analysis. Higher scores indicate poorer health. A recent study shows that cardiovascular and metabolic health scores in the UKBB predicted all-cause, cancer, and cardiovascular mortality as well as cancer and cardiovascular disease incidence (Chadeau-Hyam et al., 2020).

Because the UKBB blood assay data at the imaging visit were not available at the time of this study, the metabolic health score was based on the UKBB initial assessment that took place between 2006 and 2010. Interval between the initial assessment and the imaging visit was 8.9 ± 1.7 years, range = 4.3 – 8.9 years.

## Cognitive performance

Participants completed the automated UKBB cognitive test battery on a touchscreen computer (Fawns-Ritchie and Deary, 2020). We included 9 tests in the current study, covering cognitive domains of processing speed, cognitive flexibility, working memory,

visuospatial learning/memory, perceptual reasoning, executive functioning/planning and fluid intelligence. As the UKBB cognitive tests were brief and unsupervised, we performed quality control to enhance validity. Details of the cognitive tests, quality control, and data transformation may be found in Supplementary Table 7.

## Potential risk factors

We additionally measured potential risk factors that might be the sources of differences in non-SMI individuals across RVI clusters (see Supplementary Table 8).

## SMI polygenic risk

To compute participants' polygenic risk scores (PRS) for SMIs, we used the UKBB genetic data gathered using Affymetrix UK BiLEVE Axiom array which genotyped approximately 850,000 variants. Details on quality control and imputation are listed elsewhere (https://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web-1.pdf, https://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/imputation_documentation_May2015-1.pdf). Post-imputation quality control involved filtering single nucleotide polymorphisms (SNPs) based on minor allele frequency (< 0.01), Hardy-Weinberg Equilibrium (< $1{\cdot}10^{-6}$), R-squared (< 0.03), and call rate (< 0.95).

PRS for SSD, BD, and MDD were calculated using PRSice software and the most recent genome-wide association studies (GWAS) summary statistics available from the Psychiatric Genomics Consortium (PGC) (https://www.med.unc.edu/pgc/download-results/). The SSD PRS summary statistics were from a sample of N = 152,805 (38,131 SSD/114,674 controls) including data from 52 PGC-SSD studies of European and East Asian samples (Pantelis et al., 2014). The BD PRS meta-analytical summary statistics (Stahl et al., 2019) were based on a total sample of N = 51,710 (20,352 BD/ 31,358 controls) of European ancestry from 32 cohorts in Europe, North America and Australia, including PGC-BD working groups, the Integrative Psychiatric Research group (iPSYCH) and deCODE genetics. The MDD PRS summary statistics (Howard et al., 2019) were based on N = 143,265 (45,591 MDD / 97,674 controls) participants of European descent from 29 PGC-MDD USA and European sample sites, deCODE genetics, Generation Scotland, Genetic Epidemiology Research on Adult Health and Aging, and iPSYCH datasets. SNPs were clumped according to PRSice (Choi and O'Reilly, 2019), and thresholds for significantly associated SNPs were set at p = 0.05. We limited PRS analyses to white European participants (based on UKBB Field 22006, which combines self-identification and a principal component analysis of the genotypes) in the discovery (N = 9,714) and replication (N =9,652) samples. Regression models controlled for the first 15 genetic principal components and genotyping batch in addition to age, age squared, sex, and scanning site.

## Substance use

Because we have excluded substance use problems per self-report, inpatient record, and death registries (see Supplementary Table 1), cases of significant substance use are likely rare in the current sample. Thus, we focused on continuous measures of use for more common substances, i.e., nicotine, alcohol, and cannabis. We measured nicotine use with the

average number of pack-years smoked by an individual each year over adulthood (UKBB Field 20162), based on participants' answers to the touchscreen questionnaire at the imaging visit. We measured alcohol intake with participants' responses to the UKBB online follow-up (Davis et al., 2020), by multiplying frequency of drinking alcohol (UKBB Field 20414) and amount of alcohol drunk on a typical drinking day (UKBB Field 20403). We measured cannabis use based on the same online follow-up, where participants reported the total times of cannabis use in their lifetime on an ordinal scale (UKBB Field 20453). Details of these variables are listed in Supplementary Table 8.

### Adverse childhood experiences

We considered adverse childhood experiences reported during the UKBB online follow-up. Adverse childhood experiences were measured by items adapted from the Childhood Trauma Screener (Glaesmer et al., 2013). Participants rated the following for when they were growing up: 1) "felt hated by family member"; 2) "physically abused by family"; 3) "felt loved"; 4) "sexually molested", and 5) "someone to take to doctor when needed". Options included "never true", "rarely true", "sometimes true", "often", and "very often true", coded as 0–4. Items 3) and 5) were reverse coded. The five items were then summed, resulting in a total score ranging from 0 to 20. Participants who answered "prefer not to answer" were coded as NAs.

### Physical Activity

We measured participants' level of physical activity based on their answers to the International Physical Activity Questionnaire – Short Form (IPAQ-SF) (Craig et al., 2003). The summed metabolic equivalent task minutes per week for all activity (UKBB Field 22040) is a sum of minutes spent on walking, moderate, and vigorous activity multiplied by their metabolic equivalent task values. Per IPAQ-SF recommendations, analyses were only performed in participants 69 years old and under in the discovery (N = 8,606) and replication (N = 8,710) samples.

### Cluster analysis: Discovery

We performed unsupervised *k*-mean clustering in the discovery sample to derive RVI-based clusters. All RVIs were standardized before entering the clustering. We used the Hartigan-Wong algorithm (Hartigan and Wong, 1979) with 100 initial random sets and 50,000 maximum iterations. The optimal number of clusters was determined by examining the within cluster sum of squares as a function of the number of clusters (i.e., *k*) with the elbow method. Each participant was assigned to the cluster with the closest centroid.

### Cluster differences in brain health, physical health, and cognitive functioning: Discovery

We compared the outcomes of the cluster analysis, which we hereinafter refer to as the "RVI clusters", on demographics, subclinical depressive symptoms, total volume of white matter hyperintensities, cardiovascular and metabolic health scores, and cognitive performance. For continuous variables, we performed linear regression with RVI cluster membership as the predictor, and (except when age was the outcome variable) controlled for age, age squared, and sex due to their effects on the outcome variables and in case of age and sex differences

across RVI clusters. We additionally controlled for scanning site. For binary variables, we performed logistic regression controlling for age, age squared, sex (except when sex was the outcome variable), and scanning site. Statistical inference on the differences between one and the other RVI clusters was based on significance of the beta coefficients, setting the cluster in question as the reference group. We corrected for $m \times C_k^2$ multiple comparisons with false discovery rate (FDR) correction, $q < 0.05$, where $m = 18$ is the total number of measures and $C_k^2$ is the number of pairwise group-comparisons between $k$ clusters. All analyses were conducted in R-4.0.3.

### Cluster differences in potential risk factors: Discovery

To further explore the sources of differences in non-SMI individuals across RVI clusters, we also compared the RVI clusters on potential risk factors, including polygenic risk for SSD, BD, and MDD, C-reactive protein at the initial assessment, tobacco, alcohol, and cannabis use, adverse childhood experiences, and physical activity. FDR correction was used to correct for $n \times C_k^2$ multiple comparisons, where $n = 9$ is the total number of potential risk factors.

### Replication

To evaluate the replicability of the findings in the discovery sample, we first used the same procedure to cluster participants in the replication sample and examined if similar clusters were extracted. We then clustered the replication sample again by applying the clustering model in the discovery sample, using the 'flexclust' package (Leisch, 2006) in R. High agreement in clustering between these two approaches would indicate replicability of the clusters. Provided that the clustering results were replicable, we repeated all between-cluster comparisons in the replication sample using clustering according to the discovery sample.

## Results

### Discovery sample

**Cluster Analysis Results—**The distributions of the 9 SMI-RVI are shown in Supplementary Fig. 1 and their correlation matrix is shown in Supplementary Table 9. Correlation between RVIs tended to be higher across SMI within the same tissue type, than across tissue types for the same SMI. For example, correlation between RVI for SSD and MDD was 0.23, 0.91, and 0.60 (all $p < 0.001$) in GMT, SV, and WM respectively. On the other hand, correlations between RVI for MDD across GMT, SV, and WM were no larger than 0.03.

We used visual inspection of the scree plot to choose k=5 and identified five groups of individuals (Clusters A-E) with cluster analysis in the discovery sample (Fig. 1, Supplementary Fig. 2a). Cluster A consisted of $N = 2,133$ (1,052M/1,081F) participants with elevated RVI for all three SMIs and all three tissue types; Cluster B consisted of $N = 2,301$ (1,067M/1,234F) participants with elevated RVI in GMT for all three SMIs; Cluster C consisted of $N = 2,437$ (1,177M/1,260F) participants with elevated RVI in SV for all three SMIs; Cluster D consisted of $N = 2,275$ (1,077M/1,198F) participants with elevated

RVI in WM for all three SMIs; and Cluster E consisted of $N = 2,296$ (1,205M/1,091F) participants with low RVI across all SMIs and tissue types. The five clusters were robust to outliers (see Supplementary results). Supplementary Table 10 summarizes the demographic characteristics of Clusters A-E in the discovery sample.

Below we first describe cluster differences using Cluster E (no RVI elevation) as the reference cluster, comparing it to the cluster with the most RVI elevation (Cluster A) and then clusters with tissue-specific RVI elevation (Clusters B, C and D). Results of these pairwise comparisons are listed in Supplementary Tables 11 (for brain health, physical health, and cognitive functioning) and 12 (for potential risk factors). We then describe pairwise comparisons among Clusters A-D, listed in Supplementary Tables 13 and 14. Table 1 provides a summary of cluster differences.

## Clusters A versus E

Participants in Clusters A (overall RVI elevation) were modestly and significantly younger than participants in Cluster E (no RVI elevation) (Cohen's $d = -0.09$, $p_{FDR} = 2.8 \times 10^{-3}$, Fig. 2, Supplementary Table 11). Compared with Cluster E, participants in Cluster A were significantly less likely to be male (49.3% versus 52.5%, $p_{FDR} = 3.3 \times 10^{-2}$) and lived in more materially deprived areas based on the Townsend deprivation index (Cohen's $d = 0.09$, $p_{FDR} = 2.8 \times 10^{-3}$). They did not differ significantly in college education, household income, and subclinical depressive symptoms (all $p_{FDR} > 0.05$).

Consistent with our hypothesis, participants in Cluster A had significantly higher volume of white matter hyperintensities (Cohen's $d = 0.59$, $p_{FDR} < 10^{-16}$) and significantly elevated cardiovascular and metabolic health scores (Cardiovascular: Cohen's $d = 0.30$, $p_{FDR} < 10^{-16}$; Metabolic: Cohen's $d = 0.12$, $p_{FDR} = 9.4 \times 10^{-4}$) than participants in Cluster E. Participants in Cluster A also performed significantly worse than participants in Cluster E on all three tests of information processing speed: Reaction Time (Cohen's $d = 0.17$, $p_{FDR} = 4.6 \times 10^{-8}$), Trail 1 (Cohen's $d = 0.14$, $p_{FDR} = 1.6 \times 10^{-3}$) and Symbol Digit substitution (Cohen's $d = -0.11$, $p_{FDR} = 1.8 \times 10^{-3}$). No significant differences were found in other cognitive domains.

Among the potential risk factors (Fig. 3, Supplementary Table 12), Cluster A had significantly higher level of C-reactive protein at the initial assessment (Cohen's $d = 0.11$, $p_{FDR} = 4.1 \times 10^{-3}$) than Cluster E, as well as significantly higher alcohol intake (Cohen's $d = 0.28$, $p_{FDR} = 1.1 \times 10^{-11}$) and total times of cannabis use in life (Cohen's $d = 0.12$, $p_{FDR} = 1.3 \times 10^{-2}$). No significant differences were found in PRS for SSD, BD, and MDD, average packyears, adverse childhood experiences, or physical activity.

## Clusters B, C, and D versus E

Compared with Cluster E (no RVI elevation), participants in Clusters B (elevation in GMT), C (elevation in SV), and D (elevation in WM) were significantly younger (Cohen's $d = -0.20$, $-0.21$, and $-0.14$, $p_{FDR} = 9.5 \times 10^{-11}$, $4.5 \times 10^{-12}$, and $2.0 \times 10^{-5}$) and significantly less likely to be male (46.4%, 48.3%, and 47.3% versus 52.5%, $p_{FDR} = 2.7 \times 10^{-4}$, $1.9 \times 10^{-2}$, and $3.2 \times 10^{-3}$, Supplementary Table 11). No significant differences were found in

college education, household income, Townsend deprivation index, or subclinical depressive symptoms (all $p_{FDR} > 0.05$).

Like Cluster A, participants in Clusters B, C, and D also had significantly higher volume of white matter hyperintensities (Cohen's $d = 0.15$, 0.29, and 0.41, $p_{FDR} = 4.2 \times 10^{-6}$, $4.1 \times 10^{-21}$, and $2.7 \times 10^{-42}$) and significantly elevated Cardiovascular health score (Cohen's $d = 0.16$, 0.12, and 0.24, $p_{FDR} = 6.4 \times 10^{-7}$, $4.2 \times 10^{-4}$, and $1.9 \times 10^{-14}$) than participants in Cluster E. Participants in Clusters B and D also had significantly elevated Metabolic health score (Cohen's $d = 0.09$ and 0.09, $p_{FDR} = 1.2 \times 10^{-2}$ and $8.6 \times 10^{-3}$) compared with participants in Cluster E. In terms of cognitive performance, participants in Clusters B and C performed significantly worse than Cluster E in Reaction Time (Cohen's $d = 0.12$ and 0.09, $p_{FDR} = 5.3 \times 10^{-4}$ and $8.8 \times 10^{-3}$). Somewhat unexpectedly, participants in Cluster D performed significantly better in fluid intelligence than those in Cluster E (Cohen's $d = 0.08$, $p_{FDR} = 3.3 \times 10^{-2}$). In terms of potential risk factors, participants in Clusters B-D had significantly higher alcohol intake than Cluster E (Cohen's $d = 0.14$, 0.13, and 0.15, $p_{FDR} = 3.3 \times 10^{-3}$, $4.3 \times 10^{-3}$, and $2.6 \times 10^{-3}$, Supplementary Table 12).

## Clusters A-D

Among the four clusters with RVI elevation, Cluster A tended to be the most impaired, in measures including total volume of white matter hyperintensities, cardiovascular and metabolic health scores, and processing speed tests (|Cohen's $d$| = 0.08–0.44, $p_{FDR} < 0.05$, Supplementary Table 13). Moreover, participants in Cluster A had significantly more alcohol intake than participants in Clusters B-D (Cohen's $d = 0.14$, 0.15, and 0.14, $p_{FDR} = 3.3 \times 10^{-3}$, $2.0 \times 10^{-3}$, and $4.1 \times 10^{-3}$), and significantly higher average packyears than participants in Cluster C (Cohen's $d = 0.21$, $p_{FDR} = 9.3 \times 10^{-3}$, Supplementary Table 14). In no measures did Cluster A show significantly less impairment or risk than Clusters B-D.

Clusters B-D were comparable on most health measures and risk factors. Unsurprisingly, Cluster D, characterized by RVI elevation in WM, showed significantly higher volume of white matter hyperintensities than Clusters B and C (Cohen's $d = 0.26$ and 0.13, $p_{FDR} = 1.7 \times 10^{-17}$ and $9.5 \times 10^{-5}$).

## Replication sample

Clusters extracted from the replication sample resembled those in the discovery sample (Supplementary Fig.s 2b and 3). For 94.2% of participants in the replication sample, this clustering agreed with clustering based on the discovery sample. No clustering involved misassignment between the two most extreme clusters (i.e., being assigned to Cluster A with one approach and Cluster E with the other).

Cluster differences in demographics, subclinical depressive symptoms, health, cognition, and potential risk factors largely replicated findings in the discovery sample (see Table 1 and Supplementary Results). The pattern of worse health in Cluster A than Cluster E, intermediated by Clusters B through D, were replicated for total volume of white matter hyperintensities, cardiovascular and metabolic health scores, and processing speed tests.

## Discussion

We used an unbiased, data-driven, discovery-replication design to examine the association between similarity to severe mental illness (SMI) brain patterns and commonly observed cerebral, physical, and cognitive impairments in SMIs in a large sample of non-psychiatric individuals. A novel measure, the regional vulnerability index (RVI), was used to quantify the similarity of individual brain patterns in cortical gray matter thickness (GMT), subcortical gray matter volume (SV) and white matter (WM) fractional anisotropy to the patterns reported in these illnesses by meta-analyses. Cluster analysis identified five groups of individuals distinct by RVI patterns. Individuals in Cluster A, with uniformly elevated RVI, had significantly higher volume of white matter hyperintensities, poorer cardiometabolic health, and lower processing speed than individuals in Cluster E with no RVI elevation. Exploratory analysis on potential risk factors showed that participants in Cluster A had significantly higher level of C-reactive protein and alcohol and cannabis use than participants in Cluster E. Participants in Clusters B, C, and D, characterized by respective RVI elevation in GMT, SV, and WM, were intermediate between Clusters A and E in total volume of white matter hyperintensities, cardiometabolic health, and alcohol use. A replication sample confirmed the replicability of most findings. Our findings suggest that commonly observed co-occurring impairments in SMIs may partly arise from shared pathophysiological pathways.

Large-scale neuroimaging studies in SMIs performed by the ENIGMA consortium have led to the discovery that regional brain deficit patterns associated with SMIs are persistent, stable, replicable across ethnically diverse populations, and associated with clinical and cognitive features in SMI patients (Kochunov et al., 2020a). The RVI was developed as an analog of PRS to translate these patterns to the individual level and has demonstrated sensitivity and specificity for illnesses, association with cognitive deficits in patients, and ability to predict treatment resistance (Kochunov et al., 2021c, 2020b, 2019). Higher SMI PRS is associated with poorer cognition and mental health in non-psychiatric populations (Liebers et al., 2016; Shen et al., 2020). Likewise, higher SSD-RVI was associated with poorer processing speed and working memory in controls (Kochunov et al., 2019), suggesting that the RVI may be applicable in individuals without psychiatric symptoms. Here, we used an unbiased data-driven approach to derive five clusters of individuals in a sample of non-psychiatric individuals based on their RVI for three major SMIs. The five clusters showed few replicable differences in socioeconomic status and subclinical depressive symptoms. After controlling for age, age squared, sex, and scanning site, differences in cerebral, physical, and cognitive impairments as well as inflammation and substance use were significant and in the same directions as observed in SMIs. Our findings support health and functional implications as well as links to risk factors of SMI-RVI in the general population, possibly through shared pathophysiological pathways that affect the brain in similar ways.

We found that Cluster A, characterized by brain similarity to SMIs in all three tissue types, had significantly poorer brain health as indicated by increased volume of white matter hyperintensities. Volume of white matter hyperintensities is predictive of cognitive decline, dementia, stroke, and death (Brickman et al., 2008; Debette and Markus, 2010).

Increased volume of white matter hyperintensities is well-documented in SMIs (Herrmann et al., 2008; Lyoo et al., 2002; Pillai et al., 2002; Sachdev and Brodaty, 1999) and has been found to predict the development of depression (Godin et al., 2008). Mechanisms that are hypothesized to underlie increased volume of white matter hyperintensities in SMIs include cerebrovascular pathology, *in utero* insult, and mitochondrial dysfunction (Hulshoff Pol et al., 2000; Kato and Kato, 2000; Moore et al., 2001; Thomas et al., 2002). Similar mechanisms may underlie elevated SMI-RVI in individuals free of SMIs.

The findings of poorer brain health in Cluster A were corroborated by evidence of poorer cardiovascular and metabolic health. Cardiometabolic conditions, such as heart diseases and diabetes, are among the most common comorbidities and leading causes of years of potential life lost in SMIs (Colton and Manderscheid, 2006). These comorbidities have been linked to known side effects of psychiatric medication (Alvares et al., 2016; Kahn et al., 2008; Mitchell et al., 2013) as well as limited healthcare and SMI-related changes in health habits (De Hert et al., 2009; Pratt et al., 1996). On the other hand, findings on shared genetic etiology between SMIs and cardiometabolic risks have been mixed, ranging from positive, null, to negative relationships (Bahrami et al., 2020; Fürtjes et al., 2021; Rødevand et al., 2021; So et al., 2019; Wassertheil-Smoller et al., 2018; Zhang et al., 2021; Zheutlin et al., 2019). Particularly, several studies suggest an inverse relationship between the PRS for SSD and body mass index, high-density lipoprotein, and diabetes mellitus (Bahrami et al., 2020; So et al., 2019; Zhang et al., 2021; Zheutlin et al., 2019), which may be taken as indication that their positive relationship on the phenotypic level is consequent to having SSD. Our findings suggest another possibility, that metabolic abnormalities may be related to SSD through alternative (e.g., epigenetic, environmental) mechanisms, which may have similarly affected non-SSD individuals with similarity to SSD in brain structural patterns.

Poorer cognitive performance in Cluster A further supports poorer brain health in people with SMI-like brain patterns. Specifically, participants in Cluster A performed significantly worse than those in Cluster E on tests probing information processing speed. Impaired processing speed is among the most robust cognitive deficits in all three SMIs irrespective of medication status, symptom severity, and illness chronicity (Dickinson et al., 2007; Dixon et al., 2004; Lee et al., 2012; Robinson et al., 2006). It is also among the cognitive measurements most sensitive to normal and neurodegenerative brain aging and associated with changes in cerebral white matter such as increases in hyperintense white matter volume (Kochunov et al., 2017; Twamley et al., 2006). Our findings suggest that cognitive slowing may be intrinsic to the brain anatomical changes associated with SMI development. On the other hand, other cognitive domains (e.g., working memory and executive functioning) did not show reproducible patterns of impairment in participants with RVI elevation in this sample, potentially suggesting that these functions were impaired in SMIs due to more direct SMI related etiologies or changes.

Clusters B, C, and D, with respective similarity to SMIs in GMT, SV, and WM, were intermediate between Clusters A and E in brain and cardiovascular health, suggesting a graded effect of RVI elevation. Additionally, exposure to alcohol in these clusters was also intermediate. On the other hand, cognitive abilities appeared largely comparable to Cluster E, suggesting that cognitive abilities may be spared when RVI elevation is restricted to

specific tissues. Lastly, we failed to find reproducible differences among Clusters B-D in measures other than total volume of white matter hyperintensities and cardiovascular health score. Future studies with more comprehensive characterization of health and functioning may reveal differential implications of brain similarity to SMIs in specific brain tissues.

Perhaps counterintuitively, participants in Cluster E, characterized by no RVI elevation, were significantly older than participants in Clusters A-D. A median split (at 64 years old) revealed that Cluster E were overrepresented in older as opposed to younger participants (Supplementary Table 20). One explanation is that individuals with RVI elevation may be more likely to develop physical, neurological, and psychiatric conditions as they age and thus less included in our non-neuropsychiatric sample. This also partly explained why participants in Cluster E consisted of significantly more males than Clusters B-D, as the older half of the sample contained more males than the younger half (51.5% vs. 45.7%). Future studies that include the full, rather than non-neuropsychiatric UKBB sample may help confirm this explanation. Nonetheless, the effects of age, age squared, and sex were removed from all cluster comparisons to account for age and sex differences across clusters.

The origin of SMI-like brain patterns in people not afflicted with these illnesses is open for speculation. Participants across the clusters did not show replicable differences in subclinical depressive symptoms, suggesting similar level of subclinical or undiagnosed/unreported psychopathology. Moreover, their age range was three-to-four decades older than the typical age of onset for SSD and BD, suggesting that impending onset is unlikely (Leboyer et al., 2005; Loranger, 1984). More plausibly, we postulate that elevated RVI in non-psychiatric individuals may reflect the accumulation of deleterious factors that are shared between SMI and co-occurring impairments including accelerated brain aging, cardiometabolic impairments, and cognitive decline. In other words, our results suggest that the brain deficit patterns in SMI reported by the ENIGMA consortium may be partly driven by co-occurring conditions or poorer general health in people with mental illnesses. Moreover, our explorative analysis suggests that higher inflammation and substance use may be among mechanisms for RVI elevation. Longitudinal data spanning a long period of time are needed to elucidate whether these conditions lead to elevated RVI.

This study has several limitations. First, the UKBB sample consisted predominantly of healthy white European volunteers in mid-to-late life (Fry et al., 2017), and it is unclear if our findings will generalize to groups with different demographic profiles. Second, the RVI only characterizes the similarity of an individual brain to SMIs in relative patterns (i.e., correlation) and ignores information in absolute regional brain deviations. Third, interpretations of our findings are limited by the cross-sectional design, and little can be inferred about the complex causal relationship between RVI and the health indices. Fourth, the cluster differences we report are on a group average level and most effect sizes fell within the “small” range (Cohen’s $d < 0.2$). Our results should not be taken to mean that an individual with elevated SMI-RVI will have impaired brain health, cardiometabolic health, or cognitive functioning. Last, we used the metabolic health score to maintain consistency with previous research, but it may not reflect other important indices such as anthropometric measures for metabolic health.

To conclude, we showed that brain similarity to SMIs is associated with poorer brain health, cardiometabolic health, and processing speed in a large sample of non-psychiatric individuals, suggesting that comorbid abnormalities in these domains are intrinsic to the brain structural changes associated with SMIs rather than secondary to having SMIs.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data availability

Raw data are available through the UK Biobank. Data supporting the findings of this study are available from the corresponding author upon proof of approved access to the UK Biobank database.

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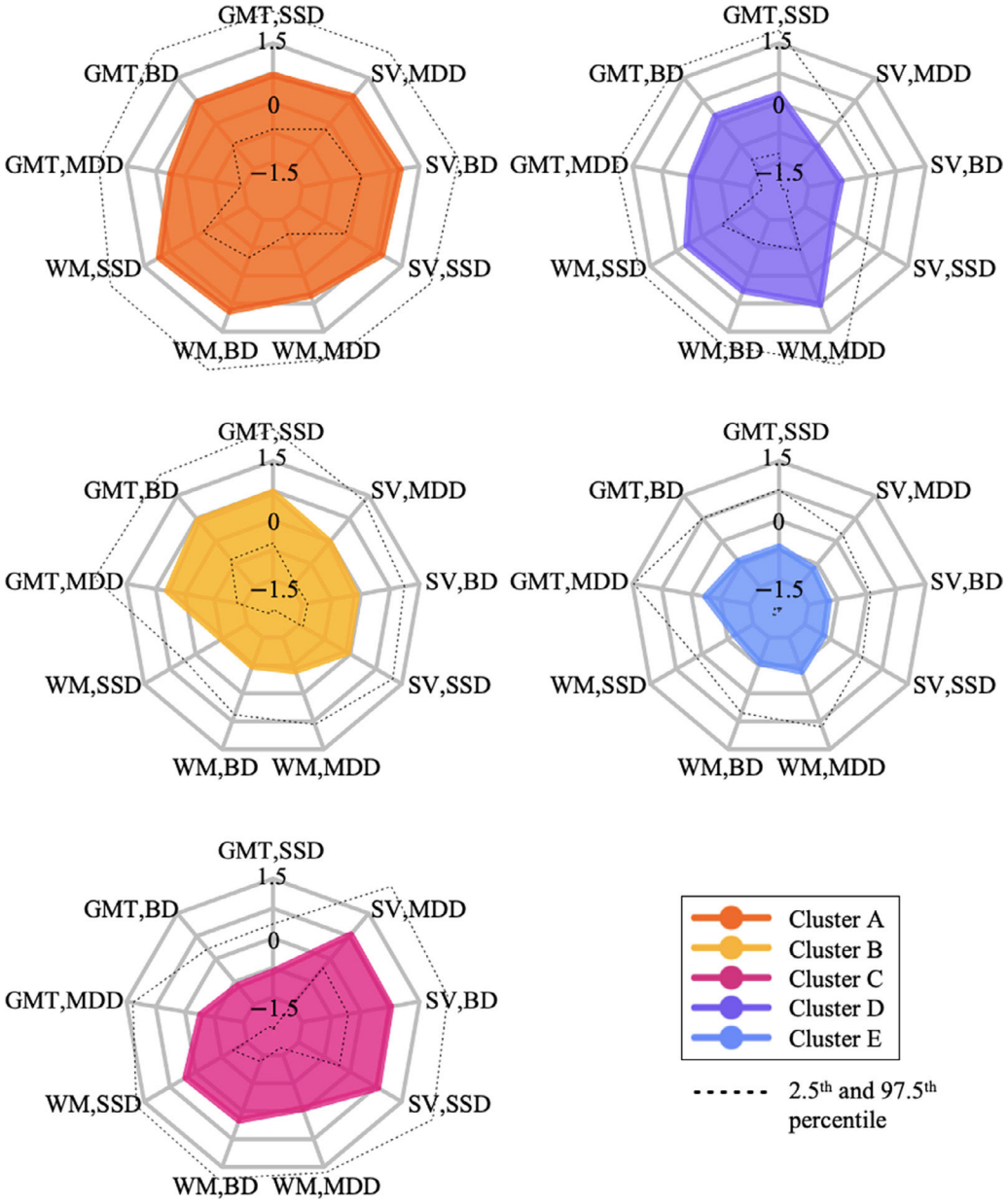


**Fig. 1.**

Centroids of the RVI clusters in the discovery sample. Each radar plot shows the centroid (i.e., mean) and the 2.5$^{th}$ and 97.5$^{th}$ percentile of all individuals within a RVI cluster. Axes of the radar plots are standardized RVI values. RVI: regional vulnerability index. GMT: cortical gray matter thickness. SV: subcortical gray matter volume. WM: white matter. SSD: schizophrenia spectrum disorder. BD: bipolar disorder. MDD: major depressive disorder.

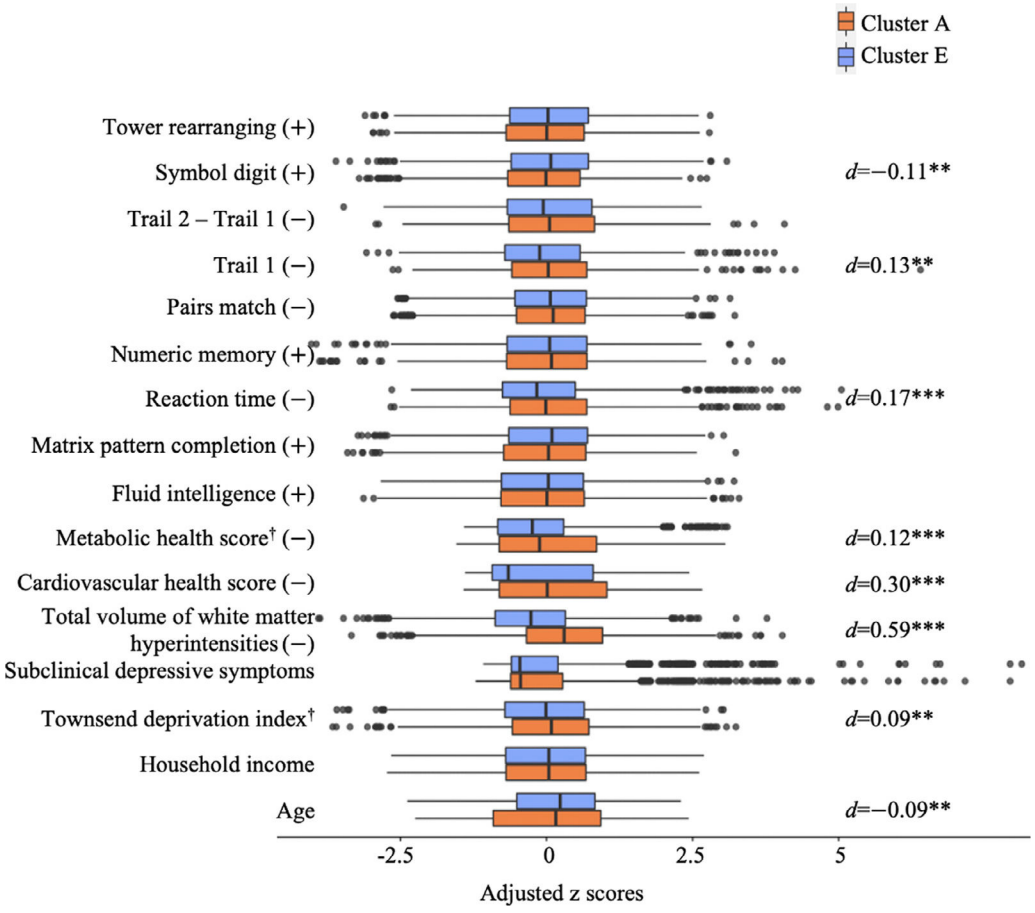


**Fig. 2.**

Differences between Clusters A and E in the discovery sample. Cluster A: RVI elevation across GMT, SV, and WM. Cluster E: no RVI elevation (reference cluster). X axis shows z scores after adjusting for age, age squared, sex, and scanning site (except for the variable Age which was not adjusted). *d*: Cohen's *d*. (+): higher score corresponds to better health/performance. (−): lower score corresponds to better health/performance. †: measured at initial assessment. Statistical inferences and effect size estimates were based on linear models comparing the five RVI clusters. *p < .05, **p < .01, ***p < .001. All p values were FDR corrected. FDR: false discovery rate. Clusters B-D are not plotted for simplicity.

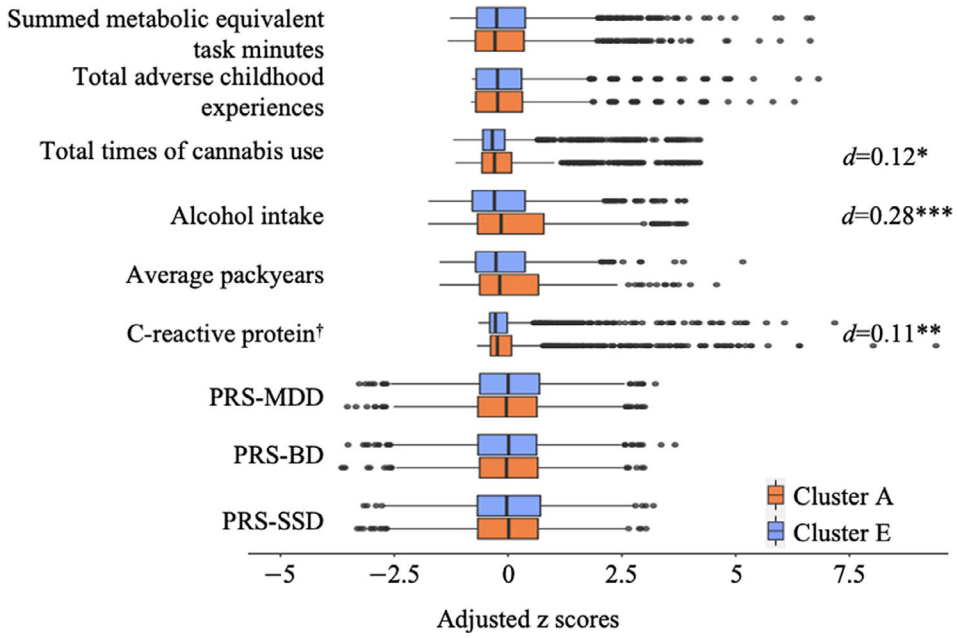


**Fig. 3.**

Differences in common risk factors between Clusters A and E in the discovery sample. X axis shows z scores after adjusting for age, age squared, sex, and scanning site. Z scores for PRS additionally adjusted for the first 15 genetic principal components and genotyping batch. PRS: polygenic risk score. SSD: schizophrenia spectrum disorder. BD: bipolar disorder. MDD: major depressive disorder. ACEs: adverse childhood experiences. *d*: Cohen's *d*. Statistical inferences and effect size estimates were based on linear models comparing the five RVI clusters. †: measured at initial assessment. *p < .05, **p < .01, ***p < .001. All p values were FDR corrected. Clusters B-D are not plotted for simplicity.

**Table 1**

Patterns of cluster differences in the discovery and replication groups

| | Discovery Group | Replication Group |
|---|---|---|
| Age | [A, B, C, D] < E; [B, C] < A; C < D | [A, B, C, D] < E; C < [A, D] |
| Sex (% male) | [A, B, C, D] < E | [B, C, D] < E |
| College (% completed) | B < C | n.s. |
| Household income | n.s. | [A, B] < [C, D, E] |
| Townsend deprivation index† | A > [C, E] | A > C |
| Subclinical depressive symptoms | n.s. | A > E |
| Total volume of white matter hyperintensities (−) | A > D > C > B > E | A > D > [C, B] > E |
| Cardiovascular health score (−) | [A, D] > [B, C] > E | A > D > [B, C, E] |
| Metabolic health score†(−) | [A, B, D] > [C, E] | [A, C, D] > E |
| Fluid intelligence (+) | [A, B, E] < D; B < C | A < D |
| Matrix pattern completion (+) | A < [C, D] | A < D |
| Reaction time (−) | A > C > E; A > D; B > E | A > [B, C, D, E] |
| Numeric memory (+) | n.s. | A < D |
| Pairs match (−) | n.s. | n.s. |
| Trail 1 (−) | A > [D, E] | A > E |
| Trail 2 – Trail 1 (−) | A > D | n.s. |
| Symbol digit (+) | A < [D, E] | A < [B, C, D, E] |
| Tower rearranging (+) | n.s. | n.s. |

Notes: Cluster A: RVI elevation across GMT, SV, and WM. Cluster B: RVI elevation in GMT. Cluster C: RVI elevation in SV. Cluster D: RVI elevation in WM. Cluster E: no RVI elevation. All comparisons are based on FDR corrected p values significant at 0.05 level. FDR: false discovery rate

+higher score corresponds to better health/performance

−lower score corresponds to better health/performance

†measured at initial assessment. n.s.: not significant

*Neuroimage*. Author manuscript; available in PMC 2023 February 09.