Clinical associations with treatment resistance in depression: an electronic health record study

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PII: S0165-1781(24)00488-8
DOI: https://doi.org/10.1016/j.psychres.2024.116203
Reference: PSY 116203

To appear in: *Psychiatry Research*

Received date: 25 June 2024
Revised date: 3 September 2024
Accepted date: 15 September 2024

Please cite this article as: Brandon J Coombes , Jorge A Sanchez-Ruiz , Brian Fennessy , Vanessa K Pazdernik , Prakash Adekkanattu , Nicolas A Nunez , Lauren Lepow , Lindsay M MelhuishBeaupre , Euijung Ryu , Ardesheer Talati , J John Mann , Myrna M Weissman , Mark Olfson , Jyotishman Pathak , Alexander W Charney , Joanna M Biernacka , Clinical associations with treatment resistance in depression: an electronic health record study, *Psychiatry Research* (2024), doi: https://doi.org/10.1016/j.psychres.2024.116203

Highlights

- Risk factors for treatment resistance in depression explored via electronic health records
- Associations between resistance and comorbidities such as anxiety, PTSD, and chronic pain
- Greater antidepressant trials associated with gut comorbidities
- Genetic risk for depression, pain, and addiction linked to increased antidepressant trials

Clinical associations with treatment resistance in depression: an electronic health record study

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Abstract

Treatment resistance is common in major depressive disorder (MDD), yet clinical risk factors are not well understood. Using a discovery-replication design, we conducted phenome-wide association studies (PheWASs) of MDD treatment resistance in two electronic health record

(EHR)-linked biobanks. The PheWAS included participants with an MDD diagnosis in the EHR and at least one antidepressant (AD) prescription. Participant lifetime diagnoses were mapped to phecodes. PheWASs were conducted for three treatment resistance outcomes based on AD prescription data: number of unique ADs prescribed, ≥1 and ≥2 AD switches. Of the 180 phecodes significantly associated with these outcomes in the discovery cohort (n=12,558), 71 replicated (n=8,206). In addition to identifying known clinical factors for treatment resistance in MDD, the total unique AD prescriptions was associated with additional clinical variables including irritable bowel syndrome, gastroesophageal reflux disease, symptomatic menopause, and spondylosis. We calculated polygenic risk of specific-associated conditions and tested their association with AD outcomes revealing that genetic risk for many of these conditions is also associated with the total unique AD prescriptions. The number of unique ADs prescribed, which is easily assessed in EHRs, provides a more nuanced measure of treatment resistance, and may facilitate future research and clinical application in this area.

Keywords: PheWAS, PRS, MDD, antidepressants, comorbidity, TRD

1. Introduction

Major Depressive Disorder (MDD) is a heterogeneous disorder with considerable variation in its clinical presentation and treatment response among individuals (Harald and Gordon, 2012; Zisook et al., 2019). Two thirds of patients undertaking antidepressant treatment for MDD do not achieve clinical remission on their first treatment trial and the probability of achieving remission to any given medication tends to decrease with each successive treatment trial—a significant number of individuals not remitting altogether (Rush et al., 2006).

The concept of treatment-resistant depression (TRD) was introduced roughly five decades ago to study non-response (Overall, 1974). TRD has had numerous categorical definitions. These definitions have ranged from no formal minimum number of treatment trials (American Psychiatric Association, 2010; Cleare et al., 2015) to at least two (Bauer et al., 2013; Fabbri et al., 2021; Kennedy et al., 2016) or three or more trials (Adekkanattu et al., 2023; McAllister-Williams et al., 2018; Taylor et al., 2018). Other categorizations attempt to stage an individual's degree of treatment-resistance (Ruhé et al., 2012) but there is no formal consensus definition or staging model for TRD (Howes et al., 2022; Souery et al., 1999).

Current operationalizations of TRD may overlook important aspects of MDD treatment (e.g., residual symptoms, next-step treatment persistence, treatment delays) (McIntyre et al., 2023). However, implementing more complex TRD operationalizations in large datasets such as electronic health records (EHRs) may not be possible given the level of detail required to ascertain most definitions (e.g., "adequacy" of treatment trials, medication adherence, heterogeneity in symptom severity rating scales). Yet, despite their unique challenges and limitations (e.g., imprecision, missingness), EHRs may be well suited to study treatment resistance in MDD by reflecting actual clinical care (Perlis et al., 2019). Thus, EHRs complement the classic clinical trial approach in research. Studies of treatment resistance in MDD based on EHRs should leverage the vast amount of available medical data. Previous studies have considered different methods to identify treatment resistance among individuals with MDD using EHR or register data (Perlis et al., 2012), and have used EHR data to explore risk factors to develop models predicting treatment resistance (Lage et al., 2022). A set of inclusion criteria using a mixture of diagnostic codes and antidepressant prescription data was previously utilized to define treatment resistance using EHR data in the UK Biobank (Fabbri et al., 2021).

One particular advantage of EHRs over clinical trials is that they enable phenotype-based phenome-wide association studies (PheWASs), which leverage the broad medical phenotyping

only available in large clinical datasets to conduct hypothesis-agnostic studies of clinical associations with different phenotypes (Denny et al., 2016). This approach may accelerate the discovery of unrecognized associations with treatment resistance, which can subsequently be further investigated by targeted trials. Moreover, this approach allows the simultaneous exploration of multiple primary phenotypes, such as different measures of resistance (Bastarache, 2021; Smoller, 2018; Wolford et al., 2018). EHR-linked biobanks also provide an opportunity for large-scale pharmacogenomic studies at low cost (Smoller, 2018).

To gain insight into clinical trait associations with treatment resistance in MDD, we used EHR-derived phenome information from two biobanks as discovery and replication samples to conduct phenotype-based PheWASs of three measures of treatment resistance in MDD based on AD prescription data: one that quantifies the number of unique antidepressants prescribed and two dichotomous measures based on antidepressant switches. To further investigate resistance-associated comorbidities that replicated across sites in the phenotype-based PheWAS, we conducted a pharmacogenomic analysis testing whether the genetic liabilities for these phenotypes quantified using polygenic risk scores (PRSs) were associated with the three outcomes.

2. Methods

2.1 Data sources

The data was derived from two biobanks: Mayo Clinic Biobank (MCB) (Olson et al., 2019) and Mount Sinai's Bio*Me*. MCB active enrollment spanned from April 2009 to March 2016 and totaled nearly 60,000 participants aged 18 years and older, selected largely through medical visits to primary care and family medicine clinics at Mayo Clinic and its health system. Bio*Me* began in 2007 and recruited more than 60,000 individuals primarily in the Mount Sinai Health System ambulatory care settings across New York, NY. At consent, both MCB and Bio*Me* participants provided biological samples, completed a questionnaire, and permitted researchers with approved access to analyze data from their EHR, which includes clinical notes, demographics, medications/prescriptions, and billing codes from the ICD, 9th and 10th editions (ICD-9/10) (WHO and World Health Organization, 1993). We mapped ICD9/10 codes to phecodes (i.e., higher order groups of diagnoses) using the Phecode map 1.2b1 (Denny et al., 2010). The current study was reviewed and approved by each site's Institutional Review Board (Mayo Clinic IRB approval 19-006227 and Mount Sinai IRB approval 07-0529). EHRs for MCB and Bio*Me* participants were extracted in September and December, respectively, in 2021.

2.2 Identifying cases with MDD

Using structured EHR data, patients with MDD were identified based on having at least one MDD-related ICD9/10 code, as shown in Supplementary Table 1, and at least one antidepressant prescription. Participants with phecodes for bipolar disorder (phecode 296.1) or psychotic disorders (phecodes 295.1, 295.2, 295.3, 295) were excluded from the MDD samples (Supplementary Table 2).

2.3 Prescription data

NLP algorithms were employed at both sites to extract and clean unstructured prescription data from the EHR and incorporate this data with more recent structured prescription data. For MCB, outpatient drug information was extracted from prescription data using Mayo Clinic's open-source cTAKES natural language processing (NLP) platform and mapping to RxNorm codes (https://www.nlm.nih.gov/research/umls/rxnorm) (Pathak et al., 2011). The process of retrieving prescription data for Bio*Me* has been previously described (Landi et al., 2021). Briefly, drug prescription data were obtained from the Mount Sinai Data Warehouse (MSDW) and standardized to RxNorm concept unique identifiers (RXCUIs) through an open source CLAMP clinical NLP pipeline (Soysal et al., 2018) and to further standardize, RXCUIs were mapped to base ingredient information using the RxNorm application program interface.

In both samples, we abstracted prescription data for the antidepressants listed in Supplementary Table 3. Notably, we excluded clomipramine, fluvoxamine, milnacipran, selegiline, and trazodone because, while in the antidepressant drug class, these drugs are commonly used to treat other neuropsychiatric symptoms and disorders.

2.4 Defining treatment resistance

For each antidepressant, we retrieved the start and end dates (i.e., after refills have run out) and calculated the total time potentially on the medication. If another antidepressant medication from the list was prescribed before the prescription end date, the duration on the given medication was truncated to end at the start of the new prescription to indicate a change in antidepressant treatment. To determine "adequate trials," an antidepressant was excluded from the patient's data if they switched treatment within 30 days of starting the antidepressant or were not prescribed the antidepressant for at least 30 days. This approach was taken to avoid capture of medications stopped due to intolerable side-effects rather than lack of efficacy. Finally, similar to recent studies (Adekkanattu et al., 2023; Fabbri et al., 2021), we defined a medication "switch" when the interval between the prescription of two consecutive drugs was less than 14 weeks, to avoid incorrectly classifying two independent medication trials as an antidepressant switch within a single treatment trial. The resulting medication trial and switch data were then used to define one quantitative measure and two dichotomous measures of treatment resistance. The quantitative measure was defined as the total number of unique antidepressants that a participant was prescribed for at least 30 days. We also defined treatment resistance using two dichotomous definitions of either two or more antidepressant switches, or one or more antidepressant switches (Bauer et al., 2013; Fabbri et al., 2021; Kennedy et al., 2016).

2.5 Phenotype-based PheWAS

To assess clinical comorbidities associated with treatment resistance in MDD, we performed a phenotype-based PheWAS in each biobank with each outcome measure for resistance. The analyses were performed using the PheWAS R package (Denny et al., 2010), with each outcome serving as the predictor of each phecode in a logistic regression model. For the PheWAS of the quantitative trait, the number of unique antidepressants was capped at seven such that someone

prescribed more than seven unique antidepressants had their outcome fixed at seven to avoid influential outliers. At least two occurrences of a diagnostic code in the EHR on different days were required to define a phecode case. For the PheWAS, we only tested associations with phecodes with a minimum of 20 cases and 20 controls. To account for potential confounders of EHR analyses such as healthcare utilization and demographics, we adjusted for the patient's length of EHR (defined as the time between the first and last ICD code in the record), total number of ICD codes (across all conditions), as well as the patient's age at time of the EHR data pull and self-reported race, ethnicity, and gender. Analyses were limited to participants with a history of regular care (at least two visits spaced at least a year apart) to improve the assessment of phenomes and reduce confounding from participants with insufficient EHR. We used MCB as a discovery sample and Bio*Me* as a replication sample. To account for multiple testing, we used a Bonferroni corrected threshold that adjusted for the total number of tests across the three discovery PheWAS ($p < 0.05/[1078 \text{ phecodes} \times 3 \text{ outcomes}] = 1.5e\text{-}5$) or the number of phecodes to be replicated ($p < 0.05/$ total number of significant phecodes in discovery PheWAS). All analyses were performed in R 4.2.2.

2.6 Polygenic risk score analyses

For treatment resistance-associated comorbidities identified in the MCB sample PheWAS and replicated in the Bio*Me* sample, we identified a set of phenotypes for which summary statistics from a large genome-wide association study (GWAS) or a set of pre-computed variant weights from PGS Catalog (Lambert et al., 2021) were available. We estimated PRSs for these phenotypes using either LDpred2 (Privé et al., 2021) with the GWAS summary statistics or with PLINK2 using the pre-computed weights from PGS Catalog. Specifically, we used genotype data for over 44,000 unrelated MCB participants of European ancestry as previously described (Coombes et al., 2023) to compute the PRSs for depression (Levey et al., 2021), suicide attempts (Docherty et al., 2023), ADHD (Demontis et al., 2023), GAD (Levey et al., 2020), insomnia (Lane et al., 2019), chronic pain (Johnston et al., 2019), panic disorder (Forstner et al., 2021), migraines (Tanigawa et al., 2022), bipolar disorder (Mullins et al., 2021), PTSD (Nievergelt et al., 2019), IBS (Tanigawa et al., 2022), SUDs (Deak et al., 2022; Hatoum et al., 2023; Johnson et al., 2020; Saunders et al., 2022; Zhou et al., 2020), GERD (Privé et al., 2022), and anorexia nervosa (Watson et al., 2019) (Table ST5). In the MCB cohort of participants with an MDD diagnosis and at least one antidepressant prescribed, we tested the association of each PRS with the number of prescribed antidepressants using Poisson regression and with the dichotomous measures of treatment resistance (1 or 2 switches) using logistic regression. All PRS analyses were adjusted for age at enrolment to the biobank, sex, and the first ten genetic principal components.

For any nominally significant PRS associations ($p < 0.05$), we assessed whether the association with treatment resistance was mediated by the depression PRS. To do this, we used the `mediation` R package with 5000 bootstrapped samples to estimate mediation p-values for mediated and direct effects. Mediation analyses used the same covariates above and we reported the average causally mediated effect (ACME) by the depression PRS, average direct effect (ADE) of each PRS, and the proportion mediated by the depression PRS.

3. Results

Table 1 describes participants with MDD and at least one antidepressant medication treatment in the two biobanks (MCB N = 12,558; Bio*Me* N = 8,206). At both sites, most of the patient population was female (72% and 68%, respectively) with a median age of 66 and 65 years, respectively. Participants from MCB were predominantly White, reflecting the population around Rochester, Minnesota, whereas Bio*Me* had enrolled roughly equal proportions of White and Black participants, and nearly half of the individuals were Hispanic, reflecting the demographics of the area surrounding Mount Sinai in New York City. Citalopram/escitalopram was the most common antidepressant prescribed at the two sites (Table S3) and the distributions of the three outcome variables were similar across the two biobanks with patients receiving on average two different antidepressant prescriptions, and about 9% (N=1896) of the MDD sample having one or more antidepressant switches and 1% (N=246) having two or more switches.

3.1 Phenotype-based PheWASs

In the MCB discovery PheWAS, the number of unique antidepressants prescribed was associated with 180 phecodes, followed by 21 phecode associations for the ≥1 antidepressant switch and 9 for the ≥2 antidepressant switches outcomes. Of these, 71 associations were replicated ($p < 0.05/210=0.0002$) in the Bio*Me* sample with strong agreement between the effect sizes in each sample. Figure 1 shows the results for the MCB phenotype-based PheWASs of the three treatment resistance measures with full results in each biobank shown in Table S4.

Notably, generalized anxiety disorder (GAD) was the strongest association across all three outcome measures in both samples. Among many of the replicated associations, consistent results were seen across all measures with phecodes including insomnia, chronic pain, suicidal ideation, posttraumatic stress disorder (PTSD), panic disorders, personality disorders, as well as

myalgia and myositis, albeit none of these reached the replication significance level for the measure of two or more switches.

Many phecodes (86% of the 63 replicated associations) were only significantly associated with the total number of antidepressants ever taken. Notably, attention deficit/hyperactivity disorder (ADHD), migraines, irritable bowel syndrome (IBS), spondylosis, GERD, symptomatic menopause, substance use disorders (SUDs) and eating disorders were associated with the number of antidepressants ever taken but did not reach Bonferroni-corrected statistical significance thresholds for the two dichotomous measures based on antidepressant switches.

3.2 PRS associations

For the associations that replicated across outcomes for which a PRS could be estimated, we tested whether the genetic liabilities for said comorbidities were associated with treatment resistance outcomes (Table ST5). Of these, the PRSs for depression, chronic pain, addiction factor, opioid use disorder, and smoking were associated with more unique antidepressants prescribed (all $p<0.05/17=0.0029$). While not reaching the Bonferroni-corrected significance level, the PRSs for ADHD, GAD, insomnia, problematic alcohol use, cannabis use disorder, and GERD correlated with a greater number of different antidepressants prescribed. No PRS was significantly associated with either of the dichotomous definitions using antidepressant switches.

For the associations above, we assessed whether the depression PRS mediated any of these relationships (Table ST6). While the depression PRS mediates a significant proportion of all of these associations, the PRS for chronic pain, addiction factor, opioid use disorder, and smoking still had significant direct effects ($p < 0.05$).

4. Discussion

Using data from two large biobanks as discovery and replication samples, we conducted a phenotype-based phenome-wide association study of three different measures of treatment resistance in MDD to identify clinical associations. Two dichotomous measures of resistance were based on a threshold number of antidepressant switches; one quantitative measure was based on the total number of unique antidepressants prescribed for at least 30 days. With each outcome measure, our analyses reproduced well-known clinical associations with TRD. Furthermore, the quantitative measure of treatment resistance showed several clinical associations not previously reported for TRD, including IBS, GERD, symptomatic menopause, and spondylosis. Additionally, PRS analyses found the genetic liability for many of these comorbidities associated with the quantitative measure of resistance, including ADHD PRS, which was previously reported to be associated with TRD (Fabbri et al., 2021). While these observations warrant further study, large EHR-based studies may benefit from the use of a quantitative measure of treatment resistance based on antidepressant prescriptions, rather than definitions based on antidepressant switches, to accelerate the discovery of factors potentially associated with TRD, including genetic risk factors.

Our hypothesis-agnostic search for clinical associations with treatment resistance in MDD using the EHR identified clinical phenotypes that have been previously associated with resistance in TRD literature such as anxiety, suicidal ideation, insomnia, PTSD, personality disorders, and chronic pain. Mounting evidence indicates that having psychiatric or medical comorbidities is linked to worse treatment outcomes for people with MDD (Kraus et al., 2020). In our study, all measures of treatment resistance were associated with a diagnosis of any anxiety disorder, consistent with prior research (Bartova et al., 2019; Carter et al., 2012; Souery et al., 1999). Among all anxiety disorders, GAD, which is also commonly treated with antidepressants, had the strongest association with resistance, as previously reported (Dold et al., 2017; Kautzky et al.,

2019). As expected, suicidal ideation, which has been consistently associated with TRD in the literature and is a symptom of MDD severity (Balestri et al., 2016; Bartova et al., 2019; Dennehy et al., 2014; Kautzky et al., 2019; Souery et al., 2007), was strongly associated with the three measures of resistance. Likewise, the PRS for depression, which has been shown to be higher in those with suicidal ideation (Li et al., 2023), was also associated with resistance in our analysis. Insomnia, both a symptom of and risk factor for MDD (Baglioni et al., 2011), was associated with all measures of resistance and was second only to anxiety disorders in the strength of its association with the total number of unique antidepressants prescribed. PTSD, which was significantly associated with all outcome measures of resistance, has also been associated with TRD in the literature (Dennehy et al., 2014; Falola et al., 2017). This relationship could be mediated by a history of trauma, which results in increased severity of depression (Friedman et al., 2012), a risk factor for TRD (Balestri et al., 2016; Bartova et al., 2019; Souery et al., 1999), yet evidence is conflicting (Papakostas, 2012). Finally, severe pain or its lack of improvement are known independent risk factors reported in TRD literature, regardless of root cause (Carter et al., 2012), which could explain some of the associations with conditions that cause chronic pain. One such example is spondylosis, which was associated with the quantitative measure of resistance; however, MDD is an independent risk factor for spondylosis (Lin et al., 2018), so the association could also be due to a more severe and protracted course of illness among individuals with TRD. Searching across the EHR also allowed us to identify new clinical associations with resistance. For example, the total number of antidepressants a participant had ever been prescribed was associated with IBS and GERD. However, the findings could be due to antidepressant side-effects or the use of antidepressants in the treatment of these conditions. Individuals with IBS have higher levels of somatization, interpersonal sensitivity, and life event stress (Locke et al., 2004) as well as increased rates of mood and anxiety disorders (Janssens et al., 2015; Solmaz et al., 2003). Furthermore, mood and anxiety disorders may share some of the same genetic pathways with IBS (Eijsbouts et al., 2021) and IBS is sometimes treated with antidepressants (Kułak-Bejda et

al., 2017). Similarly, GERD has been associated with MDD (Chen et al., 2023; Zeng et al., 2023) and antidepressants are sometimes recommended in the treatment of refractory GERD (Talley and Zand Irani, 2021).

While women in the perimenopause and early postmenopause have increased rates of MDD, there is conflicting evidence regarding the effect of menopause on MDD treatment (Freeman et al., 2014, 2006). Some studies report similar rates of response or recurrence during menopause, yet others report lower rates of response and slower recovery (Maki et al., 2018). In addition, antidepressants are oftentimes used in the treatment of vasomotor symptoms during menopause (Davari-Tanha et al., 2016), which could explain the association with the number of antidepressants prescribed, particularly if the symptoms are severe enough to warrant medical care and, consequently, inclusion in an individual's EHR.

One possible explanation for our observations is comorbidity-specific antidepressant use that is unrelated to MDD treatment. Alternatively, comorbidities such as IBS, GERD, or symptomatic menopause may increase the risk of treatment resistance among individuals with MDD. Given their associations with MDD and the inconclusive evidence on their effect on treatment response in MDD, there is no clear answer yet. Further studies are needed to examine the effect that these comorbidities might have on MDD treatment.

The quantitative outcome measure of resistance based on the number of unique antidepressants ever prescribed to an individual attempts to place treatment resistance on a continuum, closely resembling what is seen in clinical practice and what is accessible from EHR data. Moreover, this outcome measure had the most significant associations with comorbidities and PRSs in our analyses. Similar outcome measures have been used proposed in the past by studies exploring TRD (Ruhé et al., 2012). Indeed, Cepeda et al. found that using the number of unique antidepressants or antipsychotics that an individual had been prescribed in a year was better at identifying individuals with TRD in large datasets than using more complex definitions that included medication dose and duration (Cepeda et al., 2018). Relative to a quantitative measure

of resistance, dichotomous definitions of TRD reduce information and are thus expected to result in a loss of statistical power. Such increased statistical power provided by a quantitative outcome may be especially beneficial for genomic studies of treatment resistance in MDD, which have thus far been under-powered (Fabbri et al., 2021).

Our study has limitations. First, clinical phenotypes were derived solely from structured EHR data, and thus may not capture the nuances of the clinical presentations, nor do they replace standardized diagnostic assessments. However, it has been shown that phecode groupings generate a phenome that more closely resembles natural-language medical records using structured EHR data and may facilitate replication of known associations better than other diagnostic codes or groupings (Wei et al., 2017). Second, the number of unique antidepressants for a patient does not reflect TRD and could be confounded by other illnesses that are treated with antidepressants including anxiety, pain syndromes, or sleep disorders, which were among the diseases most strongly associated with the total number of unique antidepressants in our analyses. However, the number of unique antidepressants tried is clinically relevant in patient care, and similar measures have been considered in the context of assessing treatment resistance in MDD (Ruhé et al., 2012). Moreover, the high consistency of findings across outcome measures suggests that the quantitative measure of resistance accurately captures the characteristics and conditions associated with the dichotomous measures of resistance. This alignment indicates that such a quantitative outcome may be a reliable assessment of TRD. We took steps to mitigate the influence of higher healthcare utilization on the total number of antidepressants by adjusting analyses for the number of unique diagnostic codes present in an EHR, the length of each participant's medical record, and excluding antidepressants that are not routinely prescribed for MDD. In addition, we aimed to limit the impact that antidepressant tolerability may have had on the number of antidepressants exposures and number of switches by including only prescriptions that lasted at least 30 days, as earlier interruption is likely related to treatment intolerance or other factors beyond efficacy. Third, EHR prescription data does not

capture whether prescriptions are filled and taken, making it challenging to assess adequacy of dose and impossible to assess adherence, both of which are important for accurately assessing efficacy of an antidepressant. Fourth, EHR prescription data does not capture whether medication was stopped and therefore augmentation of depression treatment with additional antidepressants is difficult to ascertain. Furthermore, augmentation with other psychotropic medications such as lithium, or second-generation antipsychotics would not be considered a switch. Fifth, the rates of resistance as defined by the dichotomous outcomes in our study were lower than the reported rates of TRD in the literature, which range from 20% to 70% (Rizvi et al., 2014; Rush et al., 2006; Zhdanava et al., 2021). This could reflect the previously mentioned limitation of incomplete prescription records as well as our thresholds requiring a switch occur after 30 days and before 14 weeks of the preceding prescription. Using complete prescription data from the UK Biobank, Fabbri and colleagues found similar rates of two or more antidepressant switches among participants when using an algorithm similar to ours (Fabbri et al., 2021). Sixth, sampling of patients by biobanks, particularly those within a single healthcare system, may limit external generalizability (Beesley et al., 2020). Encouragingly, even though the two biobanks included in the analysis differ geographically and by race/ethnicity, the distributions of the three outcome measures were very similar between the two biobanks and many of the associations found in MCB were replicated in Bio*Me*. Seventh, we defined MDD in our population of interest based on the presence of ICD codes, which may have limited reliability, but we additionally required at least one antidepressant prescription to improve reliability. Additionally, the study by Fabbri et al. (2021) found significant overlap between EHR-defined MDD using at least two depressive disorder diagnostic codes and different MDD definitions. After cross-validating EHR-defined MDD with primary care data, they highlighted that using a less restrictive definition (i.e., at least one diagnostic code) resulted in sufficient diagnostic overlap and similar associations with MDD polygenic risk score. Finally, it is important to recognize that there are many correlations among phecodes and thus the associations from the PheWASs are not independent and must be

interpreted accordingly. Moreover, some of the observed relationships may be bidirectional and temporality of features has not been incorporated into the analysis.

Despite the limitations, a key strength to the large-scale EHR-based agnostic phenome-wide approach is the possible discovery of a broad range of clinical associations not limited to known or hypothesized ones, which can then be explored with targeted studies. Furthermore, data derived from EHRs represent medical diagnoses made by physicians and include details such as all prescribed medications in a defined time period – this type of data is typically not available in epidemiological studies of psychiatric disorder risk factors. Thus, EHR-based observational studies are complementary to traditional clinical research study designs and provide a unique opportunity for discovery of association patterns in a clinical context.

Our study exploring three different outcome measures of resistance in an EHR reproduced many known associated clinical risk factors for TRD such as anxiety, suicidality, and insomnia, and identified new factors such as IBS, GERD, spondylosis, and symptomatic menopause. Results from the analysis of the quantitative measure of treatment resistance were consistent with results from analyses using dichotomous outcomes of resistance. Moreover, the incorporation of the quantitative measure facilitated the discovery of additional associations that replicated across sites. Thus, this quantitative measure may aid the detection of genetic factors contributing to treatment resistance in MDD and ultimately facilitate the creation of rapid assessments of treatment resistance in clinical settings and may facilitate subtyping of TRD and potentially more nuanced, targeted treatment approaches in the future.

Acknowledgement

This study was supported by the National Institute of Mental Health (NIMH) grants: R01MH121924, R01MH121923, R01MH121922, and R01MH121921. We acknowledge the Mayo Clinic Biobank (MCB) research team, as well as the patient-participants who consented

to participate in this research program. We also acknowledge the Mayo Clinic Center for Individualized Medicine for support of the Mayo Clinic Biobank, and Regeneron Genetics Center for providing genetic data for MCB participants for the polygenic risk score analysis.

Competing Interests

Dr. Mann receives royalties for commercial use of the C-SSRS from the Research Foundation for Mental Hygiene and from Columbia University from sales of the Columbia Pathways app. Dr. Weissman has received funding from NIMH and Columbia University Institute for Developmental Sciences and receives book royalties from Perseus Press and Oxford Press. None of these represent a conflict of interest.

The other authors have nothing to disclose.

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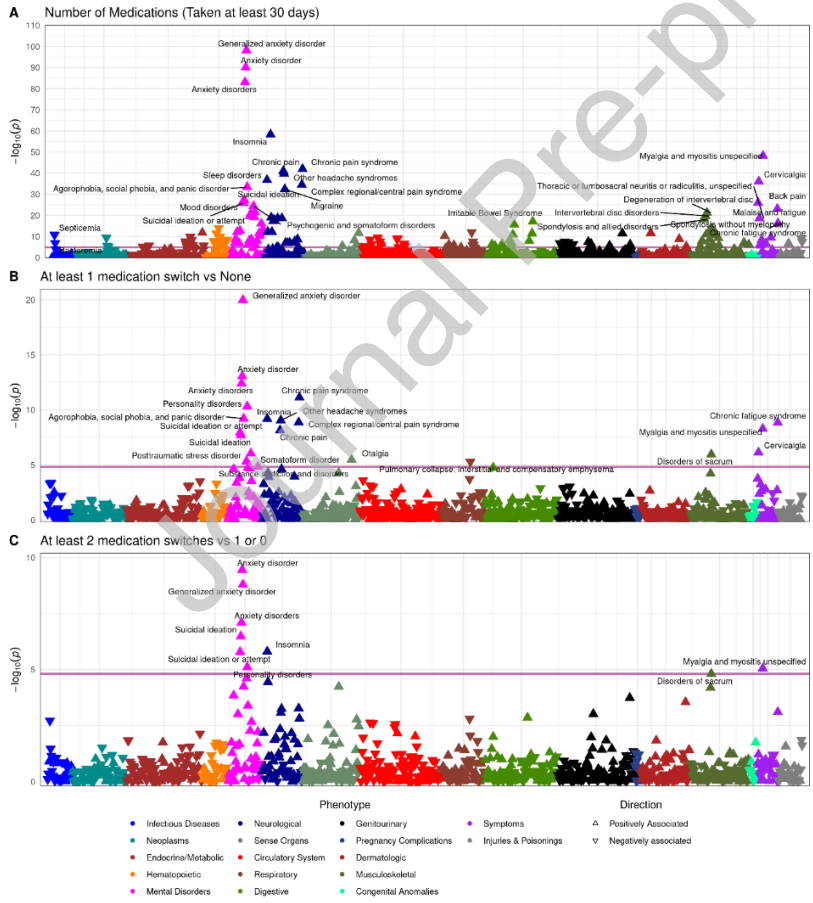
Table 1. Description of the two biobank samples of patients with at least one MDD diagnostic code and prescribed at least one antidepressant.

Characteristic		**MCB (N=12558)**	**Bio*Me* (N=8206)**
Age, y	Median (Q1, Q3)	66 (55, 76)	65 (54, 75)
Female	N (%)	9050 (72.1%)	5548 (67.6%)
Race	N (%)		
White		11371 (90.5%)	1894 (23.1%)
Black/African American		88 (0.7%)	1600 (19.5%)
Asian		72 (0.6%)	162 (2.0%)
Native American/Alaskan Native		24 (0.2%)	-
Other		63 (0.5%)	733 (8.9%)
Mixed/Unknown		940 (7.5%)	250 (3.0%)
Hispanic	N (%)	192 (1.5%)	3567 (43.5%)
EHR measures			
Length of record, y	Median (IQR)	21 (11, 31)	9 (6,12)
Log No. Diagnoses	Median (IQR)	6.0 (5.4, 6.6)	5.6 (4.8, 6.2)
TRD measures			
No. unique ADs	Mean (Range)	2.24 (1 to 12)	1.94 (1 to 9)
1+ AD switch	N (%)	1242 (9.9%)	654 (8.0%)
2+ AD switch	N (%)	179 (1.4%)	67 (0.8%)

AD: antidepressant; EHR: electronic health record; Age: age at date of data pull; Median age of record is calculated for each patient as the median time between each diagnosis date and date of data pull; Log No. diagnoses is the natural log of total number of ICD codes for a patient

Figure 1. PheWAS association plot based on the Mayo Clinic Biobank, showing associations across the EHR phenome with three measures of treatment resistance: (A) Number of unique prescriptions (capped at max of 7), (B) At least one switch of prescription within 14 weeks of previous prescription, (C) At least two switches of prescription within 14 weeks of previous prescription. Models are adjusted for patient's length of EHR, total number of ICD codes, age at biobank enrolment and self-reported race, ethnicity, and gender. Individual disease codes are color-coded by their corresponding disease category as explained in the legend. The solid lavender horizontal line represents the Bonferroni corrected *p*-value (0.05/1078 x 3 = 1.5e-5). Points are represented by either upward triangles, indicating a positive association, or downward triangles, indicating a negative association.



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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Mann receives royalties for commercial use of the C-SSRS from the Research Foundation for Mental Hygiene and from Columbia University from sales of the Columbia Pathways app. Dr. Weissman has received funding from NIMH and Columbia University Institute for Developmental Sciences and receives book royalties from Perseus Press and Oxford Press. None of these represent a conflict of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.