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Cardiovascular Risk Predicts White Matter Hyperintensities, Brain Atrophy and Treatment Resistance in Major Depressive Disorder: Role of Genetic Liability

Marco Paolini[1] | Melania Maccario[1,2] | Virginia Saredi[1] | Anna Verri[1] | Federico Calesella[1] | Laura Raffaelli[1,2] | Cristina Lorenzi[1] | Sara Spadini[1] | Raffaella Zanardi[2,3] | Cristina Colombo[2,3] | Sara Poletti[1,2] | Francesco Benedetti[1,2]

[1]Psychiatry and Clinical Psychobiology, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milan, Italy | [2]Vita-Salute San Raffaele University, Milan, Italy | [3]Mood Disorders Unit, IRCCS Ospedale San Raffaele, Milan, Italy

Correspondence: Marco Paolini (paolini.marco@hsr.it)

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ABSTRACT

Introduction: Depressive disorders are a leading cause of global disease burden, particularly with the challenge of treatment-resistant depression (TRD). Research points to a complex bidirectional relationship between cardiovascular (CV) risk factors and TRD, with CV risk negatively impacting brain structure and potentially influencing antidepressant resistance. Moreover, the association between depression and the genetic vulnerability to cardiovascular disease suggests a shared pathophysiological process between the two. This study investigates the mediating role of brain structural alterations in the relationship between CV and cerebrovascular (CeV) risk and treatment resistance in depression.

Methods: We assessed 165 inpatients with Major depressive disorder. Each patient's CV risk was assessed via the QRISK 3 calculator. For a subset of patients, CV and CeV disease polygenic risk scores (PRS) were obtained. All patients underwent a 3 T MRI scan, and white matter hyperintensities estimates and indicators of brain trophic state were obtained.

Results: Both CV risk and CV disease PRSs are associated with treatment resistance status, white matter hyperintensities, and indicators of brain atrophy. Mediation analyses suggested that CV-induced brain alterations might underlie the relation between CV genetic and phenotypic risk and antidepressant treatment resistance.

Conclusion: These results underscore the need to explore cardiovascular risk management as part of treatment strategies for depression, pointing toward a shared pathophysiological process linking heart and brain health in treatment-resistant depression.

1 | Introduction

Depressive disorders are among the leading causes of disease burden worldwide, ranking first among psychiatric conditions [1]. Available treatment strategies for depression show moderate efficacy in real-world studies [2], and the increasing number and availability of antidepressant treatments over time have not so far produced a reduction in depression prevalence [3]. Focusing specifically on treatment-resistant depression (usually defined as treatment failure on at least two oral antidepressants given at adequate dose and duration) a grim picture emerges, with a vast majority of subjects exhibiting no response after one year

Summary

- Significant outcomes
  - Both cardiovascular risk and cardiovascular disease genetic liability are associated with antidepressant treatment resistance, brain volumes, and white matter hyperintensities.
  - Individuals with treatment-resistant depression exhibited lower normalized brain volumes and higher white matter hyperintensity load.
  - Indirect associations of cardiovascular risk and cardiovascular disease genetic predisposition with treatment resistance through brain MRI markers were identified.
- Limitations
  - The cross-sectional nature of the study limits our ability to draw causal inferences.
  - Recruitment in a single centre hampers generalizability, while the absence of a healthy control group does not allow us to establish whether our findings are specific to MDD patients.
  - Genetic data were available only for a subset of patients, while resistance status was assessed retrospectively from each patient's clinical history.

of follow-up [4]. Accordingly, a recent population study found more than 30% of treated MDD patients in the United States to meet the criteria for TRD and to account for almost 50% of MDD disease burden [5].

Among risk factors for TRD, cardiovascular (CV) disease and CV risk factors have often been identified [6]. Large population studies consistently find higher rates of cardiovascular (and cerebrovascular) disease in TRD patients compared with treatment-sensitive ones [7–9] as well as a higher prevalence of cardiovascular risk factors, such as systemic autoimmune diseases and diabetes [9, 10], while the presence of TRD appears to be associated with poorer prognosis and higher mortality in coronary heart disease [11].

The relation between cardiovascular disease and depression appears indeed to be a bidirectional one, with coronary heart disease predicting the subsequent onset of depression [12], and depression being a robust risk factor for cardiovascular disease [13, 14]. Possible pathophysiological mechanisms underlying this association include immune-inflammatory alterations, autonomic and endothelial dysfunction, and changes in platelet function [15]. Interestingly, a recent mendelian randomization study performed on UK biobank data found a positive family history of heart disease to be associated with an increased risk of depression, but at the same time, coronary heart disease genetic risk score was found to have little association with depression risk: to solve this apparent paradox, the authors investigated and identified an association between depression and the genetic vulnerability to known cardiovascular risk factors (specifically triglycerides, CRP and IL-6 levels) suggesting a shared pathophysiological process—possibly involving dyslipidaemia and inflammatory alterations—to underlie the development of both depression and cardiovascular disease [16].

However, how cardiovascular risk or disease translates to depressive symptomatology and antidepressant resistance remains a largely open research question. CV risk and disease have detrimental effects on the brain, having been associated with grey matter volumetric reductions [17], increased white matter hyperintensities and mean diffusivity [18], and accelerated brain aging [19]. The largest study to date (15,104 available MRI scans) [20] robustly associated cardiovascular risk (measured via Framingham General Cardiovascular Risk Score) with lower whole brain grey matter and higher white matter hyperintensities volumes. While both grey matter volumetric reductions [21] and WMH load [22] have been associated with treatment resistance in depression, to our knowledge no study investigated their role as a possible pathophysiological link between cardiovascular risk and antidepressant resistance.

In the present study, therefore, we aimed to investigate the possible mediating role of brain structural alterations on the relation between cardiovascular and cerebrovascular risk and treatment resistance in a sample of MDD inpatients in a real-world clinical setting.

2 | Materials and Methods

2.1 | Participants

Our study was performed on 165 inpatients consecutively admitted to San Raffaele Hospital psychiatric ward in Milan (recruitment interval: January 2015—December 2023). Our inclusion criteria were diagnosis of Major depressive disorder (DSM 5 criteria), ongoing non-psychotic depressive episode, and ability and willingness to undergo a 3 Tesla MRI scan. Our exclusion criteria were: age below 25 or above 69 years, presence of other psychiatric diagnoses, intellectual disabilities, drug and alcohol abuse or dependency, and pregnancy. The lower age limit of 25 was set on the basis of QRISK calculator 25–84 age interval validity (https://qrisk.org/), while the higher bound was selected to avoid heterogeneity and confounding effects on MRI findings associated with advanced age [23].

Concerning medical comorbidities, as per QRISK calculator indications, patients with a prior diagnosis of coronary heart disease or stroke/transient ischaemic attack were excluded from the study. After a complete description of the study was given to the participants, written informed consent was obtained. All the research activities were approved by the local ethical committee (Approval Protocol Number 10-06-SO).

2.2 | Treatment Resistance Status and Cardiovascular Risk Determination

Resistance status was investigated through the patients' clinical history up until the moment of MRI scan: specifically, a trained psychiatrist assessed resistance status investigating patients' reports, available clinical documentation, and clinical notes. TRD was defined as failure to respond to at least two separate antidepressant treatments, administered with an adequate dose and duration [24, 25]; non-adherence or

treatment discontinuation was not considered sufficient to indicate treatment failure.

Individual cardiovascular risk was assessed via the QRISK 3 calculator (https://www.qrisk.org/), a validated algorithm used to calculate a person's risk of developing a heart attack or stroke over the next 10 years [26]; beside QRISK, a relative risk (i.e., the individual risk divided by the score of a healthy person of the same age, sex and ethnic group) and an Heart Age score (the age at which a healthy person of the same sex and ethnicity has the same 10-year QRISK score) were obtained. Subsequently we subtracted patients' anagraphical age from the identified heart age to obtain the difference between the two (AGEDIFF).

2.3 | Genetic Sequencing and Polygenic Risk Scores Calculation

For a subsample of 113 patients, genetic data were available. Details on genetic quality check and imputation can be found in Supporting Information.

PRS calculation was performed through the Polygenic Score Calculation extension of the Michigan Imputation Server [27–29]: among PRSs available in the PGS Catalog [30], the following were selected for cardiovascular disease (PGS002682, PGS002633, PGS002584, PGS002535, PGS002388, PGS002316) [31] and cerebrovascular disease (PGS002053) [32].

2.4 | MRI Acquisition, White Matter Hyperintensities, and Brain Volume Calculation

All patients underwent 3T MRI acquisition. 33 patients underwent a 3T MRI scan in a Philips Gyroscan Intera scanner, while 132 patients were acquired in a Philips Ingenia CX scanner. Details on MRI sequences can be found in Supporting Information.

T1 sequences were analysed using SIENAX 2.6, as implemented in FSL 6.0 [33, 34], to estimate brain tissue volume, normalized for subject head size (NBV); separate estimates of volumes of grey matter (NGV), white matter (NWV) and ventricular CSF (NCSF) were also obtained. All measures were expressed in cm3.

White matter hyperintensities were estimated from FLAIR sequences via the lesion prediction algorithm (LPA) as implemented in the LST 3.0.0 toolbox for SPM12 [35]. Lesion probability maps were used to extract total lesion volume (in mL) (WMH-V) and number (WMH-N) with the default threshold of 0.5 for the computation of binary lesion maps.

2.5 | Statistical Analyses

Statistical analyses were performed through commercially available software (StatSoft Statistica 12, Tulsa, OK, USA; Hayes' Process macro for IBM SPSS statistics 23). Normality of distribution of brain MRI indexes was tested through the Kolmogorov–Smirnov test: variables with non-normal distribution were both analysed through non-parametric statistics and log10 transformed to be entered in parametric models.

The association between variables of interest was tested through linear and logistic regressions. Further, we tested the combined predictive value of variables related to cardiovascular health on treatment resistance through a ridge regression model. To test the possible indirect effects of CV indicators on resistance status through MRI indexes, we performed mediation analyses through Hayes' Process macro [36].

Further details on statistical analyses can be found in Supporting Information.

3 | Results

Details on the clinical and demographic characteristics of the sample can be found in Table 1. The average age of participants was 51.74 ± 9.76, with a majority of women ($n = 103$, 62% of the sample) and an average of 12.94 ± 3.79 years of education.

White matter hyperintensities (WMH-V), normalised CSF (NCSF) and white matter (NWV) volumes were not normally distributed (K-S $d = 0.29$, $p < 0.01$; K-S $d = 0.11$, $p < 0.05$; K-S $d = 0.12$, $p < 0.05$, respectively). After log10 transformation, WMH-V and NCSF were normally distributed (K-S $d = 0.04$, $p > 0.20$; K-S $d = 0.06$, $p > 0.20$ respectively) while NWV remained non-normally distributed (K-S $d = 0.11$, $p < 0.05$).

Significant positive correlations were identified between cardiovascular disease PRSs and individual patients' cardiovascular risk, specifically between: relative risk and PGS002584 ($r = 0.21$, $p = 0.028$), PGS002316 ($r = 0.19$, $p = 0.044$); heart age and PGS002682 ($r = 0.21$, $p = 0.030$), PGS002584 ($r = 0.24$, $p = 0.010$), PGS002316 ($r = 0.23$, $p = 0.017$); difference between heart and anagraphical age (AGEDIFF) and PGS002682 ($r = 0.20$, $p = 0.036$), PGS002584 ($r = 0.24$, $p = 0.013$), PGS002316 ($r = 0.22$, $p = 0.020$). No significant association were identified between patients' cardiovascular risk and the PRS for cerebrovascular disease (PGS002053).

Both log10 transformed WMH-V and WMH-N correlated with NBV, NGV, and log10 transformed NCSF (WMH-V with NBV, $r = -0.27$, $p < 0.001$; with NGV, $r = -0.26$, $p = 0.001$; with NCSF, $r = 0.37$, $p < 0.001$; WMH-N with NBV, $r = -0.32$, $p < 0.001$; with NGV, $r = -0.28$, $p < 0.001$; with NCSF, $r = 0.25$, $p = 0.001$). WMH-N also negatively associated with NWV ($r = -0.19$, $p = 0.015$).

3.1 | Effect of CV Risk and PRSs on Treatment Resistance

Cardiovascular risk is significantly associated with treatment resistance. Specifically, this was observed for QRISK (OR = 1.14, LR$\chi^2 = 4.84$, $p = 0.028$) (Figure 1a) and relative risk (OR = 1.60, LR$\chi^2 = 4.24$, $p = 0.039$) (Figure 1b), with a statistical trend for heart age (OR = 1.06, LR$\chi^2 = 3.66$, $p = 0.056$) and AGEDIFF (OR = 1.06, LR$\chi^2 = 3.66$, $p = 0.056$).

TABLE 1 | Clinical and demographic characteristics of the sample.

	Whole sample ($n = 165$)	Non-TRD ($n = 73$)	TRD ($n = 92$)	χ^2/t-test p[a]
Age	51.74 ± 9.76	49.49 ± 10.22	53.52 ± 9.05	*0.008*
Sex (F/M)	103/62	50/23	53/39	0.151
Education (years)	12.94 ± 3.79	12.89 ± 3.50	12.99 ± 4.02	0.800
MRI scan	33/132	18/55	15/77	0.183
Duration of episode (weeks)	39.11 ± 43.24	29.96 ± 28.08	46.37 ± 51.23	*0.015*
Age at onset	34.34 ± 12.92	34.97 ± 12.52	33.84 ± 13.27	0.576
BMI (kg/m^2)	24.71 ± 4.44	24.14 ± 4.29	25.16 ± 4.53	0.151
QRISK (%)	5.79 ± 4.87	4.32 ± 4.17	6.96 ± 5.09	*< 0.001*
Relative risk	1.37 ± 0.75	1.23 ± 0.61	1.48 ± 0.83	*0.032*
Heart age	54.78 ± 12.85	51.47 ± 11.76	57.41 ± 11.30	*0.001*
AGEDIFF	3.04 ± 5.39	1.97 ± 4.75	3.89 ± 5.72	*0.023*
WMH-V (mL)	2.08 ± 3.79	1.19 ± 1.49	2.78 ± 4.79	*0.014*
WMH-N	11.41 ± 7.62	9.83 ± 6.00	12.65 ± 8.52	*0.018*
NBV (cm^3)	1392.17 ± 61.21	1411.26 ± 58.21	1377.01 ± 61.39	*< 0.001*
NGV (cm^3)	699.20 ± 42.16	708.97 ± 44.75	691.45 ± 38.49	*0.008*
NWV (cm^3)	692.96 ± 59.43	702.29 ± 61.89	685.56 ± 56.66	0.114
NCSF (cm^3)	48.29 ± 14.81	45.44 ± 14.16	50.55 ± 15.02	*0.011*

Note: Italic indicates significant tests.

[a]Normally distributed variables were tested through independent sample *t*-tests. Non-normally distributed variables were tested through Mann–Whitney *U* test.

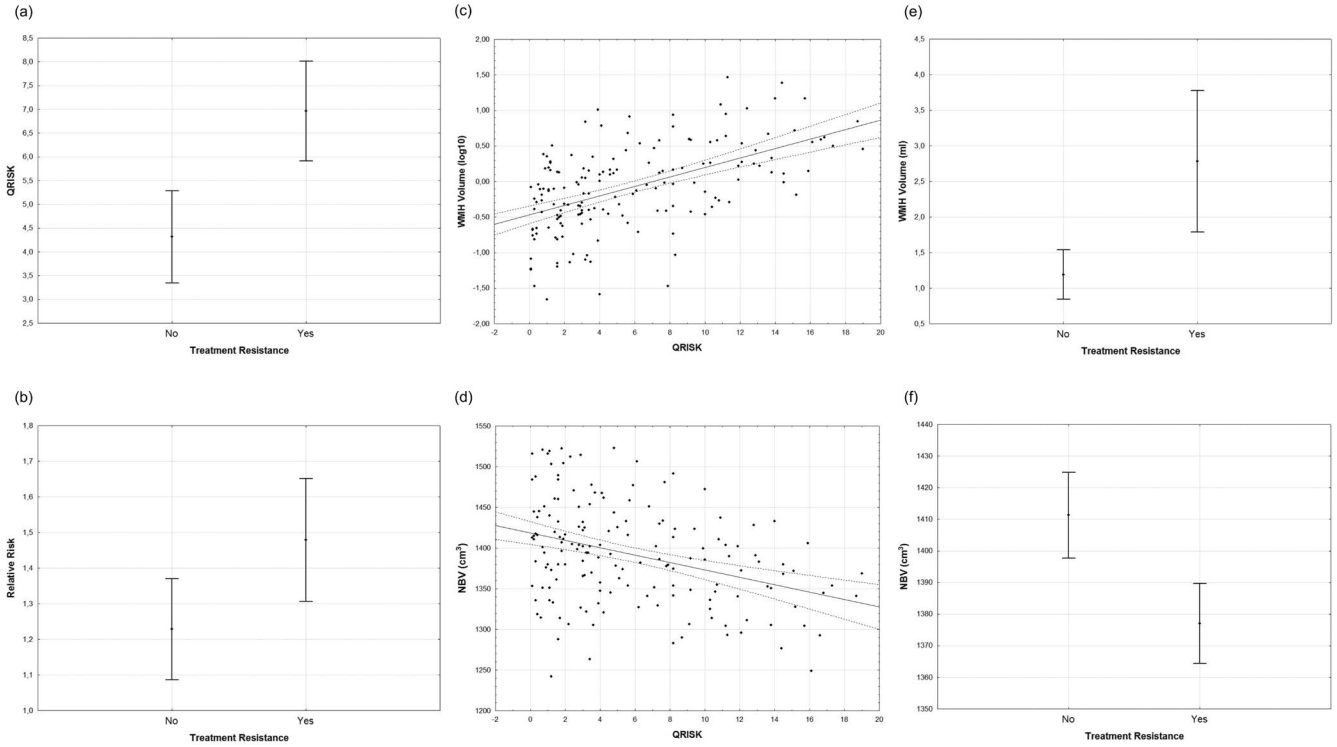


FIGURE 1 | Association between indicators of CV risk, brain structure, and treatment resistance. Points represent mean values; whiskers represent 95% confidence intervals.

Significant associations emerged between cardiovascular and cerebrovascular disease PRSs and treatment resistance status (PGS002535, OR = 2.22, LRχ^2 = 5.92, p = 0.015; PGS002584, OR = 2.40, LRχ^2 = 4.38, p = 0.036; PGS002053, OR = 1.20, LRχ^2 = 4.22, p = 0.040).

3.2 | Ridge Regression

The ridge regression predictive model reached a balanced accuracy of 66%, with sensitivity of 69% and specificity of 63%, positive predictive value of 69%, negative predictive value of 63%, and area under the curve of 0.66. The model was found to be significantly different from a distribution of permuted models with p-value = 0.014. The most predictive features were the QRISK (median weight = 0.22; 95% BCa CI [0.09, 0.32]), heart age (median weight = 0.14; 95% BCa CI [0.0004, 0.27]), PGS002535 (median weight = 0.13; 95% BCa CI [0.02, 0.22]), and PGS002053 (median weight = 0.17; 95% BCa CI [0.005, 0.32]), with a positive association with treatment resistance (Table 2).

3.3 | Effect of CV Risk on White Matter Hyperintensities and Brain Tissue Volumes

Cardiovascular risk is significantly associated with white matter hyperintensities and indicators of brain atrophy.

Specifically, positive associations were found between QRISK and WMH-V (r_s = 0.53, p < 0.001) (Figure 1c), NCSF (r_s = 0.30, p < 0.001); relative risk and WMH-V (r_s = 0.20, p = 0.009); heart age and WMH-V (r_s = 0.55, p < 0.001), NCSF (r_s = 0.28, p < 0.001); AGEDIFF and WMH-V (r_s = 0.21, p = 0.006).

Controlling for age, sex, education, and scan, only the associations between WMH-V and QRISK were confirmed (β = 0.33, F = 10.19, p = 0.002), while the other associations with VMH-V and NCSF were no longer significant.

Furthermore, VMH-N is positively associated with all indexes of CV risk (QRISK: β = 0.58, F = 32.02, p < 0.001; RR: β = 0.16, F = 5.85, p = 0.017; heart age: β = 0.45, F = 9.36, p = 0.003; AGEDIFF: β = 0.21, F = 9.35, p = 0.003), and QRISK is negatively associated with NBV (β = −0.29, F = 8.37, p = 0.004) (Figure 1d).

TABLE 2 | Results of 5000-bootstrap procedure of the ridge regression predictive model.

Feature	Median weight	SD	95% BCa confidence interval
QRISK	0.22	0.06	0.09, 0.32[a]
Relative risk	0.05	0.06	−0.09, 0.15
Heart age	0.14	0.07	0.0004, 0.27[a]
AGEDIFF	0.04	0.06	−0.08, 0.16
PGS002682	−0.04	0.06	−0.15, 0.08
PGS002633	0.05	0.06	−0.08, 0.17
PGS002584	0.06	0.06	−0.07, 0.16
PGS002535	0.13	0.05	0.02, 0.22[a]
PGS002388	0.03	0.06	−0.1, 0.14
PGS002316	0.06	0.06	−0.06, 0.17
PGS002053	0.17	0.08	0.005, 0.32[a]

[a]95% BCa CI not including 0.

3.4 | Effect of PRSs on White Matter Hyperintensities and Brain Tissue Volumes

Concerning cardiovascular disease PRS, significant positive associations were found between PGS002682, PGS002584, PGS002535, and PGS002388 and WMH-V (r_s = 0.21, p = 0.026; r_s = 0.19, p = 0.040; r_s = 0.19, p = 0.044; r_s = 0.19, p = 0.048, respectively).

Controlling for age, sex, education, and scan, strong associations between all cardiovascular disease PRS and white matter hyperintensities emerged: PGS002682 with WMH-V (β = 0.25, F = 9.77, p = 0.002) and WMH-N (β = 0.23, F = 8.27, p = 0.005); PGS002633 with WMH-V (β = 0.21, F = 7.01, p = 0.009) and WMH-N (β = 0.19, F = 5.21, p = 0.024); PGS002584 with WMH-V (β = 0.25, F = 9.93, p = 0.002) and WMH-N (β = 0.27, F = 11.65, p < 0.001); PGS002535 with WMH-V (β = 0.24, F = 9.14, p = 0.003) and WMH-N (β = 0.23, F = 8.77, p = 0.004); PGS002388 with WMH-V (β = 0.21, F = 7.36, p = 0.008) and WMH-N (β = 0.23, F = 8.45, p = 0.004); PGS002316 with WMH-V (β = 0.23, F = 8.51, p = 0.004) and WMH-N (β = 0.24, F = 8.71, p = 0.004). No association was, on the other hand, found for CeV PRS (PGS002053).

No association emerged between PRSs and indexes of brain atrophy.

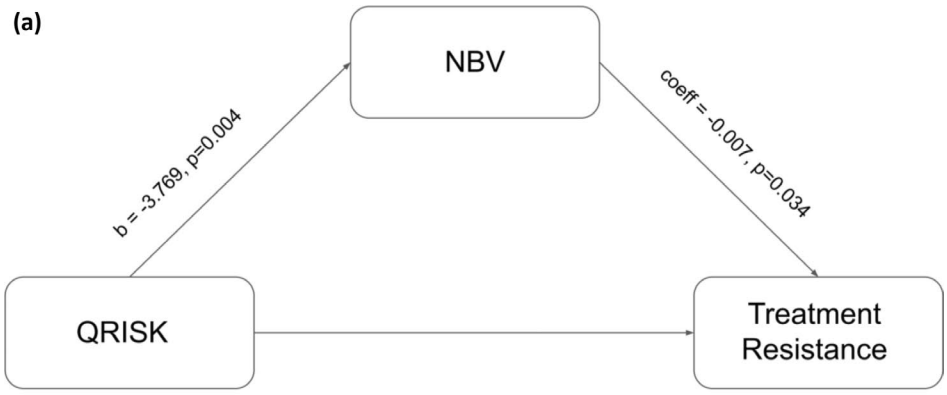
3.5 | Effect of White Matter Hyperintensities and Brain Tissue Volumes on Treatment Resistance Status

A significant positive association emerged between WMH-V and treatment resistance (OR = 1.20, LRχ^2 = 5.69, p = 0.017) (Figure 1e). Furthermore, inverse associations were found between NBV and NGV and resistance status (OR = 0.99, LRχ^2 = 6.57, p = 0.010; OR = 0.99, LRχ^2 = 6.77, p = 0.009 respectively) (Figure 1f).

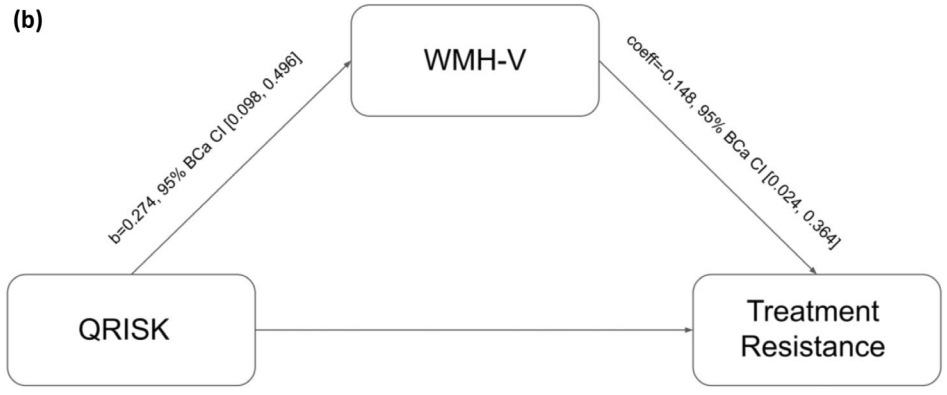
3.6 | Mediation Analyses

Finally, significant mediations were found between cardiovascular risk and CV PRSs, indices of brain atrophy and white matter hyperintensities, and treatment resistance status (Figure 2); specifically, significant indirect effects were found for the association of QRISK and treatment resistance through NBV (effect = 0.0281, 95% BCa CI [0.0016, 0.0730]) (Figure 2a) and WMH-V (effect = 0.0405, 95% BCa CI [0.0049, 0.1220]) (Figure 2b).

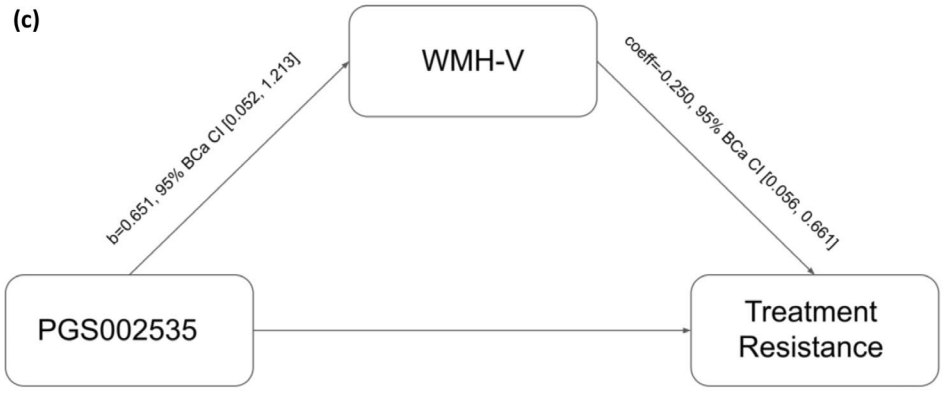
Among CV PRSs, PGS002535 was found to significantly associate with treatment resistance status through its effect on WMH-V (effect = 0.1629, 95% BCa CI [0.0017, 0.5870]) (Figure 2c).



Direct effect: effect=0.103, p=0.100
Indirect effect: effect=0.028, 95% BCa CI [0.002, 0.073]



Direct effect: effect=0.100, p=0.109
Indirect effect: effect=0.040, 95% BCa CI [0.005, 0.122]



Direct effect: effect=0.707, p=0.049
Indirect effect: effect=0.163, 95% BCa CI [0.002, 0.587]

FIGURE 2 | Results of mediation analyses. Direct and indirect effects of *X* on *Y* are on a log-odds metric.

Adding the duration of the current depressive episode as a covariate to the analyses investigating resistance status produced largely overlapping results, with the exception of the effect of PGS002053, which was no longer significant (see Supporting Information).

4 | Discussion

Our study provided several results. First, we identified a positive association between cardiovascular risk and antidepressant treatment resistance: higher QRISK and CV relative risk scores increased the likelihood of treatment resistance, with trends in the same directions for other CV indicators. This is in line with results from previous large population studies that repeatedly found CV risk and disease to be associated with TRD [6–9].

Interestingly, we identified an analogous relation with resistance status for cardiovascular (specifically PGS catalog PGS002535 and PGS002584 "cardiovascular disease" PRS) and cerebrovascular (PGS catalog PGS002053 "cerebrovascular disease" PRS) genetic risk. Furthermore, cardiovascular disease PRSs exhibited significant correlations with observed "phenotypic" cardiovascular risk, highlighting their impact on individual patients' CV health. Of particular note, on the other hand, cerebrovascular disease PRS had no correlation with any measure of CV risk, possibly suggesting its connection with distinct (albeit certainly partially overlapping) pathophysiological processes. Finally, our ridge multivariate analysis identified both phenotypic CV risk (QRISK and Heart age) and cardiovascular (PGS002535) and cerebrovascular (PGS002053) genetic risk as significant independent predictors of treatment resistance status.

While the association between CV risk and antidepressant resistance appears to be robustly established, whether cardiovascular genetic risk contributes to the genetic architecture of TRD is still an open question. In recent years, however, substantial progress has been achieved in this regard. Conceptually different but closely related to treatment resistance, antidepressant treatment response has been associated with both higher PRS scores for coronary artery disease and obesity [37], as well as to the genetic risk for various types of stroke [38]; concerning treatment-resistant depression, its association with the genetic risk of known CV risk factors, such as obesity, type 2 diabetes, and cigarette smoking, has also been reported [39, 40].

Cardiovascular risk and CV disease genetic liability are also significantly associated with brain structure in our sample. This was true both in the case of white matter hyperintensities and, only for phenotypic CV risk, of brain and grey matter volumes.

White matter hyperintensities (WMH) of presumed vascular origin are white matter lesions that appear hyperintense in FLAIR sequences [41]: being an extremely common finding with increasing age, their clinical significance is still a matter of debate [42], despite having been associated with increased risk of stroke, cognitive decline, and overall mortality [43, 44]. They are classically associated with cardiovascular risk factors [42] and they are a regular finding in individuals with cerebral small vessel disease [45]: accordingly, a recent large study associated CV risk with higher WMH burden [20]. However, their exact pathophysiology is still debated and likely multifactorial, having been linked to cerebral hypoperfusion and chronic ischemia, but also to endothelial, microglial, astrocytic, and oligodendrocytic dysfunction and to increased blood–brain barrier permeability, in a pathological process that likely encompasses the whole neuro-glio-vascular unit [42, 46]. Accordingly, a recent UK biobank study found cardiovascular risk factors to account only for about 32% of the variance in WMH volume, leaving the remaining majority of the variance unexplained [47].

Phenotypic CV risk is also associated with reduced total and grey matter volumes in our sample, again mirroring the results of a recent large UK biobank study [20], and of numerous other investigations [17, 48, 49]. Nonetheless, while again frequently reported, the association between cardiovascular health and brain volumes appears to be a complex one, with various pathophysiological mechanisms implicated [50]. Cerebral small vessel disease (SVD) might again underlie part of the association, as among its neuroradiological features (besides white matter hyperintensities and lacunae) is also brain atrophy [51, 52]. Indeed, brain volumes and WMH load were inversely correlated in our sample, even after controlling for age. A specific subtype of SVD appears to be mainly linked to CV risk factors (such as diabetes and hypertension), associated with small vessels loss of smooth muscle cells, wall thickening and narrowing of the lumen: this pathological process could then lead to brain damage through various processes, including reduced blood flow with chronic ischaemia, blood–brain barrier damage and perivascular leakages, and vessel rupture with microscopic bleedings [52, 53]. Furthermore, other processes could link CV risk to reduced brain volume, such as cerebral atherosclerosis, hypoperfusion and amyloid-β peptide deposition [51].

Both WMH burden and brain and grey matter volumes were associated with resistance status in our sample: individuals with higher WMH volume and number, and with lower brain and grey matter volumes, were more likely to be treatment resistant. Higher WMH load has been repeatedly associated with hampered response to both antidepressant and ECT [22, 54]. Surprisingly, on the other hand, the relation between whole brain volumes and antidepressant efficacy has been rarely investigated and usually yielded negative results, with the exception of a single study associating larger ventricular volumes with non-response [22, 55]. However, it must be noted that reduced response to antidepressants has been associated with grey matter volumetric reductions in widespread brain regions [21], which could also translate to whole brain volumetric reductions. Furthermore, reduced hippocampal volumes, one of the most replicated predictors of poor antidepressant response [21, 56], are classically regarded as an early marker of brain atrophic states and have repeatedly been found to be affected by CV risk [57–59].

Finally, brain structural alterations significantly mediated the relation between cardiovascular risk and treatment resistance in our sample. This was true for phenotypic CV risk (QRISK) through its association with brain volume and WMH load, and for CV genetic risk (PGS002535) through its association with WMH. While in some cases the individual paths of this mediation model had already been reported [6, 20–22, 37] no study to our knowledge explicitly tested a possible indirect effect of

CV status on antidepressant resistance through its effect on brain structure. This adds to our current understanding of TRD, providing a possible mechanistic path through which both phenotypic and genetically determined CV risk could affect antidepressant efficacy.

Despite their long history, the biological bases of antidepressant effects are not yet completely understood [60]; however, in recent years, enhancement of BDNF–TrkB transmission has emerged as a putative final path through which the plethora of available antidepressant drugs with different mechanisms of action could lead to mood elevation [61, 62]. A surprising bidirectional relation appears to exist between BDNF and CV health [63]. BDNF levels are reduced in patients with coronary artery disease [64] or subclinical cardiac dysfunction [65] and have been linked to the development of depressive symptoms [66]; at the same time, direct cardioprotective effects of BDNF have been postulated [64, 67]. Furthermore, BDNF levels have also been associated with brain volume and trophic state [68, 69] and with WMH load [70]. While the relation between peripheral BDNF levels and brain concentration is controversial [71], it is possible to speculate that BDNF alterations associated with CV factors might underlie at least part of the association we identified between CV risk, brain structure, and antidepressant resistance.

Finally, it is worth noting that while we also identified cerebrovascular disease genetic risk (PGS002053) to influence treatment resistance, no association was found between this genetic trait and brain structure or phenotypic CV risk. This might suggest that cerebrovascular genetic risk affects antidepressant efficacy through distinct pathophysiological mechanisms, partially independent from CV status and its effects on brain structure. The possible biological underpinnings of this association will have to be investigated in future research.

This study has several limitations. Recruitment was performed in a single centre, thus limiting the generalizability of our findings. The absence of a healthy controls group does not allow us to estimate how our findings could compare to a general population sample, that is, if there is a specificity in CV risk and its relation to MRI findings in MDD. Our sample size, albeit typical for a neuroimaging study, is smaller than those usually employed in genetic analyses. Further, CV genetic risk estimation is still in its infancy, with poor individual level agreement between several coronary heart disease PRSs [72]: while our findings partially replicate other published studies [37–40], much research is still needed to confirm our results and ultimately translate them at the individual clinical level. Resistance status was retrospectively assessed from the patient's clinical charts and might, therefore, be susceptible to recollection bias; likewise, while we did not consider incorrect drug intake or drug discontinuation for the determination of TRD, information on treatment adherence was obtained from patients' clinical history, as drugs plasma level determination was not available. Furthermore, we couldn't specifically investigate residual symptom domains that could be more directly related to cardiovascular health, such as fatigue and anhedonia [73]. Given the real-world nature of our study, patients were prescribed a wide variety of pharmacological treatments, both during their disease history and at the moment of assessment, which could have influenced both CV status and MRI data and that we could not control for.

A crucial limitation of our work is its cross-sectional nature, which limits our ability to draw causal inferences: this is particularly true for the association between CV risk and TRD, for which a bidirectional causal link could be at least hypothesized; future longitudinal studies with long-term follow-up will help disentangle this likely complex relation, allowing an evaluation of the effects of CV health and risk factors on the subsequent development of MRI alterations and ultimately of antidepressant resistance.

5 | Conclusion

Despite these limitations, this study sheds light on the biological basis underlying the association between CV risk and treatment resistance in depression, identifying the crucial role of CV risk-induced brain alterations in affecting antidepressant efficacy. These findings can not only improve our understanding of TRD pathophysiology, but they might also suggest novel treatment approaches in selected cases of TRD, through an intervention on modifiable CV risk factors. Indeed, while the heart might not be the seat of the soul, it may very well prove to be crucial in its healing.

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Consent

Written informed consent was obtained for all participants in the study. All the research activities were approved by the local ethical committee.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.