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Predicted plasma proteomics from genetic scores and treatment outcomes in major depression: a meta-analysis

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ABSTRACT

Proteomics has been scarcely explored for predicting treatment outcomes in major depressive disorder (MDD), due to methodological challenges and costs. Predicting protein levels from genetic scores provides opportunities for exploratory studies and the selection of targeted panels. In this study, we examined the association between genetically predicted plasma proteins and treatment outcomes – including non-response, non-remission, and treatment-resistant depression (TRD) – in 3559 patients with MDD from four clinical samples.

Protein levels were predicted from individual-level genotypes using genetic scores from the publicly available OmicsPred database, which estimated genetic scores based on genome-wide genotypes and proteomic measurements from the Olink and SomaScan platforms. Associations between predicted protein levels and treatment

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outcomes were assessed using logistic regression models, adjusted for potential confounders including population stratification. Results were meta-analysed using a random-effects model. The Bonferroni correction was applied.

We analysed 257 proteins for Olink and 1502 for SomaScan; 111 proteins overlapped between the two platforms. Despite no association was significant after multiple-testing correction, many top results were consistent across phenotypes, in particular seven proteins were nominally associated with all the analysed outcomes (CHL1, DUSP13, EVA1C, FCRL2, KITLG, SMAP1, and TIM3/HAVCR2). Additionally, three proteins (CXCL6, IL5RA, and RARRES2) showed consistent nominal associations across both the Olink and SomaScan platforms.

The convergence of results across phenotypes is in line with the hypothesis of the involvement of immune-inflammatory mechanisms and neuroplasticity in treatment response. These results can provide hints for guiding the selection of protein panels in future proteomic studies.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder and a leading contributor to disability worldwide, with a 61.1 % increase in disability-adjusted life years over the past 20 years (Vos et al., 2020). Treatments for MDD include psychotherapeutic approaches, pharmacological interventions, neuromodulation therapies such as electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS), or a combination of these strategies (Kendrick et al., 2022). However, up to 60 % of patients do not respond adequately to the initial treatment, and require changes in therapy through a trial-and-error process (De Carlo et al., 2016; van Westrhenen and Ingelman-Sundberg, 2021). With each unsuccessful treatment attempt, the likelihood of response diminishes, while the probability of developing treatment-resistant depression (TRD) increases (Bartova et al., 2019; McIntyre et al., 2023). TRD, typically defined as non-response to at least two different treatments, poses a significant burden on both patients and healthcare systems (McIntyre et al., 2023). Therefore, the identification of patients who are likely to become non-responders or treatment-resistant could guide the early prescription of intensive treatments, potentially preventing the progression to TRD.

Genomics may aid the early identification of patients at risk for non-response and TRD. Genome-wide association studies (GWASs) have demonstrated a genetic component in treatment outcomes for MDD, as evidenced by significant single nucleotide polymorphism (SNP)-based heritability (Fabbri et al., 2021; Li et al., 2020; Pain et al., 2022). Building on this foundation, several studies used polygenic scores (PGSs) as potential predictors of treatment outcomes (Fanelli et al., 2021, 2022; Oliva et al., 2024). However, the proportion of phenotypic variance explained by PGSs is limited, and no clinical application has been produced (Fanelli et al., 2022).

Other omics markers such as proteomics can provide complementary insights for predicting treatment response and resistance. Proteomics markers can be determined on serum or plasma, which represent accessible samples using minimally invasive methods. The abundance of circulating proteins provides a distinct snapshot into the function of all organs with which blood comes in contact, providing potential markers related to brain function as well (Deutsch et al., 2021; Guest et al., 2016). Previous studies in this field were mostly focused on candidate proteins, such as the brain-derived neurotrophic factor (BDNF) (Castrén and Rantamäki, 2010), cytokines and other inflammatory markers, such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8) (Mosiołek et al., 2021; Zhou et al., 2021). However, the evidence supporting their association with treatment outcomes is limited and inconsistent, with no single peripheral biomarker demonstrating predictive clinical utility (Abi-Dargham et al., 2023; Carvalho et al., 2020). In the case of a condition as complex and multifactorial as MDD, a hypothesis-free approach would allow an unbiased search for novel disease biomarkers (Geyer et al., 2017). This approach requires high-sensitivity, high-throughput methodologies that allow the entire proteome to be studied, overcoming the limitations encountered with methods focused on pre-selected candidate proteins, such as western blotting or enzyme-linked immunosorbent assay (e.g., ELISA) (Stolfi et al., 2024). Several high-throughput technologies for proteomic profiling are currently available. Mass spectrometry (MS) approaches allow for in-depth blood protein identification and quantification, however the addition of time-consuming processing steps is needed to detect a number of proteins in the order of thousands rather than hundreds (Deutsch et al., 2021). Innovative affinity-based assays for the identification of proteins provide both high-sensitivity and high-throughput results. The proximity extension assay (PEA by Olink) uses antibody pairs conjugated to unique oligonucleotides which are quantified via polymerase chain reaction (PCR). Similarly, the SomaScan technology by SomaLogic is based on slow off-rate modified aptamers, which are single-stranded DNA molecules that can specifically bind to proteins. Added together both affinity-based and MS-based methods could allow the identification of >8000 blood proteins, but further studies evaluating the comparability of these technologies are needed (Deutsch et al., 2021).

Hypothesis-free approaches for testing protein markers of treatment response in MDD have been rarely employed. Although limited by small sample sizes, a few previous proteomic studies investigated the association between treatment response and proteins, using MS (Lee et al., 2024; Turck et al., 2017) or the Multi-Analyte Profiling immunoassay platform (Chan et al., 2016). The results pointed to proteins involved in various biological pathways, such as cell communication and signalling, cell growth, and immune response. However, the comparability of results across different methods and types of samples is unclear, and therefore the criteria to guide the choice of the most suitable method/proteomics platform. A possible strategy is to prioritise the group(s) of proteins with higher chances of involvement in MDD treatment outcomes, for then selecting a proteomic platform and panel.

One promising avenue is the prediction of protein levels from genome-wide genotypes, using genetic score models created in large samples with both genomic and proteomic data. These predictive models developed in samples with both type of data can then be applied to impute protein levels from genetic variants in independent samples, where all variants corresponding to a certain protein are weighted by a coefficient determined in the predictive model (Xu et al., 2023). The rationale for this approach is fourfold: 1) it enables cost-effective and scalable studies in large cohorts when direct protein measurements are unavailable; 2) genetically predicted proteins are not influenced by treatment(s), disease severity, or other state-dependent confounders; 3) it allows the prioritisation of proteins to be followed up in proteomic or functional studies, which is useful considering that current technologies for proteomics focus on part of the proteome and costs are considerable for large panels; 4) genetic scores used to predict protein levels were developed in large and powerful cohorts, providing a standardised and reproducible framework for protein prediction in independent datasets (Dupree et al., 2020; Xu et al., 2023).

In this exploratory study, we examined the association between genetically predicted plasma proteomic profiles and treatment outcomes (i.e., non-response, non-remission, and treatment resistance) in MDD. We focused on identifying proteins consistently associated with multiple outcomes and replicated across two proteomic platforms, Olink and SomaScan. These platforms differ in the used technology: Olink uses

antibody-based proximity extension assays, offering high specificity and minimal sample requirements, whereas SomaScan relies on aptamer-based detection, providing broader proteome coverage and an extended dynamic range. By integrating genetic and proteomic data, our approach aims to contribute: 1) to suggest protein markers that may help to identify patients at risk of poor treatment outcomes at baseline, for then selecting early intensive treatments; 2) to guide the selection of proteomic approaches and panels for future hypothesis-driven studies.

2. Material and methods

2.1. Target samples

The study was based on five samples comprising a total of 4480 participants diagnosed with MDD based on DSM-IV or DSM-IV-TR criteria, recruited from various centres. These included two samples recruited in Italy (Brescia sample 1, $n = 215$; Brescia sample 2 = 286), one from the European Group for the Study of Resistant Depression (GSRD) recruited across multiple European centres ($n = 1410$), one from Germany (Münster, $n = 621$), and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which was conducted in primary care and psychiatric outpatient settings in the United States ($n = 1948$).

Depression severity was assessed using standardized scales, namely the Montgomery-Åsberg Depression Rating Scale (MADRS), the 21-item Hamilton Depression Rating Scale ($HAMD_{21}$), or the Quick Inventory of Depressive Symptomatology Clinician-Rated ($QIDS\text{-}C_{16}$), depending on the cohort. Treatment response was defined as a reduction ≥50 % in symptom severity following pharmacological therapy for ≥4 weeks in all samples, and remission was defined as a MADRS score ≤10, a $HAMD_{21}$ score ≤7, or a $QIDS\text{-}C_{16}$ score ≤ 5, depending on the sample, after pharmacological therapy for ≥4 weeks. TRD was defined as non-response to at least two different treatments (Sforzini et al., 2022). All cohorts were naturalistic and observational, with no predefined treatment protocols, except for STAR*D, where participants received citalopram during level 1, and those with insufficient response were randomised to four switch options and three citalopram augment options in level 2 (Rush et al., 2004) .

More detailed information about each sample and the genotyping procedures can be found in previous publications (Baune et al., 2010; Howland, 2008; Minelli et al., 2015; Oliva et al., 2023).

2.2. Quality control of genotypes in the target datasets

Quality control (QC) and population principal component analysis (PCA) were performed for each of the five target samples using the Ricopili pipeline (Lam et al., 2020). SNPs were retained if they met the following criteria: call rate ≥0.95, case-control missingness difference ≤0.02, minor allele frequency (MAF) ≥0.01, and Hardy-Weinberg equilibrium p-value ≥1e-6. Participants were included in the analysis if they had an autosomal heterozygosity rate within ±0.2, a call rate of ≥0.98, and no discrepancies between genetic and phenotypic sex.

To examine relatedness among subjects and address population stratification, linkage disequilibrium-pruned data (R^2 <0.2) were used to detect pairs of individuals with an identity-by-descent proportion greater than 0.2; one individual from each related pair was excluded. Population stratification was further assessed using PCA with Eigenstrat, and individuals considered outliers were removed based on being beyond ±6 standard deviations from the mean of the first 20 principal components (PCs). Only participants of European descent, determined through self-report/anamnestic data and visual inspection of PCA plots, were retained (Lam et al., 2020).

Genotype imputation was conducted on the Michigan Imputation Server (Das et al., 2016) utilizing Minimac4 and the Haplotype Reference Consortium (HRC) r1.1 2016 (GRCh37/hg19). After imputation, variants with a low imputation quality score (R^2 <0.3) and MAF <0.05 were filtered out.

2.3. Statistical analyses

2.3.1. Protein level prediction

Protein levels in our target samples were predicted from genome-wide individual-level genotypes using genetic score models, using publicly available data from the OmicsPred database (Xu et al., 2023). The authors of OmicsPred created genetic score models using Bayesian Ridge regression on the INTERVAL cohort, a large dataset including approximately 50,000 healthy individuals with both genomic and proteomic data. The models were developed to predict the levels of 308 proteins measured through Olink Target platforms (Inflammation-1 (INF-1), Cardiovascular II (CVD-2), Cardiovascular III (CVD-3) and Neurology (NEUR)) and 2384 proteins from the SomaScan v.3 platform. Variants included in the models were filtered based on a MAF>0.05, exclusion of multi-allelic and ambiguous variants, and linkage disequilibrium pruning with r^2<0.8. A Bayesian ridge regression (BR) with genome-wide variant selection using $p <$ 5e-8 was used to train genetic scores for protein levels (Xu et al., 2023).

In our target samples, we derived predicted protein levels for both the Olink and SomaScan panels using PLINK2, following the OmicsPred guidelines. PLINK2 was used to calculate genetic scores by applying the OmicsPred genetic score models to individual-level genotype data from our target samples after QC and imputation. To improve reliability, we included only proteins for which the predictions were based on ≥ five genetic variants available in the target samples, as scores with five or fewer variants tend to exhibit substantially smaller gains in predictive performance (Xu et al., 2023).

2.3.2. Associations between predicted proteins and treatment outcomes

Multiple logistic regression models were employed to test the association between predicted protein levels (standardized to a mean of 0 and standard deviation of 1) and binary treatment outcomes, categorized as response vs. non-response, remission vs. non-remission, and TRD vs. response. These models were adjusted for age, sex, baseline symptom severity (only for remission/non-remission), population principal components, and recruitment site in case of multi-centre studies (STAR*D, GSRD). This set of covariates was selected considering variables that can either affect treatment outcomes or genotypic frequencies (population principal components), and in accordance to previous studies (Fanelli et al., 2022; Oliva et al., 2023). The analyses were conducted separately for each proteomic platform (Olink and SomaScan) across all cohorts. Odds ratios (ORs) with 95 % confidence intervals (*CIs*) were computed.

All statistical analyses were performed in R (version 4.0.5). Results from each target sample were meta-analysed using the "metafor" R package (Viechtbauer, 2010), applying a random-effects model using the restricted maximum-likelihood estimator (Harville, 1977). Analyses of heterogeneity were performed using the Cochran's Q test (Cochran, 1950), and I^2 statistic (0 % indicates no heterogeneity, and 25 %, 50 %, and 75 % define the thresholds for low, moderate, and high, respectively) (Higgins et al., 2019).

To identify treatment outcome biomarkers, we specifically focused on predicted protein levels that were consistently (i.e., in the same direction) associated with at least two treatment outcomes (non-response, non-remission, and/or TRD), and those that showed cross-platform validation across both Olink and SomaScan, at significance level of $p < 0.05$. This approach is in line with the explorative nature of this study. Key results were visualised using jungle plots, which display ORs and 95 % CI for protein–outcome associations across outcomes and platforms (De Prisco and Oliva, 2024). However, we also applied the Bonferroni correction for multiple testing, considering 257 proteins from the Olink Target platform and 1502 proteins from SomaScan platform (α=0.05/1759=2.84 × 10^{-5}).

3. Results

After QC, a total of 3559 patients with MDD were included in the analyses for non-response (Brescia: n total=453; GSRD: $n = 1149$; Münster: $n = 557$; STAR*D: $n = 1400$), while non-remission and TRD were analysed in 3106, and 1878, respectively. The clinical and demographic characteristics of each target sample are reported in Supplementary Table 1.

After excluding proteins predicted based on <5 variants, 257 proteins were available from the Olink panel, and 1502 proteins from the SomaScan panel, and 111 proteins overlapped between the two platforms.

The results from both the logistic regression analyses and subsequent meta-analyses for each predicted protein are presented in Supplementary Tables 2–5. No association remained significant after the Bonferroni correction.

We examined the consistency of the associations between predicted proteins and non-response, non-remission, and TRD within each proteomic platform. Detailed results are shown in Table 1 and Fig. 1.

On the Olink platform, two proteins - Fc Receptor-like protein 2 (FCRL2) and Kit ligand (KITLG) – were nominally associated with all the analysed outcomes, while four were associated with two phenotypes, namely Integrin beta-2 (ITGB2), C-X-C motif chemokine 6 (CXCL6), Interleukin-5 receptor subunit alpha (IL5RA), and Sulfotransferase 1A1 (SULT1A1).

Using the SomaScan platform, five proteins were nominally associated with all the analysed outcomes (T-cell immunoglobulin and mucin-domain containing-3/Hepatitis A Virus Cellular Receptor 2 (TIM3/HAVCR2), Protein EVA-1 homolog C (EVA1C), Dual Specificity Protein Phosphatase 13 Isoform A (DUSP13), Stromal Membrane-Associated Protein 1 (SMAP1), and Neural cell adhesion molecule L1-like protein (CHL1)). On the same platform, 14 proteins were consistently nominally associated with two outcomes, such as Interleukin-1 receptor antagonist protein (IL1RN), Complement factor H-related protein 5 (CFHR5), Complement factor D (CFD), Neutrophil collagenase (MMP8), and Haloacid dehalogenase-like hydrolase domain-containing protein 2 (HDHD2), see Table 1.

We also examined the consistency of the associations between predicted proteins and treatment outcomes across the Olink and SomaScan platforms (Table 2 and Fig. 2). We found that the predicted levels of Retinoic acid receptor responder protein 2 (RARRES2) showed consistent associations with non-response, and two proteins already outlined for their consistent associations with multiple outcomes were also consistently associated with TRD according to both platforms, namely CXCL6 and IL5RA.

4. Discussion

In this study, we examined the association between genetically predicted plasma proteomic profiles and treatment outcomes in a total sample of 3559 patients with MDD. Although no associations remained significant after Bonferroni correction, given the exploratory nature of this study, we focused on the consistency of nominal results across phenotypes and the two proteomic platforms considered. Seven proteins were consistently associated with all three treatment outcomes, and 18 proteins showed nominal associations with two treatment outcomes, suggesting their potential as treatment outcome biomarkers to be validated in future studies. Three proteins showed consistent associations with TRD/non-response across the two platforms, two of which were also associated with multiple phenotypes, supporting their reliability as potential treatment outcome biomarkers.

Among the proteins consistently associated with all three treatment outcomes, four – FCRL2, TIM3/HAVCR2, DUSP13, and SMAP1 – are involved in immune signalling, cellular stress responses and inflammation (Capone et al., 2016; Katagiri et al., 2011; Monney et al., 2002; Sato et al., 1998). Interesting, TIM-3 and proteins of the DUSP family were studied as possible biomarkers of depression in preliminary studies (Bhore et al., 2017; Wu et al., 2017). The cross-platform validated proteins – RARRES2, IL5RA, and CXCL6 – are also consistently implicated in immune response and inflammation (Dai et al., 2023; Takatsu, 2011; Zabel et al., 2005). Our findings, obtained through the prediction of protein levels, align with studies that use novel proteomic profiling technologies. These studies have identified potential protein markers that could predict treatment response in MDD, often linked to pathways involved in complement activity, regulation, and the immune system (Lee et al., 2024; Turck et al., 2017). These results align with the hypothesis that inflammation plays a role in treatment outcomes of MDD. Dysregulation of both innate and adaptive immune systems is common among patients with depression, and inflammation can act as a critical modifier, increasing vulnerability to depression. This vulnerability may be mediated by mechanisms such as early life trauma, acute stress, microbiome alterations, or genetic predisposition (Beurel et al., 2020; Borgiani et al., 2024). Findings from GWASs supported this evidence, linking genetic variants involved in cytokine and immune regulation to MDD (Wray et al., 2018). Additionally, the role of inflammation in MDD treatment outcomes is crucial; studies suggest that antidepressants may exert anti-inflammatory effects (Köhler et al., 2018), and anti-inflammatory drugs could have antidepressant effects (Köhler-Forsberg et al., 2019), although the results are highly heterogeneous. Heterogeneity can stem from factors such as baseline inflammation, body mass index (BMI), smoking status, methodological differences, type of depression, and the class of antidepressants used. These factors were not consistently considered, often due to the lack of these data. Interestingly, individuals with TRD exhibit elevated levels of inflammation compared to treatment-responsive patients and healthy controls, further supporting the hypothesis that altered immune-inflammation pathways are involved in poor treatment response and resistance (Cattaneo et al., 2020; Chamberlain et al., 2019; Congio et al., 2020). In addition, RARRES2 has been implicated in metabolic regulation and insulin resistance (L. Zhao et al., 2024a), and insulin resistance itself has been repeatedly linked to the pathophysiology of depression (Fernandes et al., 2022). This metabolic perspective offers an additional explanatory framework for our findings, suggesting that RARRES2 may reflect broader neuroendocrine or inflammatory mechanisms contributing to poor treatment outcomes.

Two other predicted proteins – KITLG and EVA1C – associated with all three treatment outcomes influence neurodevelopmental and neurogenesis pathways crucial for neuronal survival (Hu et al., 2022; Vliagoftis et al., 1997). These findings are consistent with the knowledge that impaired neurogenesis is linked to depression, particularly in the hippocampus, a brain region involved in mood regulation, learning, and memory (Tartt et al., 2022). Stress-induced hippocampal atrophy, neuronal loss, and decreased neurogenesis may contribute to the onset and persistence of depressive symptoms. Conversely, enhancing neurogenesis shows antidepressant effects (Schoenfeld and Cameron, 2015). Several antidepressants positively affect various aspects of neurogenesis (Hanson et al., 2011), and preclinical studies suggest that increased neurogenesis is a more nuanced, compound-dependent action of antidepressants rather than a binary event (Lino de Oliveira et al., 2020). Interestingly, the rapid efficacy of ketamine and psilocybin has been linked to swift neuroplastic changes (Kopelman et al., 2023; X. Zhao et al., 2024b).

Despite these promising findings, several limitations should be acknowledged. First, it is important to note that genetically predicted protein levels are not a direct measure of circulating protein concentrations. Although they capture inter-individual variability driven by genetic variants, they do not reflect context-specific protein expression. As previously shown, prediction accuracy (R^2) varies substantially across proteins, and only a minority achieve high concordance with measured levels (Xu et al., 2023). Therefore, our findings should be considered exploratory and useful to guide the selection of proteomics panel for future studies. In addition, none of the associations remained

Table 1
Predicted proteins nominally associated with at least two treatment outcomes (A. Olink; B. SomaScan).

A. Olink

Protein	OMICSPRED.ID	Outcome	OR	95 %CI	p-value	Q p-value	I^2	k
Fc Receptor-like protein 2 (FCRL2)	OPGS002423	Non-response	0.92	0.853 - 0.993	0.031	0.582	0	5
		Non-remission	0.915	0.843 - 0.994	0.036	0.949	0	3
		TRD	0.872	0.786 - 0.968	0.01	0.986	0	2
Kit ligand (KITLG)	OPGS002549	Non-response	1.086	1.006 - 1.172	0.034	0.175	0.053	5
		Non-remission	1.12	1.03 - 1.218	0.008	0.589	0	3
		TRD	1.115	1.003 - 1.239	0.043	0.767	0	2
Integrin beta-2 (ITGB2)	OPGS002608	Non-response	0.923	0.852 – 0.999	0.049	0.729	0	5
		Non-remission	0.917	0.843 – 0.998	0.046	0.779	0	3
C-X-C motif chemokine 6 (CXCL6)	OPGS002493	Non-response	0.923	0.856 – 0.995	0.038	0.552	0	5
		TRD	0.897	0.808 – 0.995	0.039	0.935	0	2
Interleukin-5 receptor subunit alpha (IL5RA)	OPGS002439	Non-remission	1.098	1.006 – 1.119	0.037	0.27	8.2	3
		TRD	1.127	1.015 – 1.252	0.025	0.359	0	2
Sulfotransferase 1A1 (SULT1A1)	OPGS002524	Non-remission	0.885	0.786 – 0.997	0.045	0.713	0	3
		TRD	0.825	0.707 – 0.964	0.015	1	0	2

B. SomaScan

Protein	OMICSPRED. ID	Outcome	OR	95 %CI	p-value	Q p-value	I^2	k
T-cell immunoglobulin and mucin-domain containing-3/ Hepatitis A Virus Cellular Receptor 2 (TIM3/HAVCR2)	OPGS000267	Non-response	0.909	0.843 - 0.98	0.013	0.774	0	5
		Non-remission	0.919	0.846 - 0.999	0.047	0.619	0	3
		TRD	0.902	0.815 - 0.999	0.048	0.422	0	2
Protein EVA-1 homolog C (EVA1C)	OPGS000284	Non-response	1.097	1.017 - 1.184	0.017	0.328	0.016	5
		Non-remission	1.126	1.037 - 1.223	0.005	0.562	0	3
		TRD	1.142	1.027 - 1.27	0.014	0.966	0	2
Dual Specificity Protein Phosphatase 13 Isoform A (DUSP13)	OPGS000640	Non-response	0.889	0.82 - 0.965	0.005	0.277	7.559	5
		Non-remission	0.894	0.823 - 0.972	0.008	0.443	0	3
		TRD	0.898	0.809 - 0.997	0.043	0.533	0	2
Stromal Membrane-Associated Protein 1 (SMAP1)	OPGS000776	Non-response	0.91	0.844 - 0.982	0.015	0.678	0	5
		Non-remission	0.879	0.809 - 0.955	0.002	0.847	0	3
		TRD	0.87	0.785 - 0.965	0.008	0.999	0	2
Neural cell adhesion molecule L1-like protein (CHL1)	OPGS001312	Non-response	1.091	1.007 - 1.182	0.034	0.377	6.042	5
		Non-remission	1.103	1.015 - 1.198	0.021	0.398	0	3
		TRD	1.157	1.028 - 1.304	0.016	0.261	20.977	2
	OPGS001449	Non-response	1.104	1.023 - 1.192	0.011	0.681	0.029	5
		Non-remission	1.097	1.009 - 1.192	0.031	0.845	0	3
		TRD	1.142	1.027 - 1.27	0.014	0.712	0	2
Protein Z-dependent protease inhibitor (SERPINA10)	OPGS000096	Non-response	1.095	1.015 - 1.181	0.019	0.468	0.016	5
		Non-remission	1.096	1.009 - 1.19	0.03	0.578	0	3
	OPGS000104	Non-response	1.098	1.016 - 1.187	0.019	0.415	3.486	5
		Non-remission	1.111	1.024 - 1.206	0.012	0.519	0	3
Complement factor H-related protein 5 (CFHR5)	OPGS000308	Non-response	0.921	0.851 - 0.996	0.041	0.164	2.429	5
		Non-remission	0.89	0.818 - 0.97	0.008	0.534	0	3
Complement factor D (CFD)	OPGS000483	Non-response	1.14	1.007 - 1.291	0.038	0.096	49.575	5
		Non-remission	1.125	1.007 - 1.256	0.038	0.187	39.062	3
Mediator of RNA polymerase II transcription subunit 1 (MED1)	OPGS000589	Non-response	1.138	1.022 - 1.267	0.018	0.273	34.172	5
		Non-remission	1.12	1.001 - 1.255	0.049	0.205	38.327	3
Ragulator complex protein LAMTOR3 (LAMTOR3)	OPGS000884	Non-response	0.924	0.856 - 0.997	0.042	0.604	0	5
		Non-remission	0.909	0.837 - 0.988	0.024	0.695	0	3
Kynurenine–oxoglutarate transaminase 3 (KYAT3)	OPGS001230	Non-response	0.887	0.8 - 0.983	0.022	0.83	0	4
		Non-remission	0.844	0.748 - 0.952	0.006	0.818	0	2
Afamin (AFM)	OPGS001505	Non-response	1.101	1.004 - 1.207	0.04	0.86	0	2
		Non-remission	1.11	1.01 - 1.22	0.03	0.922	0	2
Basic leucine zipper transcriptional factor ATF-like 3 (BATF3)	OPGS001571	Non-response	0.925	0.858 - 0.998	0.044	0.571	0	5
		Non-remission	0.906	0.833 - 0.984	0.019	0.515	0	3
Interleukin-1 receptor antagonist protein (IL1RN)	OPGS001833	Non-response	0.888	0.823 - 0.959	0.002	0.266	0.001	5

(*continued on next page*)

Table 1 (*continued*)

B. SomaScan								
Protein	OMICSPRED. ID	Outcome	OR	95 %CI	p-value	Q p-value	I^2	k
		Non-remission	0.867	0.798 - 0.942	0.001	0.631	0	3
Myeloid cell surface antigen CD33 (CD33)	OPGS000053	Non-response	0.907	0.841 - 0.979	0.012	0.4	0.02	5
		TRD	0.871	0.785 - 0.966	0.009	0.518	0	2
NTF2-related export protein 1 (NXT1)	OPGS000541	Non-response	0.909	0.843 - 0.98	0.013	0.767	0	5
		TRD	0.877	0.786 - 0.979	0.019	0.295	8.856	2
E3 ubiquitin-protein ligase RNF13 (RNF13)	OPGS000565	Non-response	0.919	0.849 - 0.996	0.039	0.121	5.117	5
		TRD	0.883	0.795 - 0.98	0.019	0.538	0	2
Ribonuclease pancreatic (RNASE1)	OPGS001198	Non-response	1.097	1.009 - 1.193	0.031	0.482	0.06	4
		TRD	1.121	1.008 - 1.246	0.035	0.587	0	2
Neutrophil collagenase (MMP8)	OPGS000129	Non-remission	1.122	1.032 - 1.22	0.007	0.825	0	3
		TRD	1.131	1.019 - 1.255	0.021	0.56	0	2
Macrophage-capping protein (CAPG)	OPGS000253	Non-remission	0.914	0.842 - 0.992	0.031	0.891	0	3
		TRD	0.871	0.787 - 0.964	0.008	0.78	0	2
Haloacid dehalogenase-like hydrolase domain-containing protein 2 (HDHD2)	OPGS000669	Non-remission	0.89	0.82 - 0.964	0.005	0.391	0	3
		TRD	0.897	0.809 - 0.995	0.039	0.816	0	2

Abbreviations: CI, Confidence intervals; I^2, Higgin and Thompson's I^2 estimating how much of the total variability in the effect size estimates can be attributed to heterogeneity among the true effects; k, number of studies included in meta-analysis; OR, Odds ratio; Qp, p-value for the Cochran's Q-test of (residual) heterogeneity.

significant after Bonferroni correction, indicating that our findings should be interpreted cautiously and require replication. The predictive performance of the genetic score models used to estimate protein levels was variable. According to the original work that developed the genetic scores that we used to predict protein levels, only up to 39 % of proteins in the Olink platform and 17 % in the SomaScan platform were predicted with a coefficient of determination (R^2) greater than 0.1, with a smaller subset achieving R^2 values exceeding 0.5 (Xu et al., 2023). This may have reduced the power to detect associations in our study. Additionally, the sample size may have further constrained the ability to detect significant effects (De Prisco and Vieta, 2024). In line with recommendations for exploratory studies, we did not perform a formal a priori power calculation, as our goal was not to test predefined hypotheses but to explore a broad set of protein–outcome associations (Haile, 2023). In this regard, it should also be noted that only 111 proteins were predicted through both proteomic platforms, which limits the possibility to replicate findings between them. For example, among the top proteins identified using Olink (Table 1), only two were available also using SomaScan, and both showed replicated effects. Heterogeneity in the definitions of outcomes is another concern, stemming from differences in scales, time points, and treatments across studies. While all studies used validated scales and focused on short-term treatment response after at least four weeks of treatment, which is considered adequate for evaluating the therapeutic effects of medications (Fabbri et al., 2021), the lack of full harmonization may reduce comparability. To address these differences, we adopted a meta-analytic framework based on random-effects models, which accounts for between-sample variability and allows for broader generalizability. Future research would benefit from more homogeneous outcome definitions and protocol alignment (Oliva and De Prisco, 2022). In addition, there are inherent limitations to the study design. The cross-sectional nature of the analyses precludes establishing causal relationships between the identified associations (Vieta and De Prisco, 2024). In addition, this study is a post hoc analysis of studies that were originally designed with different pre-specified hypotheses. Reliance on post hoc analyses increases the risk of false positives. These results should be considered exploratory and highlight the importance of developing and adhering to predefined hypotheses in future research to ensure robustness and replicability (Oliva and Vieta, 2025). Finally, all analyses were conducted in individuals of European ancestry. This limits the generalizability of our findings and highlights the need to include more diverse populations in future studies.

In conclusion, our study supports the hypothesis that genetically predicted proteomic profiles could help to identify preliminary biomarkers of treatment outcomes in MDD, useful to guide the selection of proteins to include in panels used by future studies. Proteins implicated in immune signalling and neurogenesis pathways are the ones showing better potential for investigation in future studies, which could contribute to identify predictors of poor response and resistance and implement early intensive treatments in patients at risk.

Statement of ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants were included after obtaining their written informed consent. Brescia study protocol was approved by the Ethics Committee of the province of Verona, Italy; the European Group for the Study of Resistant Depression (GSRD) study protocol was approved by the Ethics Committee of the coordinating center at Hôpital Erasme, Cliniques universitaires de Bruxelles (Université Libre de Bruxelles, approval number B406201213479), Belgium, and the local ethical committees of all the other participating centres; the Münster study protocol was approved by the ethical board of the University of Münster, Germany; the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study protocol received ethics approval from 14 participating institutional review boards, a National Coordinating Center, a Data Coordinating Center, and the Data Safety and Monitoring Board at the National Institute of Mental Health (NIMH), Bethesda, Maryland, US.

Declaration of generative AI and AI- assisted technologies in the writing process

None.

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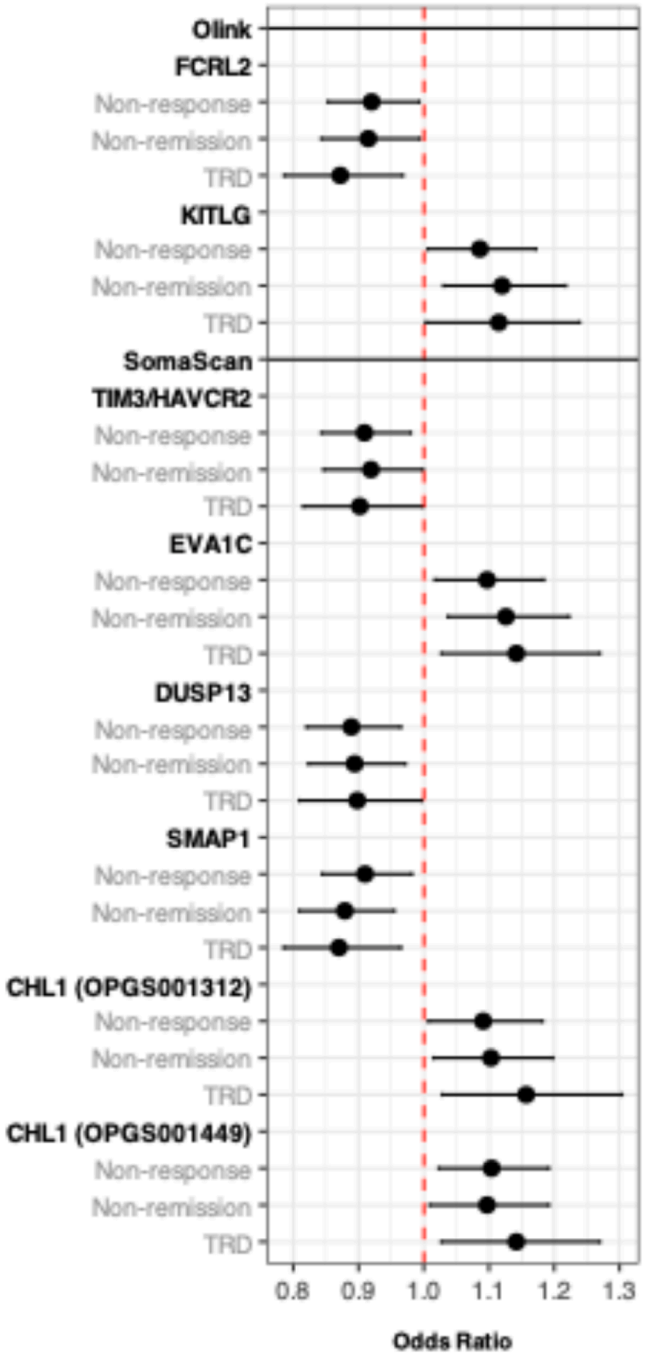

Fig. 1. Predicted protein–outcome associations consistently nominal across all treatment outcomes (response, remission, and treatment-resistant depression) Abbreviations: CHL1, Neural cell adhesion molecule L1-like protein; DUSP13, Dual specificity protein phosphatase 13 isoform A; EVA1C, Protein EVA-1 homolog C; FCRL2, Fc receptor-like protein 2; KITLG, Kit ligand; SMAP1, Stromal membrane-associated protein 1; TIM3/HAVCR2, T-cell immunoglobulin and mucin-domain containing-3/Hepatitis A virus cellular receptor 2; TRD, Treatment Resistant Depression.

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VO contributed to the conceptualisation of the study, interpreted the results, and wrote the first draft of the manuscript. VO and CF conducted proteomic prediction and performed the analyses. GF performed quality control and imputation of individual genotype data in each target sample and reviewed the first draft of the manuscript. AS and CF conceptualised the study, helped with the interpretation of the results, reviewed the first draft of the manuscript. CF supervised the process leading to the final version of the work. The other authors contributed to data collection, data preparation and/or provided comments, suggestions, and revisions, leading to the final version of the paper. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Declaration of competing interest

Vincenzo Oliva, Chiara Possidente, Giuseppe Fanelli, Alessandra Minelli, Massimo Gennarelli, Paolo Martini, Marco Bortolomasi, Alessio Squassina, Claudia Pisanu, Diego Albani, Gianluigi Forloni, Panagiotis Ferentinos, Dan Rujescu, Julien Mendlewicz, Alessandro Serretti, and Chiara Fabbri declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Giuseppe Fanelli is Managing Editor for International Clinical Psychopharmacology (Wolters Kluwer Health, Inc.) and Associate Editor for Frontiers in Psychiatry (Frontiers) and was not involved in the editorial review or the decision to publish this article. Katharina Domschke is an

Table 2
Predicted proteins consistently associated with treatment outcomes using genetic scores from both the Olink and SomaScan platforms.

Protein	OMICSPRED.ID	Outcome	Platform	OR	95 %CI	p-value	Q p-value	I^2	k
Retinoic acid receptor responder protein 2 (RARRES2)	OPGS002423	Non-response	Olink	0.909	0.843 - 0.98	0.013	0.184	0	5
			SomaScan	0.914	0.847 - 0.986	0.02	0.357	0	5
C-X-C motif chemokine 6 (CXCL6)	OPGS002493	TRD	Olink	0.897	0.808 – 0.995	0.039	0.935	0	2
			SomaScan	0.898	0.81 - 0.996	0.042	0.938	0	2
Interleukin-5 receptor subunit alpha (IL5RA)	OPGS002439	TRD	Olink	1.127	1.015 – 1.252	0.025	0.359	0	2
			SomaScan	1.129	1.019 - 1.251	0.021	0.607	0	2

Abbreviations: CI, Confidence intervals; I^2, Higgin and Thompson's I^2 estimating how much of the total variability in the effect size estimates can be attributed to heterogeneity among the true effects; k, number of studies included in meta-analysis; OR, Odds ratio; Qp, p-value for the Cochran's Q-test of (residual) heterogeneity.

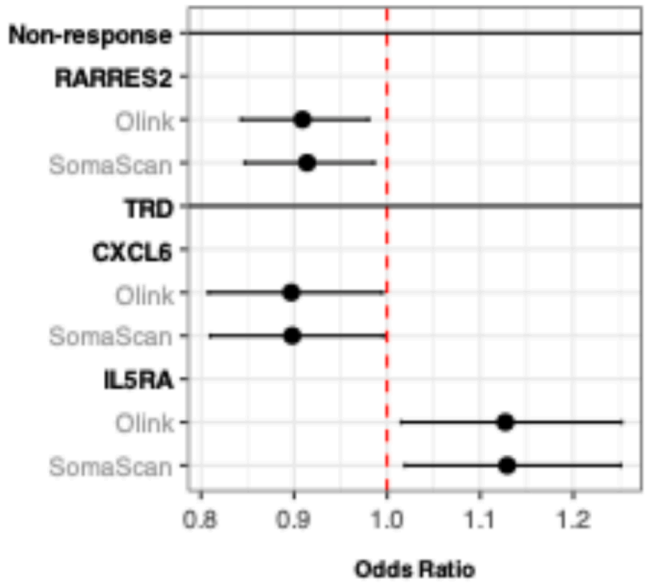

Fig. 2. Predicted protein–outcome associations consistently nominal using genetic scores estimated from both the Olink and SomaScan platforms
Abbreviations: CXCL6, C-X-C motif chemokine 6; IL5RA, Interleukin-5 receptor subunit alpha; RARRES2, Retinoic acid receptor responder protein 2; TRD, Treatment Resistant Depression.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Katharina Domschke has been a member of the Steering Committee Neurosciences, Janssen Pharmaceuticals, and has received speaker's honoraria from Janssen Pharmaceuticals. Inc. In the past 3 years Siegfried Kasper served as a consultant or on advisory boards for Angelini, Biogen, Boehringer, Esai, Janssen, IQVIA, Mylan, Recordati, Rovi, and Schwabe; and he has served on speakers bureaus for Angelini, Aspen Farmaceutica S.A., Biogen, Janssen, Recordati, Schwabe, Servier, Sothema, and Sun Pharma. Joseph Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultant on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GSK, Jazz, and Solvay. Daniel Souery has received grant/research support from GlaxoSmithKline and Lundbeck, and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Stuart Montgomery has been a consultant or served on advisory boards for Lundbeck. Bernhard T Baune: Advisory Board - Lundbeck, Janssen-Cilag; Consultant - National Health and Medical Research Council, Australia; Grant/Research Support - AstraZeneca, Fay Fuller Foundation, James & Diana Ramsay Foundation, National Health and Medical Research Council, Australia, German Research Council (DFG), Sanofi, Lundbeck; Honoraria - AstraZeneca, Bristol-Myers Squibb, Lundbeck, Pfizer, Servier Laboratories, Wyeth Pharmaceuticals, Takeda, Janssen, LivaNova PLC. Eduard Vieta has received grants and served as a paid consultant, advisor, or CME speaker for AB-Biotics, Abbott, AbbVie, Adamed, Angelini, Biogen, Biohaven, Boehringer Ingelheim, Cambridge University Press, Casen-Recordati, Celon, Compass, Dainippon Sumitomo, Elsevier, Ethypharm, Ferrer, Galenica, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Medincell, Merck, Neuraxpharm, Newron, Novartis, Oxford University Press, Orion, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, out of the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2025.05.004.

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