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RESEARCH ARTICLE

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Brain deficit patterns of metabolic illnesses overlap with those for major depressive disorder: A new metric of brain metabolic disease

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Abstract

Metabolic illnesses (MET) are detrimental to brain integrity and are common comorbidities in patients with mental illnesses, including major depressive disorder (MDD). We quantified effects of MET on standard regional brain morphometric measures from 3D brain MRI as well as diffusion MRI in a large sample of UK BioBank participants. The pattern of regional effect sizes of MET in non-psychiatric UKBB subjects was significantly correlated with the spatial profile of regional effects reported by the largest meta-analyses in MDD but not in bipolar disorder, schizophrenia or Alzheimer's disease. We used a regional vulnerability index (RVI) for MET (RVI-MET) to measure individual's brain similarity to the expected patterns in MET in the UK Biobank sample. Subjects with MET showed a higher effect size for RVI-MET than for any of the individual brain measures. We replicated elevation of RVI-MET in a sample of MDD participants with MET versus non-MET. RVI-MET scores were significantly correlated with the volume of white matter hyperintensities, a neurological consequence of MET and age, in both groups. Higher RVI-MET in both samples was associated with obesity, tobacco smoking and frequent alcohol use but was unrelated to antidepressant use. In summary, MET effects on the brain were regionally specific and individual similarity to the pattern was more strongly associated with MET than any regional brain structural metric. Effects of MET overlapped with the reported

brain differences in MDD, likely due to higher incidence of MET, smoking and alcohol use in subjects with MDD.

KEYWORDS
brain imaging, major depressive disorder, metabolic disorders, regional vulnerability index

1 | INTRODUCTION

Chronic metabolic illnesses (MET), including hypertension, diabetes, and hyperlipidemia, are common but often overlooked comorbidities in individuals with mental illness, especially those with major depressive disorder (MDD) (Clarke et al., 2017; Papakostas et al., 2005; Wu et al., 2012). Patients with MDD have a two- to six-fold higher risk of having MET than non-psychiatric controls and individuals with other mental illnesses (Maaroganye et al., 2013; Mitchell et al., 2013; Toalson et al., 2004). The high co-occurrence of MET in subjects with mental illness was hypothesized to be due to sharing of genetic vulnerabilities and environmental risks, higher smoking and alcohol consumption, and side-effects of psychiatric medications (Andersohn et al., 2009; Hennekens et al., 2005; Kirkpatrick et al., 2008; Kochunov et al., 2009, 2010; Kochunov, Glahn, Lancaster, et al., 2011). MET have strongly deleterious effects on brain integrity including accelerated brain aging, lower cognitive scores, formation of hyperintensive white matter necrotic regions and higher rates of dementia (Angoff et al., 2022; Du et al., 2022; Marseglia et al., 2021). Neuroimaging studies in psychiatric illnesses may not fully account for higher rates of MET in patients versus controls, and some of the brain effects reported in mental disorders may be due to higher rates of MET comorbidity in people with mental illnesses (Ferri et al., 2021; Ryan et al., 2022; Zheng et al., 2022).

MET are common and chronic disorders that typically emerge in the third to fourth decades of life, although some reports suggest adolescence as the age of onset of pathological processes leading to MET (Buterbaugh, 2021; Suvila et al., 2021). MET-related deficits are observed throughout the brain, including lower cortical thickness and subcortical volumes and lower integrity of cerebral white matter and gliotic changes with detrimental effects on cognition (Hannesdottir et al., 2009; Liang et al., 2019; Osama et al., 2020). Neuroimaging and genetic studies report many similarities between MET and neuropsychiatric illnesses including lower cerebral integrity and shared genetic risk loci and environmental risk factors (Kochunov et al., 2009, 2010; Kochunov, Glahn, Lancaster, et al., 2011; Ryan et al., 2022). For instance, individuals with diabetes tend to have impaired white matter connections between the hippocampus and frontal lobes, as well as reduced volumes of gray matter and subcortical structures and impaired cognitive performance in tests of attention and executive function, information-processing speed, and memory (Jongen et al., 2007; Manschot et al., 2006; van Bussel et al., 2016; van Harten et al., 2007). Diabetes is also associated with altered rates of cerebral glucose metabolism leading to premature aging of the brain (Cohen et al., 2011; Reiman et al., 2010) and cognitive deficits (Pannacciulli et al., 2006; Patriarca et al., 2017; Smucny et al., 2012; Xu et al., 2011). Hypertension is also associated with reduced integrity of white matter microstructure, increased volumes of white matter hyperintensities (WMH) and reduced performance on cognitive tests, in otherwise cognitively healthy participants (Haight et al., 2018; Liang et al., 2022; Scott et al., 2015).

The higher rates of MET in patients with mental illnesses raise the concern of potential side effects of long-term use for psychiatric medications. Antipsychotics in particular, may increase the risk of developing metabolic syndrome, obesity, hypertension, and diabetes (Khandker et al., 2022; Ouyang et al., 2022). Specifically, people taking second generation antipsychotics are at increased risk for developing diabetes compared to patients taking first generation antipsychotics (Nishtala & Chyou, 2017). Antipsychotic use in adolescent and young adult patients with schizophrenia has been associated with higher overall MET rates (Man et al., 2022). Similarly, a study by Andersohn et al. reported that long term antidepressant use was associated with higher rates of diabetes (Andersohn et al., 2009). The dose and duration of antidepressant use was significantly correlated with total cholesterol in adults (Noordam et al., 2015), including both LDL and HDL levels (Olguner Eker et al., 2017). Another study found a positive correlations between the cumulative dose of antidepressants and hypertension (Crookes et al., 2018). Conversely, the combined use of antidepressants and antihypertensive drugs resulted in better control over blood pressure in a 24-week trials versus taking only antihypertensive drugs, especially in older populations (Diminic-Lisica et al., 2014; Fu et al., 2015). Overall, there is strong evidence that long-term use of antipsychotics is associated with risks for MET, but the links between the use of antidepressants and MET are more tenuous.

Neuroimaging and genetic studies of psychiatric illness may not fully exclude or account for higher MET rates in cases versus controls. Studies by the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium and other collaborations use large, multi-site, standardized data to report regional effect size patterns of brain deficits in patients with neuropsychiatric illnesses (Kelly et al., 2018; Renteria et al., 2017; Schmaal et al., 2017; van Erp et al., 2016, 2018; van Velzen et al., 2020). These large-scale studies have reported robust findings of abnormal white matter microstrucuture, along with lower cortical thickness and subcortical volumes in MDD, bipolar disorder (BD) or schizophrenia spectrum disorder (SSD) (Kochunov, Hong, et al., 2020), and other illnesses. The effects of mental illness on brain integrity, as mapped using neuroimaging, are not regionally uniform; instead, some structures such as the hippocampus and the white matter association tracts show deleterious

effects of the illness, while many others do not (Schmaal et al., 2016; Schmaal et al., 2017; van Velzen et al., 2020). Regional brain deficit patterns show both similarities and unique features when compared across mental illnesses (Kochunov, Hong, et al., 2020). Recently, we showed that an individual brain's similarity to the overall representative pattern of a specific brain illness may serve as a phenotype more sensitive and specific in predicting disease severity than the disease effect on any individual brain structures (Kochunov et al., 2022). Here we develop an individual similarity index for MET and use it to study whether effects of MET have contributed to imaging results in mental illnesses.

We developed a regional vulnerability index (RVI) as a tool to quantify the similarity between brain features of an individual and the pattern of a specific mental illness reported by ENIGMA. Prior studies found that higher RVI for SSD was correlated with poorer treatment response and greater negative symptoms in patients, as well as decreased processing speed in controls (Kochunov, Huang, et al., 2019). Alzheimer's disease (AD) RVI measures also revealed similarities between brain abnormalities in SSD and AD (Kochunov, Zavaliangos-Petropulu, et al., 2021), but this index was not significantly elevated in patients with MDD or BD and vice versa (Kochunov et al., 2022; Kochunov, Ryan, et al., 2021) suggesting RVI also offers some disease specificity. The direct testing of RVI versus a similar index derived from genetic effect sizes—the polygenic risk score (PRS)—showed that RVI had greater specificity and stronger effect sizes for case–control differences than the PRS, further supporting the validity of the RVI construct (Kochunov et al., 2022).

We developed an RVI for MET (RVI-MET) to further research similar and distinct brain deficits between MET and MDD. We hypothesized that the effects of MET may contribute to the regional neuroimaging patterns of patient-control differences in mental disorders; we also tested the confounding effects of psychiatric medications and substance use that are higher in people with mental illness. We used a large and representative sample of participants collected from the UKBB to first measure the effects of MET on average and regional brain measures. We then used the anatomical profile of MET deficit patterns to derive an RVI-MET score for each individual, and to compare the group difference effect sizes for the RVI versus effects of MET on individual brain structures. We then used an independent group of UKBB subjects who were diagnosed with MDD as a replication sample. We replicated the effects of MET on RVI and examined the effects of MDD diagnosis, medication, substance use and depression scores on RVI-MET.

2 | METHODS

2.1 | Participants

We analyzed data for N = 37,047 (53% Female; age = 63.7 ± 7.5 years) participants in the UK BioBank (UKBB) study from before 2022 (Figure 1) for whom neuroimaging phenotypes were available. We excluded the N = 9510 (48% female, age = 65.1 ± 7.5 years) participants, considered the neuropsychiatric group, who had an ICD10 diagnosis of BD, SSD, AD, Parkinson's disease, stroke, head injury, anxiety, substance abuse/addiction, or demyelinating disease.

The remaining N = 27,537 participants who made up the target cohort (55% female, age = 63.1 ± 7.5 years; other summary data in Table S1) were categorized based on ICD10 diagnosis of hyperlipidemia, hypercholesterolemia, diabetes (Type 1 and Type 2), hypertension, and MDD. Of the remaining participants, we identified the clinical cohort N = 5354 (53% female, age = 62.1 ± 7.7 years) who had an ICD10 diagnosis of MET or MDD or who were MET and MDD complete controls (criteria found in Tables 1 and 2) (flowchart on Figure 1). These participants were divided into four sub-groups: participants with both MET and MDD, MET+MDD+ (N = 772, 56% female, age = 65.1 ± 7.0 years); participants with MET but no MDD, MET+MDD− (N = 926, 34% Female, age = 67.5 ± 6.8 years); participants with no MET but with an MDD diagnosis, MET−MDD+ (N = 990, 74% female, age = 59.0 ± 7.1 years); and participants with neither MET nor MDD, MET−MDD− (N = 2666, 52% female, age = 60.5 ± 7.2 years) (Figure 1). The MET−MDD− and MET

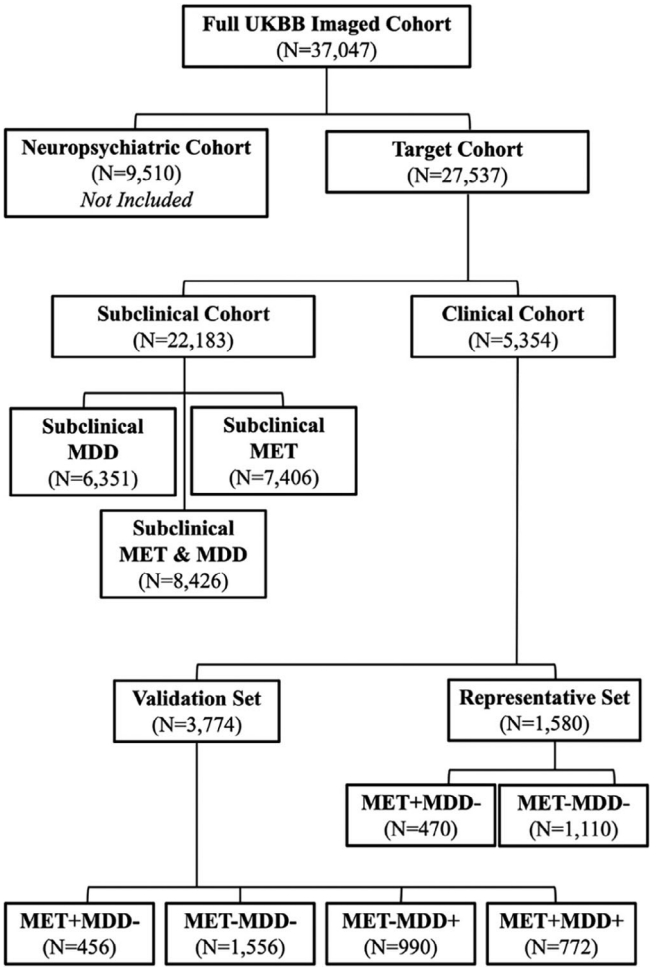

FIGURE 1 Flowchart of data sets used for the analyses.

+MDD− groups were further subdivided and selected for age to create a representative group, which was used to derive the MET related brain changes, and a validation group which was used for the later analyses (Table 3) (UKBB field IDs for MET and MDD Diagnosis found in Table S2).

Of the target cohort, the remaining $N = 22{,}183$ participants (57% female, age = 63.4 ± 7.4 years) did not meet the criteria for complete MET or MDD controls (Tables 1 and 2) nor were they diagnosed. Because of this, they were considered the subclinical cohort and were used as an independent sample to study associations between individual brain similarity with MET and measures associated with MDD, such as the volume of hyperintensive white matter and a subclinical depression score. This group consisted of $N = 7406$ (48% female, age = 64.0 ± 7.4 years) participants who did not have a diagnosis of hyperlipidemia, hypertension or high cholesterol, but had elevated blood pressure (≥140/90), body mass index (≥30), and/or cholesterol (total ≥ 6.2, LDL ≥ 4.9, HDL ≤ 1.0) based on the physicals performed for the UKBB, and were thus considered "at risk" for MET (UKBB field IDs for subclinical MET and MDD found in Table S3).

Similarly, $N = 6351$ individuals (63% female, age = 61.7 ± 7.5 years) were not diagnosed with MDD but also had scored highly for subclinical depression and therefore did not meet the conditions for controls (Table 3) only. The remaining $N = 8426$ individuals (57% female, age = 64.0 ± 7.1 years) were considered "at risk" for both MDD and MET as they had elevated blood pressure, cholesterol, or lipids and/or scored highly on the subclinical depression measures (Figure 1).

TABLE 1 Criteria for MET based on UKBB blood work, physical data, and diagnoses.

MET measure	Criteria
Body mass index	<30 BMI
Cholesterol	<6.2 mmol/L
LDL	<4.9 mmol/L
HDL	>1.0 mmol/L
Blood pressure	<140/90 mmHg
MET medication[a]	No
MET diagnosis	No

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; MET, metabolic illnesses; UKBB, UK BioBank.
[a]See Table SS1.

TABLE 2 Criteria for MDD-controls based on the UKBB online mental health follow up and diagnoses.

1.	Probable recurrent major depression (moderate)	No
2.	Probable recurrent major depression (severe)	No
3.	Single episode of probable major depression	No
4.	Seen doctor (GP) for nerves, anxiety, tension or depression	No
5.	Seen a psychiatrist for nerves, anxiety, tension or depression	No
6.	Depression possibly related to childbirth	No
7.	Depression possibly related to stressful or traumatic event	No
8.	Activities undertaken to treat depression	No
9.	Substances taken for depression	No
10.	Number of depression episodes	<1
11.	Days depressed for a whole week	No
12.	Duration (days) of worst depression	<1
13.	Psychiatric medication[a]	No
14.	Major depressive disorder diagnosis	No

Abbreviations: MDD, major depressive disorder; UKBB, UK BioBank.
[a]See Table SS1.

2.2 | Neuroimaging data acquisition and processing

Neuroimaging data were extracted from the UKBB website using the "`ukbfetch`" bulk data command. The UK UKBB imaging data were collected using a Siemens Skyra 3 T scanner 32-channgel RF head coil with high resolution T1-weighted (resolution = $1 \times 1 \times 1\ mm^3$, FOV = $208 \times 256 \times 256$, duration = 5 min, 3D MPRAGE, sagittal, in-plane acceleration iPAT = 2, prescan-normalize) and T2 FLAIR (resolution = $1.05 \times 1 \times 1\ mm^3$, FOV = $192 \times 256 \times 256$, duration = 6 min, 3D SPACE, sagittal, in-plane acceleration iPAT = 2, partial 7/8 Fourier sampling) images. Diffusion data were collected with a resolution = $2 \times 2 \times 2\ mm^3$ and two diffusion shells of $b = 1000$ and $2000\ s/mm^2$ with 50 diffusions direction per shell, $5b = 0$ images, FOV = $104 \times 104 \times 72$, and a 7-min duration.

TABLE 3 Demographics of representative and validation datasets.

Dataset	MET diagnosis	MDD diagnosis	*N*	Percent female	Age ± SD
Representative	MET−	MDD−	1110	51%	64.6 ± 3.0
	MET+	MDD−	470	33%	65.9 ± 3.1
Validation	MET−	MDD−	1556	53%	57.7 ± 7.9
	MET+	MDD−	456	35%	69.1 ± 8.8
	MET−	MDD+	990	74%	59.0 ± 7.1
	MET+	MDD+	772	56%	65.1 ± 7.0

Abbreviations: MDD, major depressive disorder; MET, metabolic illnesses.

We used regional data including cortical gray matter thickness, gray matter volume (subcortical structures), and white matter fractional anisotropy (FA) tract imaging data provided by the UKB. Data were extracted using the UKBB workflow, based on the ENIGMA structural and DTI pipelines. Imaging preprocessing and analysis are all recorded in the UKBB Brain Imaging Document (biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf), which provides left and right hemisphere measurements of regional cortical gray matter thickness (35), subcortical gray matter volume (7) and white matter FA (24). Hemispheric data were averaged.

Fluid attenuated inversion recovery (FLAIR) T2-hyperintensive volumes for white matter were extracted directly from the UKBB category and normalized using the natural log.

2.3 | Non-imaging data acquisition

Non-imaging data were extracted using the UKBB's Data Access Guide (https://biobank.ctsu.ox.ac.uk/~bbdatan/Data_Access_Guide_v3.0.pdf) command "`ukbconv`" to a csv file. Field IDs that were used to extract data can be found in Tables S2–S8. Non-imaging data were extracted from timepoints that corresponded with imaging data collection. Some data were only collected by the UKBB at one timepoint. Data were then binarized based on the criteria in the following sections.

2.4 | Depression symptoms, medication usage, and alcohol and smoking habits

Subclinical depression symptom scores were created from participant ratings of subclinical symptoms from the online survey including: "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", over a two-week period. Symptoms were scored as feeling "not at all" to "nearly every day" (0–3). Scores were then summed for each participant and transformed to a four-point scale of subclinical depression severity: 0—no symptoms, 1—few symptoms, 2—mild symptoms, and 3—increased symptoms (UKBB field IDs found in Table S5).

Medication usage was recorded from the UKBB medication and treatment codes (Tables S6 and S7), as well as the online survey. The survey collected information on medication usage for depression (prescribed and unprescribed), diabetes, high blood pressure, and high cholesterol.

Fifty-one percent of the participants in the validation set had records of weekly alcohol consumption information, and all participants had daily smoking habit information recorded. Daily smokers were defined as participants who smoked every day. Social drinkers were considered those drinking an average of 7 or fewer alcoholic beverages per week, while heavy drinkers were defined by drinking an average of more than 7 alcoholic beverages weekly (UKBB field IDs found in Table S8).

2.5 | Metabolic effect size comparison with neuropsychiatric effects

All statistical analyses were performed in RStudio v4.1.1 (RStudioTeam, 2020). Metabolic effect sizes were created from the representative set, comparing regional imaging data in the MET+ and MET-free testing group (Table 1) with the R packages "effsize" (Torchiano, 2020) and "psych" (Revelle, 2021). Effect sizes were calculated for ENIGMA-based regional cortical thickness, subcortical volume, and white matter FA values, as well as whole-brain average cortical thickness, subcortical gray matter volume and white matter FA. The neuropsychiatric effect sizes, including those for SSD, BD, MDD (Schmaal et al., 2016, 2017; van Velzen et al., 2020), and AD (Kochunov et al., 2022), were calculated in the largest meta-analytical samples for corresponding illnesses.

2.6 | Metabolic regional vulnerability index

The metabolic effects were used to create the cortical, subcortical, and white matter Metabolic Regional Vulnerability Index (RVI-MET) scores based on the protocol documented in Kochunov, Fan, et al. (2020), using the "RVIpkg" (Gao et al., 2021). Briefly, RVI-MET scores were calculated by first regressing the effects of age, sex, and intracranial volume from the imaging phenotypes for each individual, transforming the residuals of the imaging phenotypes by inverse normalization, and then standardizing the normalized residuals to *z*-scores using the average and standard deviation of the MET controls. The Pearson correlation coefficient was then calculated between the individual participants' *z* scores and corresponding effect sizes for metabolic versus control group differences previously created. The whole-brain RVI-MET was calculated by averaging the three regional RVIs.

2.7 | Statistical analysis of RVI-MET

The significance of statistical analyses was evaluated after adjusting for multiple effect size comparisons using Benjamini–Hochberg correction. Cohen's *d* effect sizes were used to present the differences between MET+ and MET− groups in the RVI validation dataset (Table 3), with no overlap with participants used to derive RVI. First, the MDD- groups were compared to investigate how well the RVI-MET captured the effects of MET in the non-psychiatric group (MET+MDD− vs. MET−MDD−). Then the effects of MET on RVI-MET were assessed within the psychiatric group (MET+MDD+ vs. MET−MDD+). Analysis of variance (ANOVA) in the validation set, using Tukey's test of honest significance difference, was used to test the significant differences between the mean RVI-MET in each group for all regional and whole-brain RVIs.

Increased FLAIR volume is a common neurological consequence of MET. We used it as a proxy measure to evaluate the sensitivity of the whole-brain and tissue specific RVI to a well-known effect of

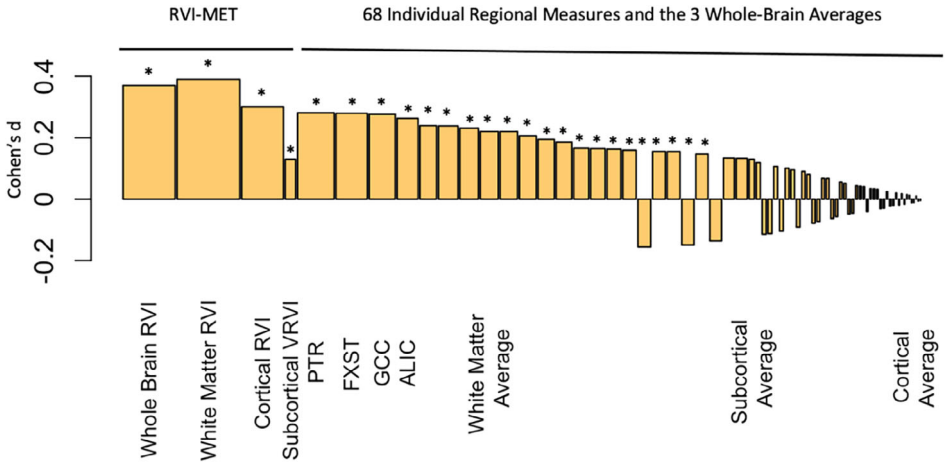

FIGURE 2 Metabolic illness effect sizes are ranked here, for the average white matter, subcortical volume and grey matter thickness, and regional effect sizes (largest significant effects: PTR, posterior thalamic radiation; FXST, fornix/stria terminalis; GCC, genu of the corpus collosum; ALIC, anterior limb of the internal capsule). Significance set at Benjamini–Hochberg adjusted $p < .05$.

MET on the brain. We hypothesized that RVI will capture the whole-brain nature of MET and therefore, cortical and subcortical RVI will be associated with higher white matter hyperintensity volumes. We tested this hypothesis using a correlation analysis between whole-brain and tissue specific RVI-MET and the age and sex corrected residuals for the total FLAIR hyperintensity volume.

The separate smoking and alcohol habits as well as MET and MDD medication and subclinical depression score *t*-test analyses were performed in the validation set and subclinical set combined. Correlation analyses with the whole-brain and regional RVIs were performed using the average weekly number of drinks and daily number of cigarettes, with a Holm's adjusted *p*-value.

A full linear regression model was run on the whole-brain and regional RVI-MET (Equation 1):

$$\begin{aligned}\mathrm{RVI} \sim \beta_0 + \beta_1{}^{*}\mathrm{DX_{MET}} + \beta_2{}^{*}\mathrm{DX_{MDD}} + \beta_3{}^{*}\mathrm{Smoke} + \beta_4{}^{*}\mathrm{Alcohol} \\ + \beta_5{}^{*}\mathrm{DX_{MET}}{}^{*}\mathrm{DX_{MDD}} + \beta_6{}^{*}\mathrm{BMI} + \beta_7{}^{*}\mathrm{Age} + \beta_8{}^{*}\mathrm{Sex} + \beta_9{}^{*}\mathrm{Age}{}^{*}\mathrm{Sex} + \varepsilon,\end{aligned} \quad (1)$$

where elevation in the whole-brain and tissue-specific RVI-MET scores were predicted using the following variables: DX is the MET and MDD diagnosis, Smoke is whether a participant smokes regularly or not, Alcohol is whether a participant is a social, heavy or non-drinker, and BMI is the body mass index. β_0 is the intercept, $\beta_{1,2,3,4,5,6,7,8,9}$ are the regression coefficients, and ε is the random error.

3 | RESULTS

3.1 | Effects of MET on average and regional brain integrity

In the representative dataset, the average FA of cerebral white matter (WM) was significantly lower in MET participants than in controls ($d = -0.22$, $p = .0004$). The effects of MET were not significant for the average subcortical gray matter (SUB) ($d = -0.13$, $p = .06$) nor for the average gray matter (GM) thickness ($d = 0.02$, $p = .84$) (Figure 2).

MET effects were significant for 23 out of 68 regional measurements, following the Benjamini–Hochberg procedure for multiple comparisons (Table 4). The strongest effects were observed for the FA of the posterior thalamic radiation ($d = -0.28$, $p = 2.54 \times 10^{-5}$), the fornix ($d = -0.28$, $p = 1.48 \times 10^{-5}$), the genu of the corpus collosum ($d = -0.28$, $p = 1.26 \times 10^{-5}$), and the anterior limb of the internal capsule ($d = -0.26$, $p = 3.23 \times 10^{-5}$). For subcortical GM, the volume of thalamus ($d = -0.23$, $p = 2.74 \times 10^{-4}$) was the only structure that showed significant MET effects. The cortical thickness of the insula showed the strongest negative effects ($d = -0.19$, $p = .004$), followed by the superior temporal gyrus ($d = -0.16$, $p = .01$).

The regional effects of MET in non-psychiatric MET individuals and regional effect sizes for MDD as estimated in ENIGMA showed significant correlation ($r = 0.70$, adj. $p < .0001$) (Figure 3), although the effect was mainly driven by white matter and subcortical effects. There was no significant correlation between SSD ($r = 0.18$, adj. $p = .9$), BD ($r = 0.28$, adj. $p = .2$), and AD ($r = -0.03$, adj. $p = .9$), and MET regional effect sizes.

3.2 | Effect size of MET on RVI versus regional measures

We used the regional effect sizes (Table 4) to calculate RVI-MET in the target cohort and used the validation dataset to compare RVI-MET between participants with MET and those without in both the MDD patients and controls. Compared to MET-free participants, the effect size for the elevation of the whole-brain RVI in nonpsychiatric individuals with MET (Cohen's $d = 0.37$, $p = 1 \times 10^{-12}$) was significantly higher than those for average and regional brain measurements (Table 4). The tissue specific RVIs also showed significant elevation in MET subjects with the highest effect sizes observed for cerebral WM ($d = 0.39$, $p = 5 \times 10^{-13}$), followed by cortical thickness ($d = 0.30$, $p = 1.7 \times 10^{-8}$), and subcortical RVI values ($d = 0.13$, $p = .01$) (Figure 4a).

TABLE 4 Regional effects of MET on brain integrity with *p*-values adjusted for $N = 68$ calculations using the Benjamini–Hochberg adjusted *p*-values.

	Region	Cohen's *d*	Adjusted *p*-values
White matter	Posterior thalamic radiation	−0.28	**2.54×10^{-5}**
	Fornix (crus)/stria terminalis	−0.28	**1.48×10^{-5}**
	Genu of the CC	−0.28	**1.26×10^{-5}**
	Anterior limb of the IC	−0.26	**3.23×10^{-5}**
	Sagittal stratum	−0.24	**2.01×10^{-4}**
	Superior longitudinal fasciculus	−0.24	**1.82×10^{-4}**
	Superior frontooccipital fasciculus	−0.22	**5.18×10^{-4}**
	Anterior CR	−0.21	**1.24×10^{-3}**
	External capsule	−0.19	**2.59×10^{-3}**
	Corona radiata	−0.17	**.01**
	Uncinate fasciculus	−0.16	**.01**
	Corpus collosum	−0.16	**.02**
	Internal capsule	−0.16	**.02**
	Fornix	−0.16	**.02**
	Body of the CC	−0.15	**.03**
	Cingulum cingulate gyrus	−0.13	**.04**
	Superior CR	−0.12	.08
	Posterior CR	−0.10	.15
	Retrolenticular limb of the IC	−0.10	.18
	Tapetum	−0.04	.65
	Cingulum hippocampus	0.04	.65
	Posterior limb of the IC	−0.03	.72
	Cortico spinal tract	0.02	.83
	Splenium of the CC	0.01	.92
	Average effect	−0.22	**4.36×10^{-4}**
Grey matter thickness	Insula	−0.19	**4.27×10^{-3}**
	Superior temporal	−0.16	**.01**
	Lateral occipital	0.16	**.02**
	Pericalcarine	0.15	**.02**
	Superior parietal	0.14	**.04**
	Medial orbitofrontal	−0.13	**.04**
	Cuneus	0.11	.10
	Lingual	0.11	.10
	Rostral middle frontal	0.10	.14
	Frontal pole	0.09	.20
	Middle temporal	−0.08	.28
	Pars orbitalis	0.08	.29
	Precuneus	0.07	.34
	Inferior temporal	−0.07	.39
	Paracentral	−0.07	.39
	Pars opercularis	0.06	.43
	Postcentral	0.06	.50
	Parahippocampal	−0.05	.55
	Pars triangularis	0.05	.58
	Lateral orbitofrontal	−0.04	.63
	Rostral anterior cingulate	−0.04	.64

TABLE 4 (Continued)

	Region	Cohen's *d*	Adjusted *p*-values
	Caudal middle frontal	0.03	.74
	Transverse temporal	0.03	.75
	Supramarginal	−0.02	.82
	Inferior parietal	0.02	.84
	Isthmus cingulate	−0.02	.83
	Posterior cingulate	0.02	.83
	Fusiform	−0.02	.84
	Precentral	−0.01	.85
	Banks of superior temporal sulcus	−0.01	.88
	Entorhinal	0.01	.87
	Caudal anterior cingulate	−0.01	.89
	Superior frontal	0.00	.93
	Average effect	0.01	.84
Subcortical volumes	Thalamus	−0.23	$\mathbf{2.74 \times 10^{-4}}$
	Palladium	−0.11	.12
	Accumbens	−0.09	.20
	Hippocampus	−0.06	.50
	Caudate	0.05	.62
	Amygdala	−0.03	.73
	Putamen	−0.03	.73
	Average effect	−0.13	.06

3.3 | Replication of MET effects on RVI in subjects with MDD

The elevation in RVI was replicated in a cohort of MDD subjects who were not a part of the group used to derive RVI for MET. MDD subjects with MET showed significantly higher RVI-MET than MET-free MDD subjects (Cohen's $d = 0.35$, $p = 1.13 \times 10^{-13}$). Among the tissue specific RVIs, the effects of MET were strongest in cortical GM ($d = 0.38$, $p = 3.3 \times 10^{-15}$), followed by the WM ($d = 0.29$, $p = 3.5 \times 10^{-9}$) and subcortical ($d = 0.12$, $p = .02$) values. However, when examining MDD subjects between ages of 60–66 years, the effects were larger in all regions (GM: $d = 0.55$, $p = 2.3 \times 10^{-8}$; WM: $d = 0.53$, $p = 9.9 \times 10^{-8}$; SUB: $d = 0.20$, $p = .04$) and in the whole-brain RVI-MET ($d = 0.58$, $p = 5.2 \times 10^{-9}$). The effects of MET on RVI were not significantly different between non-psychiatric and MDD samples (Figure 4b).

3.4 | A four-group analysis of RVI-MET values

A two-way ANOVA in the validation set demonstrated significant differences ($F = 52.4$, $p = 3.8 \times 10^{-33}$) in the mean of the whole-brain RVI-MET scores across the non-psychiatric and MDD groups. The follow up test of Tukey's honest significant difference demonstrated significance in average RVI-MET values between participants with MET in both the non-psychiatric group ($p < 10^{-8}$) and the MDD patients ($p < 10^{-8}$). There was also significant elevation in the mean RVI-MET between non-psychiatric and MDD subjects within the corresponding MET status ($p < 10^{-4}$) (Figure 5a). ANOVA was significant for all tissue specific RVI (WM: $F = 46.3$, $p = 2 \times 10^{-29}$; GM: $F = 40.4$, $p = 1 \times 10^{-25}$; SUB: $F = 9.2$, $p = 4 \times 10^{-6}$). For white matter RVI, MET+ had significantly elevated RVI scores than MET− both in the MDD group ($p < 10^{-8}$) and control group ($p < 10^{-8}$), as well as between MDD patients and controls in the MET− group ($p = 1 \times 10^{-5}$) (Figure 5b). Similarly, cortical RVIs were significantly higher between the MET+ and MET− in both the MDD ($p < 10^{-8}$) and control groups ($p = 2.0 \times 10^{-7}$) (Figure 5c). The subcortical RVI also was only significantly elevated between the MDD patients and controls in a MET− group (.036) (Figure 5d).

3.5 | Effects of MET and MDD diagnosis and substance abuse, BMI, age, and sex on RVI

We evaluated the full model with RVI from the combined subclinical and validation sets to test the significance of diagnoses in the presence of covariates. This model was significant for the whole-brain ($F = 87.7$, $p = 1.6 \times 10^{-160}$) and tissue-specific RVI (white matter: $F = 54.2$, $p = 5.4 \times 10^{-98}$; cortical thickness: $F = 106.2$, $p = 1.0 \times 10^{-194}$; subcortical volume: $F = 30.0$, $p = 1.4 \times 10^{-52}$) (Table 5).

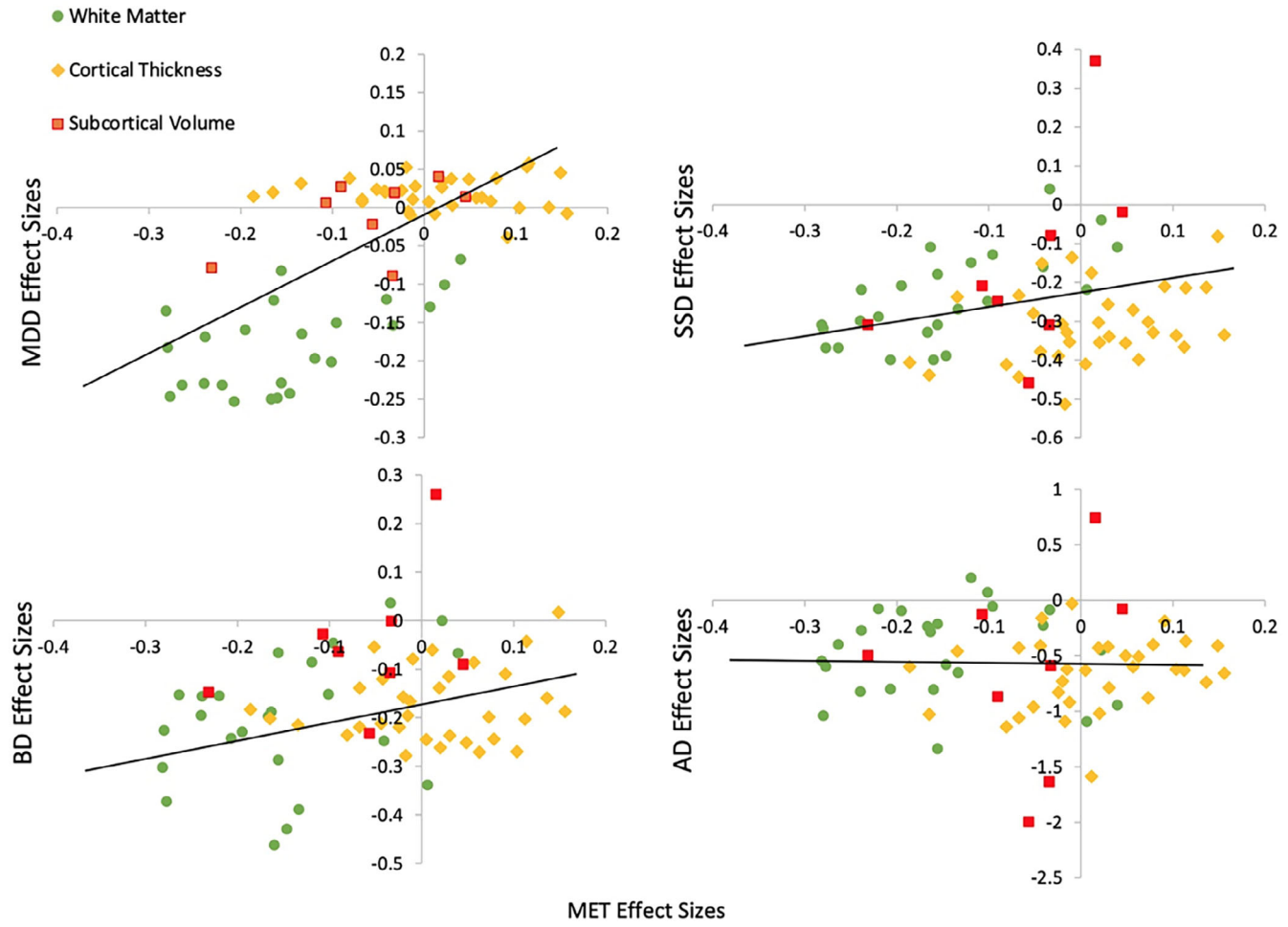

FIGURE 3 Correlation between the UK Biobank based metabolic regional effect sizes and the ENIGMA based major depressive disorder effect sizes.

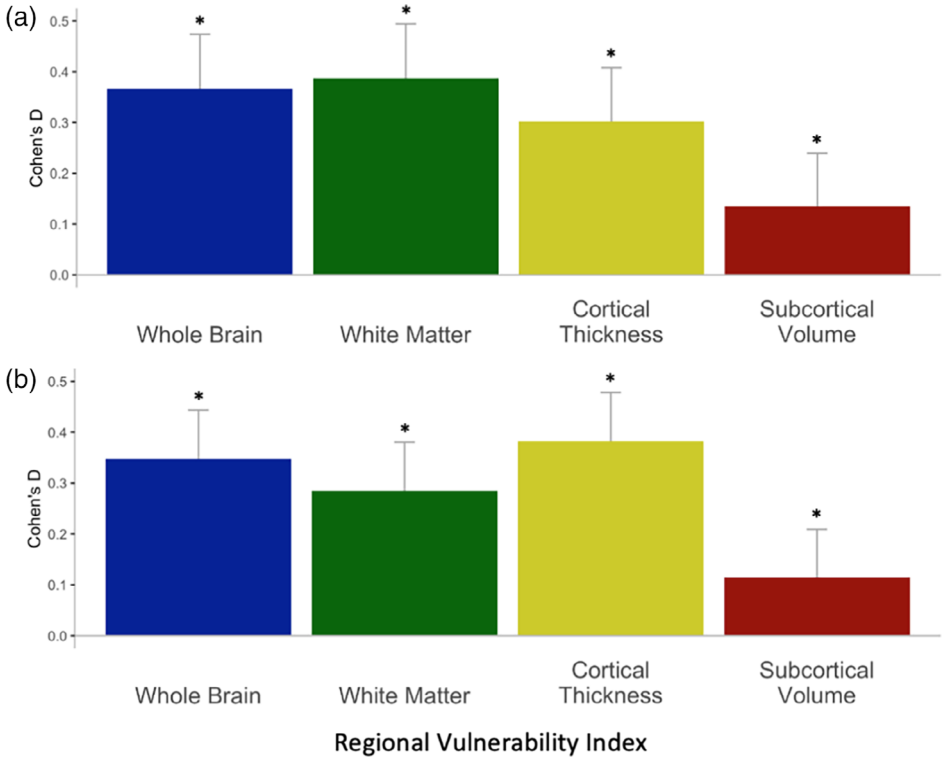

FIGURE 4 Effect sizes of the whole-brain, white matter fractional anisotropy (FA), cortical thickness, and subcortical volume regional vulnerability indices (RVIs) in (a) metabolic illnesses (MET) diagnosis and (b) major depressive disorder (MDD) diagnosis.

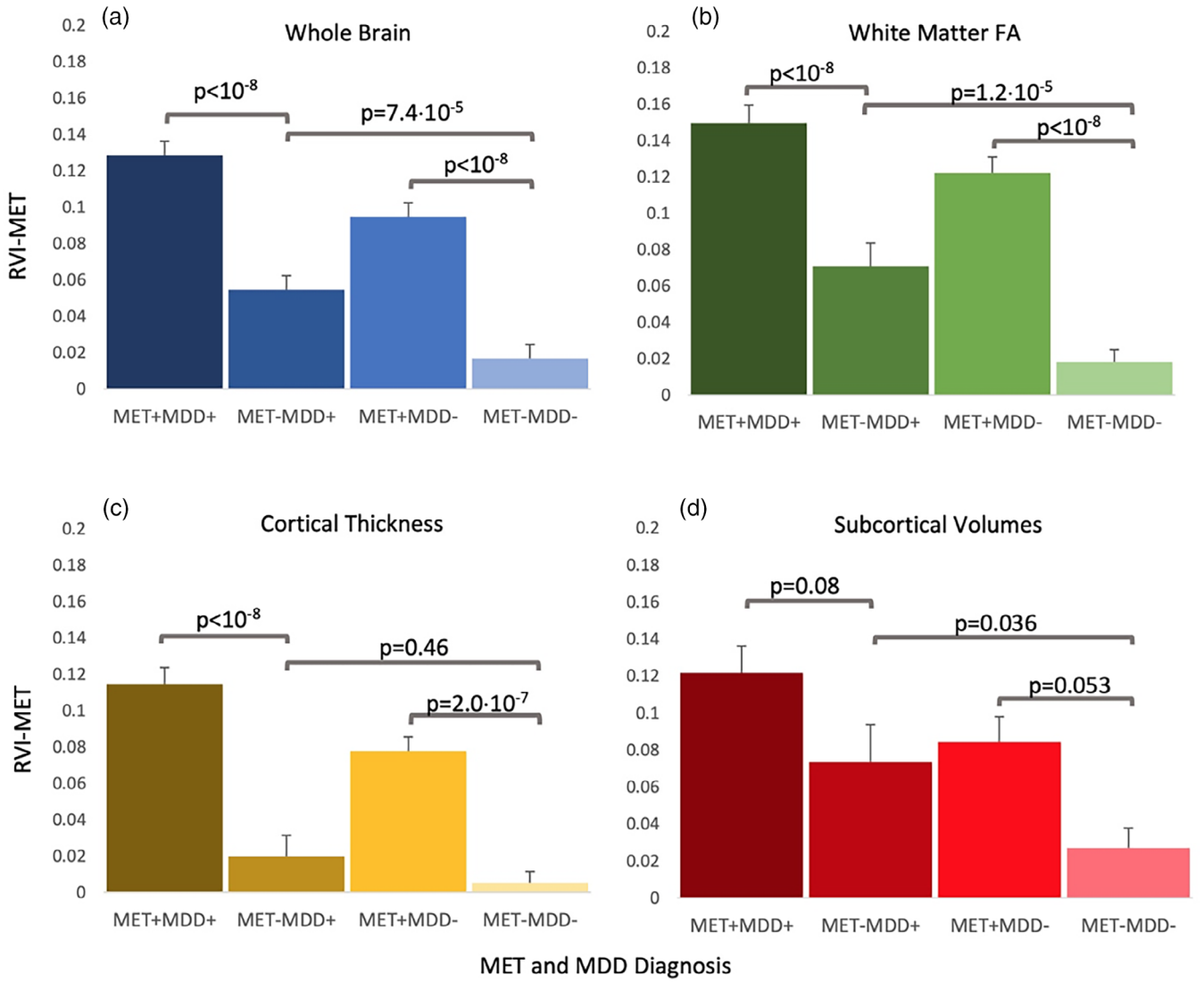

FIGURE 5 Mean regional vulnerability index (RVI) scores in the major depressive disorder (MDD) and metabolic illnesses (MET) diagnosis and control groups for (a) whole-brain, (b) white matter fractional anisotropy (FA), (c) cortical thickness, and (d) subcortical volume.

Whole-brain RVI was significantly and independently associated with MET and MDD diagnosis, but not with their interaction. Smoking, alcohol consumption, BMI, age, sex and the interaction of age and sex were likewise significant predictors of RVI (Figure 6). White matter RVI showed a similar pattern of association (Table 5). The cortical RVI was only significantly associated with alcohol consumption, BMI, age, sex, and the interaction between age and sex. The subcortical RVI-MET was only significantly associated with smoking and drinking habits as well as BMI, age, sex, and the interaction of age and sex.

3.6 | Repeat of the four-group analysis of RVI values in the non-smoking, social drinking cohort

There were $N = 1307$ total non-smoking, social drinkers included in the repeated ANOVA. Within the whole-brain ANOVA, there were still significant differences in the mean RVI-MET scores between MET + diagnosis and MET− free in both the MDD ($p = .001$) and control groups ($p = 2.7 \times 10^{-4}$) after Tukey's test of honest significant difference. The white matter RVI-MET scores were also significantly different between MET+ diagnosis and MET− free individuals in the MDD ($p = .01$) and control ($p = 3.5 \times 10^{-5}$) groups. There was also a significant difference in the mean scores of the gray matter RVI-MET between MET+ and MET− free in both the MDD ($p = .03$) and control groups ($p = 4.9 \times 10^{-4}$). There were no significant differences in the subcortical RVI-MET ($p > .1$).

3.7 | RVI-MET and WM hyperintensity volume

The FLAIR hyperintensive white matter volume is an index used to quantify negative effects of MET on brain integrity. In the validation set, FLAIR volume was significantly elevated in MET in non-psychiatric subjects ($t = 12.1$, $p < 2.3 \times 10^{-16}$). Within the MDD patients, total

TABLE 5 Regression of MET regional vulnerability index with MET and MDD diagnosis and substance use.

RVI	MET diagnosis	MDD diagnosis	Smoke rank	Alcohol rank	BMI	MET × MDD	Age	Sex	Age × sex	Full model
Whole brain	$t = 4.1, \mathbf{p = 4.1 \times 10^{-5}}$	$t = 2.3, \mathbf{p = .02}$	$t = 4.1, \mathbf{p = 4.5 \times 10^{-5}}$	$t = 3.5, \mathbf{p = 4.3 \times 10^{-4}}$	$t = 17.0, \mathbf{p = 1.3 \times 10^{-64}}$	$t = 0.9, p = .34$	$t = -12.7, \mathbf{p = 6.3 \times 10^{-37}}$	$t = -11.9, \mathbf{p = 1.7 \times 10^{-32}}$	$t = 11.2, \mathbf{p = 6.9 \times 10^{-29}}$	$F = 87.7, \mathbf{p = 1.6 \times 10^{-160}}$
White matter	$t = 5.8, \mathbf{p = 7.0 \times 10^{-9}}$	$t = 3.4, \mathbf{p = 7.1 \times 10^{-4}}$	$t = 3.2, p = .001$	$t = 3.4, \mathbf{p = 7.1 \times 10^{-4}}$	$t = 12.7, \mathbf{p = 9.6 \times 10^{-37}}$	$t = -0.8, p = .4$	$t = -8.5, \mathbf{p = 1.6 \times 10^{-17}}$	$t = -5.6, \mathbf{p = 1.7 \times 10^{-8}}$	$t = 5.1, \mathbf{p = 3.6 \times 10^{-7}}$	$F = 54.2, \mathbf{p = 5.4 \times 10^{-98}}$
Cortical thickness	$t = 2.0, p = .05$	$t = 0.2, p = .8$	$t = -0.3, p = .8$	$t = -2.2, \mathbf{p = .03}$	$t = 26.0, \mathbf{p = 1.7 \times 10^{-146}}$	$t = 1.4, p = .2$	$t = -3.9, \mathbf{p = 7.4 \times 10^{-5}}$	$t = -4.7, \mathbf{p = 2.9 \times 10^{-6}}$	$t = 4.3, \mathbf{p = 2.1 \times 10^{-5}}$	$F = 106.2, \mathbf{p = 1.0 \times 10^{-194}}$
Subcortical volume	$t = 1.3, p = .2$	$t = 1.2, p = .2$	$t = 4.2, \mathbf{p = 2.2 \times 10^{-5}}$	$t = 4.3, \mathbf{p = 1.4 \times 10^{-5}}$	$t = 3.0, \mathbf{p = .003}$	$t = 1.1, p = .3$	$t = -11.5, \mathbf{p = 2.7 \times 10^{-30}}$	$t = -11.7, \mathbf{p = 2.3 \times 10^{-31}}$	$t = 11.2, \mathbf{p = 6.5 \times 10^{-29}}$	$F = 30.0, \mathbf{p = 1.7 \times 10^{-52}}$

Note: Bolded *p*-values passed the FDR threshold at <.05.
Abbreviations: MDD, major depressive disorder; MET, metabolic illnesses; RVI, regional vulnerability index.

FLAIR volume was also significantly elevated in MET ($t = 13.5$, $p < 2.3 \times 10^{-16}$). The RVI-MET and FLAIR volume were significantly correlated ($r = 0.22$, adj. $p < .0001$). All tissue-specific RVI likewise showed significant correlation with FLAIR volume, suggesting that cortical and subcortical RVI were also sensitive to brain changes reflected by accumulation of FLAIR volume. The highest correlation with FLAIR volume was observed for RVI values for cerebral white matter ($r = 0.20$, adj. $p < .0001$), followed by cortical gray matter ($r = 0.17$, adj. $p < .0001$) and subcortical volumes ($r = 0.10$, adj. $p < .0001$).

3.8 | Effects of antidepressants on RVI-MET

$N = 2977$ (77%) participants from the MDD sample in the validation and subclinical datasets were reported to take antidepressant medications. There were no significant differences in the whole-brain RVI-MET in MDD subjects who took antidepressant versus those who did not ($t = 0.15$, $p = .9$).

3.9 | Effects of antihypertensive, cholesterol-lowering, and diabetes medications on RVI-MET

The MET medication analyses were completed using the MDD controls from the validation dataset and subclinical MET datasets. The participants from the subclinical MDD or subclinical MDD and MET datasets had no overlap with the representative dataset. From these data, $N = 2378$ (32%) participants reported taking medication for hypertension, hyperlipidemia, and/or diabetes. Subjects who took MET medication showed significantly higher whole-brain RVI ($t = 6.5$, $p = 1.0 \times 10^{-10}$). They also showed significantly higher WM ($t = 6.0$, $p = 71.7 \times 10^{-9}$), cortical ($t = 5.4$, $p = 7.1 \times 10^{-8}$), and subcortical ($t = 3.0$, $p = .003$) RVI. However, when these analyses were performed in the MET+ group, to correct for MET status, these differences became non-significant.

3.10 | MET and depression symptom severity

In the MDD samples from the validation and subclinical datasets, MET diagnosis was associated with higher MDD symptom severity than subjects without MET ($t = 3.1$, $p = .002$). The subjects in the non-psychiatric group did not show significant differences in depression symptoms between MET+ versus controls ($t = -0.9$, $p = .34$). The whole-brain RVI-MET was significantly correlated with depression scores in the MDD sample ($r = 0.06$, adj. $p < .0001$), as were the cortical ($r = 0.06$, adj. $p < .0001$), white matter ($r = 0.06$, $p < .0001$), and subcortical ($r = 0.03$, $p < .0001$) RVI-MET.

3.11 | BMI and MDD

In the validation dataset, subjects with MDD showed significantly higher BMI than the non-psychiatric subjects ($t = 13.44$,

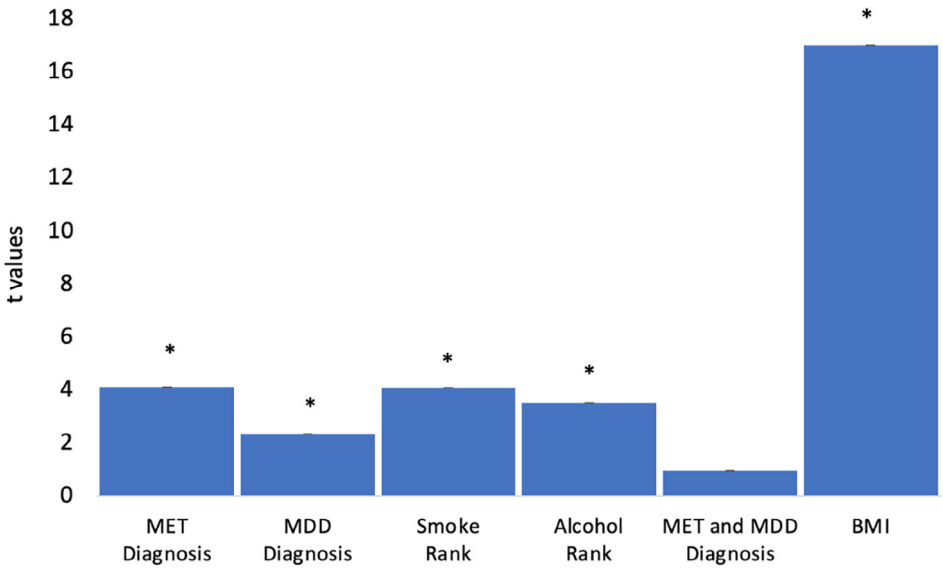

FIGURE 6 Regression coefficients of metabolic illnesses (MET) and major depressive disorder (MDD) diagnosis, smoking rank, alcohol consumption rank, and the interaction of MET and MDD diagnosis on the whole brain regional vulnerability index (RVI)-MET scores. Significance at FDR = 0.05.

$p < 2.2 \times 10^{-16}$). The MET-free MDD subjects showed significantly higher BMI than MET-free non-psychiatric subjects ($t = 2.1$, $p = .03$). Moreover, there was a significant correlation between depression scores and BMI ($r = 0.11$, adj. $p < .0001$) in MDD cohorts but not in the non-psychiatric subjects ($r = -0.03$, $p = .7$).

3.12 | RVI-MET and BMI

The whole-brain ($r = 0.13$, adj. $p < .0001$), white matter ($r = 0.12$, adj. $p < .0001$), and cortical thickness ($r = 0.19$, adj. $p < .0001$) RVIs were significantly correlated with BMI in the non-psychiatric sample of the validation and subclinical datasets. The correlation between subcortical RVI and BMI was not significant ($r = 0.009$, $p = .4$). After correction for MET status, only the correlation between gray matter thickness RVI and BMI remained significant ($r = 0.12$, adj. $p < .0001$). In the MDD subsample, we replicated the significant correlations for the whole brain ($r = 0.15$, adj. $p < .0001$), white matter ($r = 0.13$, adj. $p < .0001$), and cortical thickness ($r = 0.16$, adj. $p < .0001$) RVI and BMI. In contrast to non-psychiatric status, most correlations remained significant even after correction for MET status (whole-brain: $r = 0.20$, adj. $p < .0001$; white matter: $r = 0.14$, adj. $p = .0001$; cortical thickness: $r = 0.25$, adj. $p < .0001$; subcortical: $r = 0.05$, $p = .4$).

4 | DISCUSSION

We evaluated the effects of MET on cerebral integrity in a large and representative sample provided by the UK Biobank. MET exerted deleterious effects that were tissue and region-specific. We used the anatomical profile of effect sizes of MET to develop a RVI as a measure of the similarity between individual and expected deficit patterns in MET (Schmaal et al., 2016, 2017). Participants with MET had significant elevation in whole-brain RVI compared to subjects without MET. The effect sizes for the whole-brain and tissue specific RVI were higher for both whole-brain average and individual brain measures. We replicated this finding in an independent cohort of MDD subjects with and without MET. This suggested that the similarity to a regional pattern of MET was a phenotype that was more sensitive and specific than any regional brain measures. The individual RVI values were positively associated with the volume of the FLAIR T2-hyperintensive white matter regions and BMI in both non-psychiatric and MDD samples. The cortical, subcortical, and white matter regional pattern of these effect sizes overlapped closely with those reported by independent large-scale meta-analyses of MDD findings (Schmaal et al., 2016, 2017; van Velzen et al., 2020). MDD subjects had significantly higher RVI-MET values versus the corresponding non-psychiatric group. BMI, alcohol, and tobacco use contributed to elevated RVI values but not the antidepressant medications. In summary, we developed and replicated RVI for MET, which is a more sensitive index of effects of MET on the brain than individual brain measurements. The overlap between MET and MDD regional deficit patterns was partially explained by higher incidence of MET and substance use in subjects with MDD.

MET are common disorders that begin in early to mid-adulthood and act as significant risk factors for the integrity of cerebral tissues through hormonal, inflammatory, cerebrovascular, and cardiometabolic pathways. The effects of the MET are especially severe for the cerebral white matter, which is considered the end-target organ for MET (Bateman, 2002; Henry Feugeas et al., 2005; Marks et al., 2011; Spieker et al., 2015). Chronic MET is associated with damage to the long-penetrating cerebral blood vessels (Kochunov et al., 2010) that leads to hypoperfusion, reduced white matter integrity and formation of hyperintense T2-FALIR lesions (Jagust et al., 2005). The linkage between white matter damage in MET has been confirmed by genetic studies that showed shared genetic variance (Kochunov et al., 2012) as well as the overlap in the associated genetic loci between two illnesses (Kochunov et al., 2009, 2010, 2012). We replicated the significant negative effect sizes for MET on the average cerebral white matter FA values ($d = 0.2$), while subjects

with MET did not show significant differences in average cortical thickness and subcortical measures. We further plotted the regional effect sizes for MET versus those found in common neuropsychiatric illnesses.

MET are common comorbidities in neuropsychiatric illnesses and are hypothesized to contribute to accelerated brain aging in patients (Lung et al., 2007; Simon et al., 2006; Wolkowitz et al., 2011). We plotted the regional effect size for MET calculated in non-psychiatric sample against the patient-control SSD (Kelly et al., 2018), MDD (van Velzen et al., 2020), BD (Favre et al., 2019), and AD (Kochunov, Ryan, et al., 2021). This provided the first opportunity to evaluate how effects of MET may overlap with findings in neuropsychiatric disorders. The effect sizes of the neuropsychiatric illnesses were tabulated from the independent studies of the largest samples of the respective disorders that consisted of hundreds to thousands of patients and controls that were independent of the current sample. Among the three psychiatric and one neurological illness, regional effects of the MET were significantly correlated with the effects of the MDD with a remarkable overlap between effects of the two illnesses ($r = 0.70$, adj. $p < .0001$). This is consistent with findings that MET co-occur with MDD at nearly five times versus normal controls and double the rates versus other mental illnesses (Jantaratnotai et al., 2017; Luo et al., 2018; Malmir et al., 2019; Milaneschi et al., 2019). We calculated RVI for MET to measure individual similarity to expected MET patterns in both non-psychiatric and MDD cohorts to evaluate the potential causes of this overlap.

RVI is a linear measure of similarity between regionally derived metrics from an individual's brain MRI (e.g., regional volumes, thicknesses, microstructure measurements) and the expected pattern of those metrics with respect to the patient-control effect sizes. The RVI approach assumes that the effects of the disorder on the brain are regionally specific and that the regional pattern of the illness is more stable and replicable than effects of the illness on any individual structure (Kochunov, Thompson, et al., 2019). The utility of this approach was demonstrated by showing that RVI for schizophrenia predicted treatment resistance in schizophrenia better than any individual imaging measure (Kochunov, Huang, et al., 2019) and later findings suggested that RVI serves as an important index for cross-disorder research (Kochunov, Hong, et al., 2020; Kochunov, Zavaliangos-Petropuli, et al., 2021). Prior research using RVI has primarily focused on neuropsychiatric illness, but this study showed that the effects of the MET are likewise regionally specific, and the pattern of MET effect sizes is stable, replicable, and informative. The whole-brain RVI showed approximately twice the effect sizes for MET versus whole-brain average values. The RVI derived for cortical and subcortical difference demonstrate the significance effects of MET replicating previous findings (Alfaro et al., 2016; Kochunov et al., 2010, 2012; Kochunov, Glahn, Lancaster, et al., 2011; Kochunov, Glahn, Nichols, et al., 2011), even in the absence of significant effects of MET for the average cortical thickness or subcortical gray matter volume.

The whole brain and tissue-specific RVIs were significantly correlated with the volume of FLAIR T2-hyperintensive lesions and BMI of the non-psychiatric subjects, supporting the sensitivity of this approach. FLAIR T2-hyperintensities are regions of accumulation of extracellular water due to focal degradation of the myelin sheath and are considered as an end-organ damage of MET in the brain (Fazekas et al., 1993; Kochunov et al., 2009). The cortical and subcortical RVI were likewise significantly correlated with T2-FLAIR volume. This suggests that RVI is capturing the whole-brain nature of MET-related damage. Whole-brain and cortical RVI were also significantly correlated with BMI, thus capturing the well-known risks that obesity exerts on cerebral integrity (Marks et al., 2011; Ryan et al., 2017). The causative links between obesity and lower cerebral integrity are complex and occur through multiple pathways. Obesity is associated with hypertension and atherosclerosis, and both are direct cerebrovascular risk factors associated with lower cerebral integrity (Allen et al., 2016; Després et al., 1990; Lewington et al., 2007; Spieker et al., 2015). Obesity is also associated with elevated systemic inflammatory activity which in turn impairs cerebral healing abilities and leads to cognitive changes (Luo & Lin, 2021; Miller & Spencer, 2014). MET, including hypertension, diabetes, fatty liver disorder and others, is an outcome of chronic obesity and the relationship between obesity and cerebral integrity, as captured by RVI, was continuous and was readily replicable in an independent sample.

The elevation of whole-brain and regional RVI in subjects with MET was replicated in an independent group of MDD subjects. The absolute values of the effect sizes of the whole brain MET on RVI in subjects with and without MET were similar to those observed in the non-psychiatric subjects ($d = 0.36$ vs. 0.39 for MDD and non-psychiatric groups, respectively). The tissue-specific RVI also showed significant elevations in subjects with MET in the MDD cohort. For MDD subjects, cortical RVI showed the biggest effect versus white matter RVI in controls, but this difference was not statistically significant ($Z = 0.7$, $p > .6$). We also replicated the positive correlation between all RVI and FLAIR volume. The direct comparison among the four groups demonstrated subjects with MDD had significantly higher RVI than the corresponding group from the non-psychiatric participants. MDD subjects with MET had significantly higher whole-brain RVI ($p = .03$) than non-psychiatric subjects with MET. Likewise, MET free subjects with MDD had significantly higher RVI versus MET free non-psychiatric controls ($p = 7.4 \times 10^{-5}$).

Daily use of alcohol and tobacco are the most common environmental risk factors associated with MET (Bertoglia et al., 2017; Friedman et al., 1982). Drinking and smoking frequencies are directly associated with insulin resistance, pancreatic health, and genetic pathways, which culminate in MET (Bertoglia et al., 2017; Duell, 2012; Maisonneuve et al., 2005). We thus asked if smoking and alcohol use and/or use of antidepressant medication in patients with MDD could account for the differences between subgroups using RVI as an intermediate phenotype to quantify effects of MET on brain integrity. The negative effects of daily use of alcohol and tobacco on cerebral health were readily captured by the elevation of RVI in both samples. The effects of these substances on RVI were consistent between the two samples but subjects with MDD had significantly higher rates of smoking and daily alcohol drinking vs. non-psychiatric samples. In contrast, the use of antidepressant medications was not associated with

significant differences in the whole-brain or tissue specific RVI in the MDD cohort. The use of common medications to treat effects of MET was robustly associated with higher RVI but this difference became non-significant once the MET status was included in the model. Together these findings suggest that heavy alcohol and tobacco use—but not antidepressants—contribute to higher RVI for MET and potentially to group differences in RVI between MDD and non-psychiatric samples.

We modeled the effects of the MET and MDD diagnosis together with substance use on the RVI in the combined sample. The diagnosis of MET and MDD remained significant predictors for the whole-brain RVI even after correcting for other factors. The interaction between MET and MDD was not statistically significant. Among the tissue specific RVI, MET, and MDD diagnosis was significant for white matter and cortical thickness, while subcortical RVI showed significant association with smoking and alcohol use, only. Considering these findings together, we can conclude that RVI-MET is a sensitive and useful tool to evaluate the effect of MET on cerebral integrity as compared to regional brain structures. Higher RVI-MET values in MDD patients were to a large extent explained by differences in the tobacco and alcohol use rather than antidepressant medication, suggesting that population biases in MDD patients are skewed toward MET risks and contributed to regional patterns of MDD-control differences.

This study has some limitations. The representative, validation, and subclinical datasets consisted of non-overlapping subjects but were derived from the same UK biobank cohort which may limit the generalizability to other non-British cohorts. The neuropsychiatric RVIs have been accurate across diverse cohorts (Kochunov, Fan, et al., 2020), but this analysis did not test the validity of RVI-MET outside of data provided by UK BioBank. Another limitation is in the population data: UKBB subjects have a limited age range, chiefly Caucasian British and were less likely to be the current smokers or have depression compared to the general population (Adams et al., 2020). The hyperlipidemia, hypertension, and Type 2 diabetes—the main components of MET—often manifest in people in their 50s or later, while MDD often begins in adolescence. Because of this, and the relatively older mean age of the UKBB participants, we were unable to fully test the directions of causality between MET and MDD, which was beyond the focus of this study but is a potential direction for the future studies. Also, participants may have underdiagnosed MET or MDD and may not have reported medications. For example, there was a category for participants to disclose if they were taking insulin, blood pressure, or cholesterol medication, but they were not asked to disclose which specific medications at that point in the interview. Similarly, though we attempted to make the requirements for MET-controls as stringent as possible, there could be some contamination of at-risk for MET participants in representative set. We mitigated risk of contamination by checking each participant's bloodwork data and blood pressure measures, as well as checking the mental health survey answers. We checked survey questions about recreational drug or alcohol use as unprescribed medicine, survey questions about specific medication usage, and alcohol and smoking data.

In summary, the deleterious effects of the MET lead to a formation of a tissue and region-specific cerebral deficit pattern. We developed RVI-MET as a measure of similarity between individual and expected deficit patterns in MET. The whole-brain RVI values were significantly elevated in subjects with MET and the effect sizes for the whole-brain and tissue specific RVI were higher than for standard brain measures. The individual RVI values, including these for cortical thickness and subcortical volumes were positively associated with the volume of the FLAIR T2-hyperintensive white matter regions and BMI, suggesting whole-brain nature of the MET deficits. The cortical, subcortical, and white matter deficits patterns for MET overlapped closely with those reported by independent large-scale meta-analyses of MDD findings and MDD subjects had significantly higher RVI-MET values versus the corresponding non-psychiatric group. This overlap was partially explained by contributions of higher BMI, alcohol, and tobacco use in subjects with MDD.

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CONFLICT OF INTEREST STATEMENT

L. Elliot Hong has received or plans to receive research funding or consulting fees on research projects from Mitsubishi, Your Energy Systems LLC, Neuralstem, Taisho, Heptares, Pfizer, Luye Pharma, IGC Pharma, Sound Pharma, Takeda, and Regeneron. None was involved in the design, analysis, or outcomes of the study. Paul M. Thompson and Neda Jahanshad received grant support from Biogen, Inc. (Boston, MA, USA) for research unrelated to the topic of this manuscript. Aristeidis Sotiras has equity in TheraPanacea and received compensation for reviewing grants with BrightFocus Foundations (Clarksburg, MD, USA). All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the UK BioBank. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the UK BioBank.

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SUPPORTING INFORMATION

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

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