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Phenotypic distinctions in depression and anxiety: a comparative analysis of comorbid and isolated cases

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Original Article

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Abstract

Background. Anxiety and depression are frequently comorbid yet phenotypically distinct. This study identifies differences in the clinically observable phenome across a wide variety of physical and mental disorders comparing patients with diagnoses of depression without anxiety, anxiety without depression, or both depression and anxiety.

Methods. Using electronic health records for 14 994 participants with depression and/or anxiety in the Mayo Clinic Biobank, a phenotype-based phenome-wide association study (Phe^{2}WAS) was performed to test for differences between these groups across a broad range of clinical diagnoses observed in the electronic health record. Additional analyses were performed to determine the temporal sequencing of diagnoses.

Results. Compared to patients diagnosed only with anxiety, those diagnosed only with depression were more likely to have diagnoses of obesity (OR 1.75; $p = 1 \times 10^{-27}$), sleep apnea (OR 1.71; $p = 1 \times 10^{-22}$), and type II diabetes (OR 1.74; $p = 9 \times 10^{-18}$). Compared to those diagnosed only with depression, those diagnosed only with anxiety were more likely to have diagnoses of palpitations (OR 1.91; $p = 2 \times 10^{-25}$), benign skin neoplasms (OR 1.61; $p = 2 \times 10^{-17}$), and cardiac dysrhythmias (OR 1.45; $p = 2 \times 10^{-12}$). Patients with comorbid depression and anxiety were more likely to have diagnoses of other mental health disorders, substance use disorders, sleep problems, and gastroesophageal reflux relative to isolated depression.

Conclusions. While depression and anxiety are closely related, this study suggests that phenotypic distinctions exist between depression and anxiety. Improving phenotypic characterization within the broad categories of depression and anxiety could improve the clinical assessment of depression and anxiety.

Introduction

Although anxiety and depression are often clinically differentiated, they are frequently comorbid (Gorman, 1996). Pharmacologically, the two disorders are treated similarly with agents chiefly active on the serotoninergic system. Genetic studies further suggest almost complete overlap between anxiety and depression (Kendler, Gardner, Gatz, & Pedersen, 2007; Smoller, 2016). However, despite these similarities and hypotheses of a shared etiology (Beurel, Toups, & Nemeroff, 2020; Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017; Zorn et al., 2017), there is support for their diagnostic distinction (Beard et al., 2016; Middeldorp, Cath, Van Dyck, & Boomsma, 2005), and we continue to have a limited understanding of why certain individuals develop anxiety disorders, others develop depressive disorders, and many develop both.

Both depression and anxiety have been widely studied in relation to their co-occurrences with common physical disorders (Hare, Toukhsati, Johansson, & Jaarsma, 2014; Kessler, Ormel, Demler, & Stang, 2003; Milaneschi, Simmons, van Rossum, & Penninx, 2019; Wang et al., 2020). Depression and anxiety have also both been found to be associated with functional impairment and adverse outcomes ranging from increased disability and days off from work (Kessler et al., 2003) to elevated risk for cardiovascular events and lower rates of cardiovascular recovery (Hare et al., 2014). Some evidence suggests depression and anxiety vary in the strength of their correlations with specific physical conditions. Depression, particularly depression with atypical features such as hyperphagia, hypersomnia, and lethargy, has been correlated with obesity, metabolic, and inflammatory conditions more strongly than anxiety (Milaneschi et al., 2019). By contrast, skin diseases have been associated with panic severity, but not with depression severity (Öksüz, Günver, Oba, & Arıkan, 2020).

Temporal factors such as the age at onset of illness or the timing of illness onset relative to the onset of comorbidity also distinguish clinical course in anxiety and depression. Anxiety disorders are much more likely to present at younger ages and to predate diagnosis of depressive disorders (Kessler et al., 2008, 1996). New onsets of anxiety or depression symptoms, particularly in older populations, may be indicative of cognitive impairment or dementia (Schuurmans & van Balkom, 2011). The relationship between mental and physical disorders is often further complicated by bidirectional causality. Observed comorbidity rates of depression and anxiety exceed what would have been predictable by heritability suggesting common environmental stressors as well as common genetic predisposition (Kessler et al., 2008; Nguyen et al., 2022). Adverse health outcomes can also themselves act as stressors and contribute psychologically and physiologically to symptoms of depression and anxiety (McFarland, Breitbart, Miller, & Nelson, 2020; Murphy, Le Grande, Alvarenga, Worcester, & Jackson, 2020).

Many previous studies associating depression or anxiety with physical disorders have focused on testing specific hypotheses regarding single conditions. Recently, however, phenome-wide association studies (PheWAS) have provided an agnostic approach to the study of many disease outcomes (Mulugeta, Zhou, King, & Hyppönen, 2020). PheWAS originally involved testing for association between genetic variation and the clinical phenome observed in the electronic health record (EHR) as measured using a broad hierarchy of diagnostic codes called phecodes (Bastarache, Denny, & Roden, 2022; Mulugeta et al., 2020). However, in principle, the same analytic technique can be employed to better understand associations between clinical phenotypes, and to differentiate clinical conditions, such as depression and anxiety.

We aimed to extend existing profiles of comorbidity risk for depression by evaluating the comorbidity profiles of patients with depression and anxiety. To do so, we conducted an exploratory analysis identifying differences in the clinically observable phenome of mental and physical health disorders, between patients with diagnoses of depression, anxiety, or both. Using the Mayo Clinic Biobank, we performed a phenotype-based phenome-wide association (Phe^{2}WAS). Instead of using genetic data as the predictor, the Phe^{2}WAS approach uses a primary phenotype as the predictor to identify phenotypic correlations across the EHR with this phenotype of interest. We apply this approach to further test for differences between different groups of patients based on diagnoses of depression and anxiety. Specifically, we defined three clinical phenotypes of interest within the broader categories of depression and anxiety: those diagnosed with depression without a diagnosis of anxiety (isolated depression), those diagnosed with anxiety without a diagnosis of depression (isolated anxiety), and comorbid depression and anxiety. We then applied the Phe^{2}WAS approach to test for differences between these clinical groupings across the EHR phenome. We also performed a LASSO regression to identify which of the many significant associations remained strongest after controlling for all other comorbidities. Finally, we examined the impact of temporality of other diagnoses compared to that of anxiety/depression diagnoses on the Phe^{2}WAS results.

Methods

Data for this study were derived from the EHR of participants in the Mayo Clinic Biobank (Bielinski et al., 2011). All patients in the study gave informed consent for biobank research and the study was approved by the Mayo Clinic Institutional Review Board and the Mayo Clinic Biobank Access Committee.

The EHR includes clinical data derived from both inpatient and outpatient documentation as well as data on demographics, medications/prescriptions, laboratory values, billing codes from the International Classification of Diseases, 9th and 10th editions (ICD-9-CM and ICD-10-CM), and Current Procedural Terminology (CPT) codes (World Health Organization, 1993). We mapped ICD-9-CM and ICD-10-CM codes to phecodes (i.e. higher order group of diagnoses) as described and validated by the Phecode map 1.2b1 (Denny et al., 2010). For the current study, we included all available EHR data from before 6 April 2020. Patients were defined as having a given phecode diagnosis if they had at least two instances of codes from that phecode in their EHR with the index date of each code defined as the first instance in the EHR.

Defining cases with MDD and ANX

Using structured EHR data, depression was defined as having at least two depression-related ICD codes on two different dates, using an initial list of codes mapped to phecodes for major depressive disorder (MDD) (phecodes 296.2 and 296.22), available from https://phewascatalog.org/phecodes (He et al., 2020; Wei et al., 2017) with the addition of dysthymic disorder [ICD-9: 300.4; ICD-10: F34.1], depressive type psychosis [ICD-9: 298.0], and atypical depressive disorder [ICD-9: 296.82]. Anxiety was defined as having at least two anxiety-related codes, using an initial list of codes mapped to phecodes for anxiety disorders (phecode: 300.1, 300.11, 300.12, 300.13), available from https://phewascatalog.org/phecodes (He et al., 2020; Wei et al., 2017) with the addition of separation anxiety disorder (ICD-9: 309.21; ICD-10: F93.0) and selective mutism (ICD-9: 313.23; ICD-10: F94.0) and removing hysteria (ICD-9: 300.1), anxiety disorder in conditions classified elsewhere (ICD-9: 293.84; ICD-10: F06.4) and overanxious disorder (ICD-9: 313). The complete lists of codes for defining MDD and anxiety are presented in online Supplementary Tables S1 and S2. Patients with only one or fewer codes for depression or anxiety were excluded from the analyses.

Phe^{2}WAS

We first used logistic regression models to assess how the phenome of those with isolated depression differed from those with isolated anxiety (MDD-only *v.* ANX-only) using a Phe^{2}WAS approach. In this approach, the phenotype MDD-only *v.* ANX-only was tested for association with each phecode in the EHR that was not rare (>20 cases of the phecode in the analysis). To account for potential demographic confounders, we adjusted the analyses for current age, self-reported gender, race, and ethnicity. To account for potential confounding by length and depth of EHR, we also adjusted for length of record (defined as the length of time from a patient's first ICD code (any ICD code, not limited to depression/anxiety) in the EHR to most recent ICD code), median age of record (median time from date of each ICD code in a patient's record to date of data extraction) which captures how long ago half of the number of diagnoses recorded for a patient occurred, and total number of ICD codes (defined as the total number of codes in a patient's EHR while allowing for duplicated codes on different dates).

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Physical and psychiatric symptoms can influence each other; for example, reduced mobility due to medical illness can potentiate subsequent depressive symptoms, or neurovegetative symptoms of depression can potentiate deconditioning and poorer health. Because temporality is important for characterizing illness phenotype and suggesting potential points of intervention, we repeated the analyses comparing MDD-only *v.* ANX-only separately restricting to phecodes that occur before diagnosis of depression/anxiety or by restricting to phecodes that occur after diagnosis of depression/anxiety. In these analyses, we adjusted analyses for age at diagnosis of depression/anxiety instead of current age to account for the fact that we truncated the EHR. We also updated the length of record in these analyses to account for the truncated EHR.

Finally, we assessed whether the phenome of those with comorbid depression and anxiety (MDD + ANX) differed from those with isolated depression. To do this, MDD + ANX *v.* MDD was tested for association with each phecode in the EHR with adjustments as described above for current age, self-reported gender, race, ethnicity, length of record, median age of record, and total number of ICD codes.

The significance threshold was set using a strict Bonferroni correction for the number of phecodes tested in each Phe^{2}WAS ($p < 0.05/1618 = 3 \times 10^{-5}$).

LASSO regression

In the Phe^{2}WAS, the goal is to identify which diagnoses (or 'phecodes') were associated with the MDD/ANX outcomes of interest. However, many diagnoses may be correlated with one another, making it difficult to interpret the results of a Phe^{2}WAS, as it is not clear whether the observed association between a particular phecode and the trait of interest is due to direct association or due to its correlation with other phecodes. One way to address this issue is to use LASSO regression, which incorporates a penalty term to allow selection of a parsimonious model. Our LASSO analysis aimed to identify a subset of variables that were most strongly associated with an outcome, while simultaneously reducing the influence of associations with other correlated variables.

We used *glmnet* in R to perform the LASSO regression using the outcome of interest (e.g. isolated anxiety *v.* isolated depression) as the outcome and the phecodes as predictors. We included the same covariates as in the Phe^{2}WAS, leaving these terms unpenalized in the LASSO model. We used 10-fold cross-validation to find the largest value for the penalty term that gave cross-validated error within 1 standard error of the minimum. Phecodes with non-zero beta coefficient estimates from the LASSO that were significant in the Phe^{2}WAS are reported.

Results

We identified 14 994 patients from the Mayo Clinic Biobank with at least two codes for anxiety or depression. Of these, 5246 (35.0%) had isolated depression, 3213 (21.4%) had isolated anxiety, and 6535 (43.6%) had comorbid depression and anxiety. Proportions of isolated *v.* comorbid diagnosis differed between men and women: 46.9% of women in our sample were diagnosed with comorbid depression and anxiety compared to 36.1% of men. The sample was older (mean current age 66.4 years) and mostly non-Hispanic (95.0%), white (90.2%), and female (69.3%) with no large differences in demographics among the different diagnostic groups (Table 1). Of note, patients with isolated anxiety and isolated depression were diagnosed at an older age (mean age of 57.5 and 56.1 years, respectively) than those with comorbid anxiety and depression (mean age of 52.3 and 50.2 years for first diagnoses of anxiety and depression, respectively). Furthermore, while those with isolated anxiety and isolated depression had fewer total ICD codes in their record (mean = 514 and 585, respectively) compared to patients with the comorbidity (mean = 848 codes), all groups had similar length of record and median age of record indicating that those with the comorbidity could have higher rates of other comorbid conditions as well.

Phe^{2}WAS of isolated depression v. isolated anxiety

We first used a Phe^{2}WAS to compare diagnoses between patients with isolated depression and isolated anxiety. Of the 1485 phecodes tested, p values for 79 were less than the Bonferroni-corrected significance threshold and of these 53 were also selected in the LASSO regression model. This means these were key group differences even after adjusting for all other phecodes.

Among many significant differences in diagnoses in relation to patients with isolated anxiety, patients with isolated depression had a notably higher frequency of obesity [OR 1.61 (1.58–1.93); $p = 3 \times 10^{-22}$], sleep apnea [OR 1.71 (1.53–1.90); $p = 1 \times 10^{-22}$], type II diabetes [OR 1.74 (1.53–1.97); $p = 9 \times 10^{-18}$], and schizophrenia [OR 16.50 (8.45–32.21); $p = 2 \times 10^{-16}$] (Fig. 1). In analyses assessing the temporality of these findings, we found that the higher comorbidity frequencies of obesity and schizophrenia in those with isolated depression were only significantly higher if we restricted to phecodes occurring after diagnosis of depression or anxiety (online Supplementary Table S3). Differences in the groups found with sleep apnea and type II diabetes persisted regardless of truncation.

We found that rates of many conditions including palpitations [OR 1.92 (1.70–2.17); $p = 2 \times 10^{-25}$], benign neoplasms of the skin [OR 1.61 (1.45–1.81); $p = 2 \times 10^{-17}$], cardiac dysrhythmias [OR 1.45 (1.31–1.61); $p = 2 \times 10^{-12}$], and dyspepsia [OR 1.51 (1.30–1.76); $p = 8 \times 10^{-8}$] were higher in patients with isolated anxiety than those with isolated depression. After truncating the phecodes to either before or after diagnosis, we found that the higher comorbidity rates for benign neoplasms of the skin and cardiac dysrhythmias were only significantly higher in those with isolated anxiety if we restricted to phecodes occurring before diagnosis of anxiety or depression (online Supplementary Table S3). Differences between the groups in rates of palpitations and dyspepsia persisted regardless of truncation.

Phe^{2}WAS of comorbid depression and anxiety v. those with isolated depression

We next performed a Phe^{2}WAS to compare diagnoses between patients with comorbid depression and anxiety *v.* those with only one disorder. Of the 1618 phecodes tested, p values for 58 were less than the significance threshold and of these 18 were also selected in the LASSO regression model suggesting these were key differences between the two groups even after adjusting for all other phecodes.

In comparing the lifetime diagnostic phecodes of patients with comorbid depression and anxiety to those diagnosed with isolated depression (Fig. 2), patients with the comorbidity were more likely to have other mental health disorders, substance use

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Table 1. Demographics and EHR description

Variable	Level		All N = 14 994	MDD + ANX N = 6535	MDD-only N = 5246	ANX-only N = 3213
Gender	Male	*N* (%)	4608 (30.7%)	1664 (25.5%)	1808 (34.5%)	1136 (35.4%)
	Female	*N* (%)	10 386 (69.3%)	4871 (74.5%)	3438 (65.5%)	2077 (64.6%)
Race	White	*N* (%)	13 525 (90.2%)	5824 (89.1%)	4779 (91.1%)	2922 (90.9%)
	Black/African American	*N* (%)	108 (0.7%)	51 (0.8%)	38 (0.7%)	19 (0.6%)
	Asian	*N* (%)	96 (0.6%)	34 (0.5%)	29 (0.6%)	33 (1.0%)
	Native American/Alaskan Native	*N* (%)	31 (0.2%)	18 (0.3%)	9 (0.2%)	4 (0.1%)
	Other	*N* (%)	74 (0.5%)	37 (0.6%)	21 (0.4%)	16 (0.5%)
	Mixed	*N* (%)	771 (5.1%)	379 (5.8%)	239 (4.6%)	153 (4.8%)
	Unknown/Missing	*N* (%)	389 (2.6%)	192 (2.9%)	131 (2.5%)	66 (2.1%)
Ethnicity	Non-Hispanic	*N* (%)	14 305 (95%)	6205 (95%)	5022 (96%)	3078 (96%)
	Hispanic	*N* (%)	233 (1.6%)	101 (1.6%)	86 (1.6%)	46 (1.4%)
	Unknown	*N* (%)	456 (3.0%)	229 (3.5%)	138 (2.6%)	89 (2.8%)
Age	Current age (years old)	mean (s.d.)	66.4 (16.3)	63.9 (16.7)	69.0 (15.5)	67.1 (16.0)
	Age at 1st Dx of ANX (years old)	mean (s.d.)	54.0 (17.5)	52.3 (17.5)	n/a	57.5 (16.8)
	Age at 1st Dx of MDD (years old)	mean (s.d.)	52.8 (17.6)	50.2 (17.6)	56.1 (17.0)	n/a
Record	Median age of record (years)	mean (s.d.)	8.24 (3.7)	8.0 (3.65)	8.9 (3.76)	7.64 (3.54)
	Length of record (years)	mean (s.d.)	21.5 (10.7)	22.4 (10.4)	21.4 (11.0)	19.7 (10.6)
	Number of Dx codes in EHR	mean (s.d.)	684 (819)	848 (1000)	586 (631)	514 (591)

EHR, electronic health records; MDD, depression; ANX, anxiety; Current age, age at date of data extraction; Median age of record, median age of all ICD codes in a patient's record; Dx, diagnosis.

disorders, sleep problems, and gastroesophageal reflux. In particular, among many codes, rates of insomnia [OR 1.72 (1.57–1.88); $p = 1 \times 10^{-31}$], personality disorders [OR 3.36 (2.62–4.30); $p = 1 \times 10^{-23}$], suicidal ideation or attempt [OR 3.25 (2.54–4.17); $p = 1 \times 10^{-20}$], post-traumatic stress disorder [OR 3.13 (2.46–3.99); $p = 3 \times 10^{-20}$], alcohol-related disorders [OR 1.72 (1.50–1.97); $p = 1 \times 10^{-14}$], sleep disorders [OR 1.35 (1.25–1.47); $p = 8 \times 10^{-13}$], myalgia and myositis [OR 1.38 (1.26–1.52); $p = 2 \times 10^{-12}$], substance use disorders [OR 1.79 (1.51–2.12); $p = 2 \times 10^{-11}$], and gastroesophageal reflux disease [OR 1.33 (1.23–1.45); $p = 2 \times 10^{-11}$] were higher in those with the comorbidity than those with isolated anxiety or depression.

Discussion

In contrast to prior studies, we defined phenotypes of isolated depression and isolated anxiety as opposed to comorbid depression and anxiety (Kessler et al., 1996; Mulugeta et al., 2020). Compared to patients with isolated anxiety, patients with isolated depression had a higher frequency of metabolic abnormalities such as obesity and type II diabetes, as well as sleep apnea. Differences between patients with isolated anxiety and those with isolated depression in rates of obesity and mental disorders such as schizophrenia were especially pronounced for diagnoses that were made after the initial depression or anxiety diagnosis. By contrast, the isolated anxiety group had significant comorbidity with dermatologic diagnoses such as benign neoplasms, as well as cardiac symptoms such as palpitations and dysrhythmia; these differences were especially pronounced for medical diagnoses made before the first diagnosis of depression or anxiety.

These findings have several implications for our understanding of depression and anxiety and their relationships with other organ systems or disorders. First, consistent with prior research, we found strong associations between depressive and gastrointestinal disorders (Fond et al., 2014; Foster & Neufeld, 2013; Neuendorf, Harding, Stello, Hanes, & Wahbeh, 2016; Taylor & Holscher, 2020). The autonomic nervous system and serotonergic systems are implicated in gastrointestinal functions: gastric smooth muscle cells express 5-HT1 and 5-HT2 receptors where serotonin induces contractions in the gastric fundus and activity at 5-HT3 receptors caused gastric relaxation and accelerated intestinal transit (Kindt & Tack, 2007; Lychkova, 2009). The common gastrointestinal side effects associated with SSRI antidepressants are illustrative of this relationship, however, so too are reports that ondansetron, a 5-HT3 receptor antagonist, improves depressive symptoms (Bétry et al., 2011; Kindt & Tack, 2007). These, at times, contradictory claims may suggest that multiple phenotypes occur within the subpopulation of patients presenting with co-occurring depressive and gastrointestinal disorders, and that perhaps even within individuals, relationships between a given set of symptoms and single neurotransmitter activity may be nonlinear. Our findings suggest that despite the potentially extensive relationship between central nervous and gastrointestinal systems, patients with concurrent depression and anxiety appear to be at particular risk, though we did not test specifically for differences between comorbid depression and anxiety and isolated depression. Future investigations may also consider exploring the interplay

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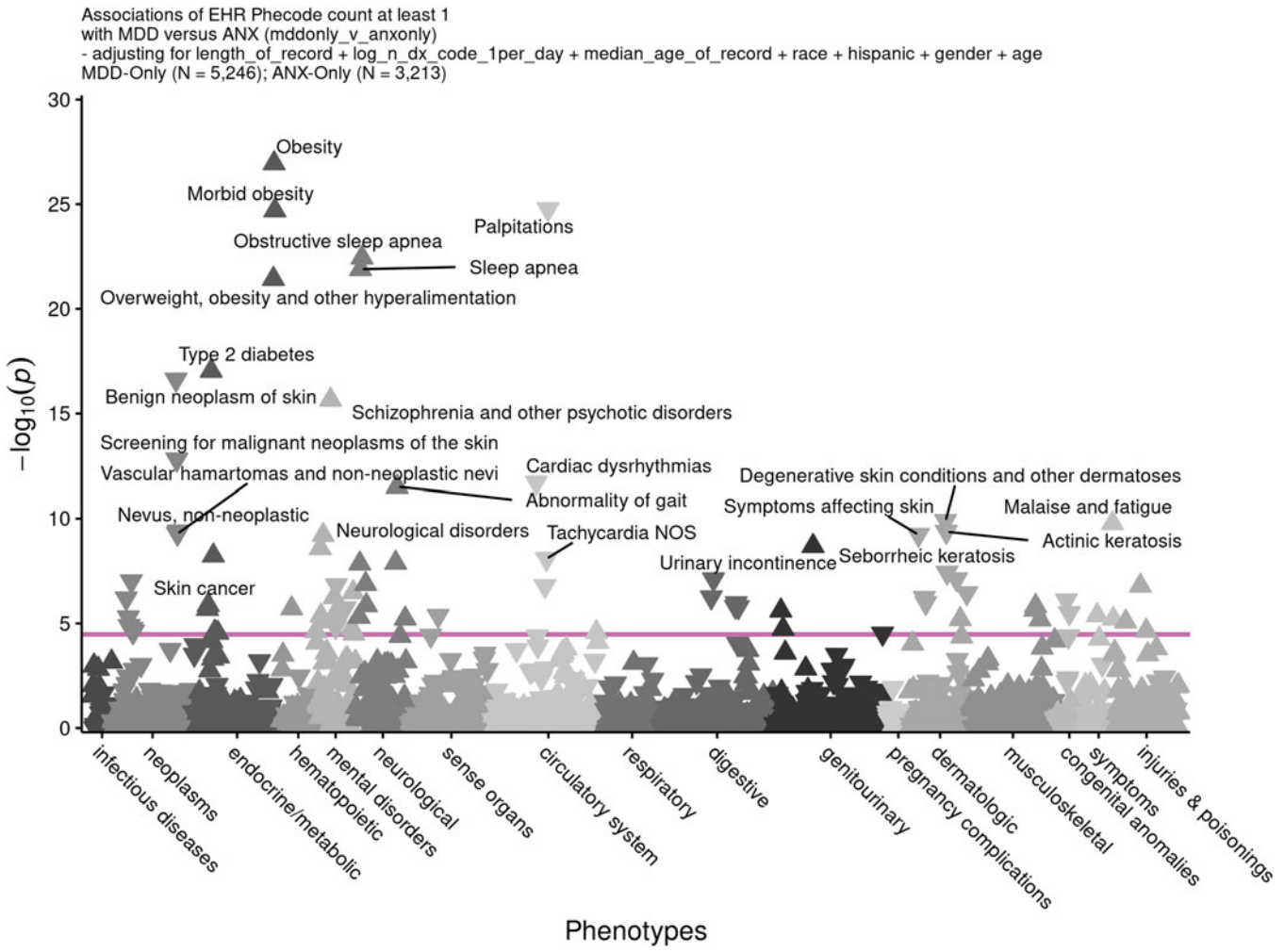

Figure 1. Manhattan plot comparing the phenome of those with isolated depression to those with isolated anxiety. Triangles with single point upward indicate phecodes more commonly observed in patients with isolated depression than in patients with isolated anxiety. Triangles with single point downwards indicate phecodes more common in patients with isolated anxiety than in those with isolated depression. Associations are adjusted for current age, self-reported gender, race, and ethnicity, length of EHR record, median age of all ICD codes in a patient's record, and total number of ICD codes. Participants with comorbid depression and anxiety, and those with neither condition, are excluded from this analysis.

of serotonergic medications and medical comorbidity in phenotype.

Second, a less explored relationship between anxiety and skin disorders that we observed also implicates autonomic nervous system and serotonergic responses (Dixon, Link to external site, Witcraft, & Perry, 2019; Fabrazzo et al., 2021; Kage et al., 2021). 5-HT2A is found in the upper epidermis of skin and 5-HT3 is expressed in the basal epidermal layer (Slominski et al., 2002; Slominski, Wortsman, & Tobin, 2005). Topical doxepin, used orally as an antidepressant, has been used to treat cold urticaria (Gupta & Gupta, 2001). Although it is possible that temperamental anxiety might provoke treatment seeking, it is significant that we observed a specific association with dermatologic diagnoses over other previously reported associations between anxiety and conditions that might mimic anxiety symptoms such as asthma (Goodwin, Fergusson, & Horwood, 2004; Goodwin, Jacobi, & Thefeld, 2003). Similarly, although a variety of conditions such as a positive screening mammogram or prostate-specific antigen might provoke reactive anxiety, the association with anxiety and skin conditions appears especially strong. Although inflammation has been generally implicated in the association of skin disorders with psychiatric symptoms, inflammation is systemic (Michopoulos et al., 2017). Thus, we add to the literature on phenotypic specificity.

Third, we observed the previously characterized relationship involving isolated depression associated with obesity, sleep apnea, and other related chronic health sequelae (Hare et al., 2014; Milaneschi et al., 2019; Mulugeta et al., 2020), though, compared to our comorbid depression group, the isolated depression group exhibited lower concurrent psychiatric risk. While some studies have suggested that obesity is a causal risk factor for MDD (Tyrrell et al., 2019), we found that isolated depression diagnosis preceded obesity and related chronic health sequelae. These findings add to our understanding of the bidirectional relationship between depression and obesity and may aid in the identification of clinical phenotypes that could provide clinical opportunities for intervention.

Fourth, associations of isolated depression with mental disorders and specifically schizophrenia were pronounced relative to isolated anxiety in the period after first depression diagnosis. Because population prevalence of depressive symptoms is high relative to the prevalence schizophrenia-spectrum disorders

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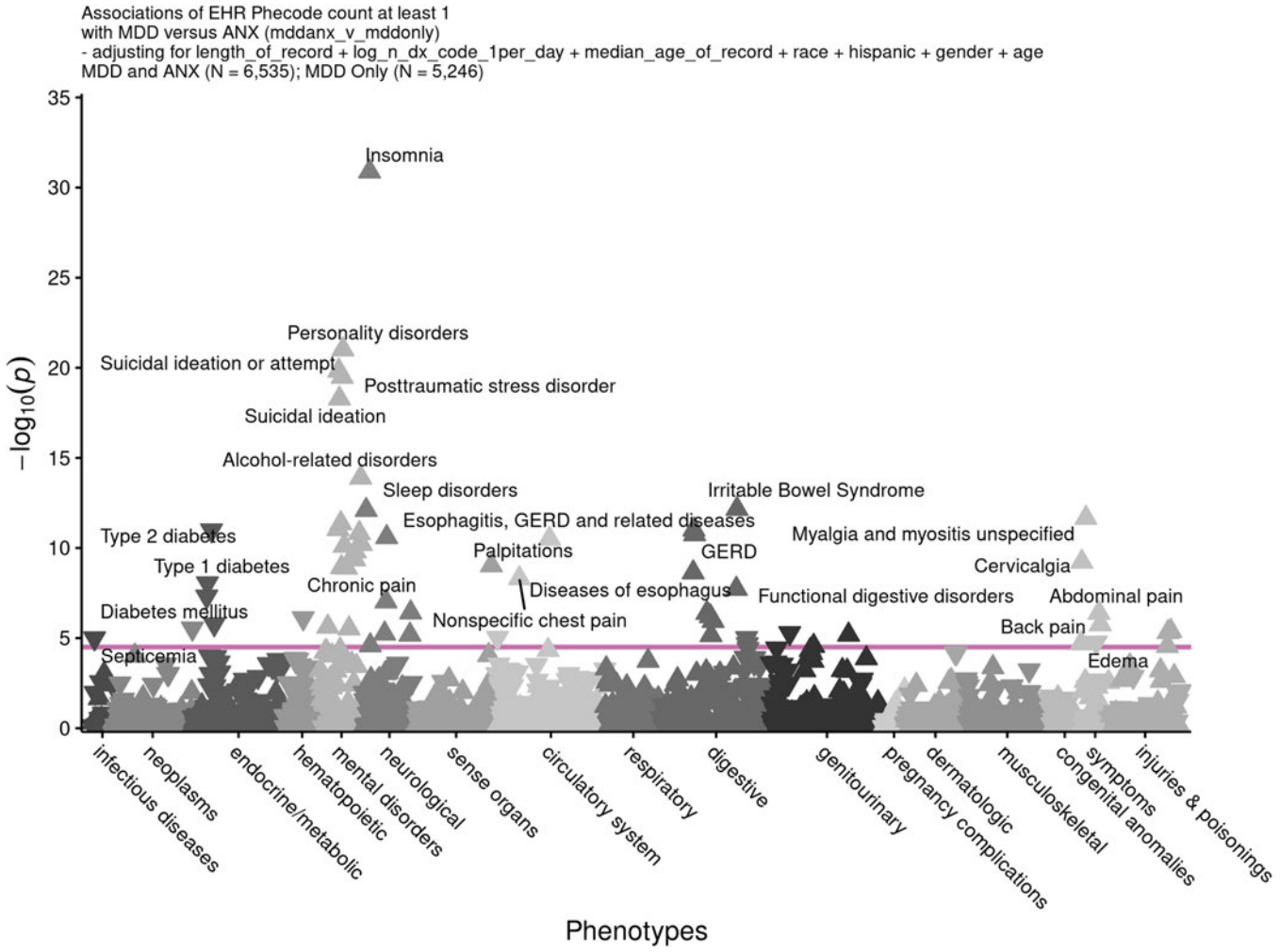

Figure 2. Manhattan plot comparing the lifetime phenome of those with comorbid depression and anxiety to those with isolated depression. Triangles with single point upward indicate phecodes more commonly associated with comorbid depression and anxiety as compared to either isolated depression. Triangles with single point downwards indicate phecodes more commonly occurring with either isolated depression or isolated anxiety than with comorbid depression and anxiety. Analyses are adjusted for current age, self-reported gender, race, and ethnicity, length of EHR record, median age of record, and total number of ICD codes.

(Kessler et al., 2005; McGrath, Saha, Chant, & Welham, 2008), prodromal depressive or emerging negative symptoms of schizophrenia (Häfner, Maurer, Trendler, an der Heiden, & Schmidt, 2005) may initially be misattributed to a primary mood disorder. However, to the extent that depression without anxiety may differentiate schizophrenia from other psychiatric conditions that are correlated with both depression and anxiety symptoms, these findings may suggest attention to depression or anxiety symptoms can also assist with our understanding of constellations of comorbidity among other psychiatric disorders.

The results from these Phe^{2}WAS analyses indicate that comorbid diagnoses of depression and anxiety are highly associated with several psychiatric conditions including suicidal ideation, post-traumatic stress disorder, and substance use disorders, even compared to those with isolated depression, which is consistent with prior literature (Brainstorm Consortium et al., 2018; Clayton et al., 1991; Mulugeta et al., 2020). Among patients with depression diagnoses, those with comorbid depression and anxiety still outnumbered those with isolated depression, thus it is not surprising that aggregated studies conducted with samples of patients with depression are dominated by this subset. Depression has been associated with higher rates of gastroesophageal reflux, esophagitis, and gastroenteritis (Martín-Merino, Ruigómez, García Rodríguez, Wallander, & Johansson, 2010; Mulugeta et al., 2020). We found rates of gastroesophageal reflux were higher among those with comorbid depression and anxiety than those with isolated depression.

Most patients with depression or anxiety presented with either isolated depression or isolated anxiety. In previous studies, the reported rate of comorbid anxiety with depression has been as high as 85% of patients with depression and 90% of patients with anxiety (Gorman, 1996). However, our estimates are not out of line with estimates from other biobank samples (Nguyen et al., 2022). Because the average median record length was 8.2 years, one explanation for this discrepancy is that, relative to surveys, EHRs are less sensitive at detecting lifetime psychiatric diagnoses. However, the phenotypic profiles of patients with isolated depression and isolated anxiety differed significantly from those with both depression and anxiety, after adjusting for potential confounders, suggesting that these phenotypes correspond to distinct risk groups. This aligns with a recent genetic study of depression, anxiety, and their comorbidity, which showed independent

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depression and anxiety polygenic contributions to the comorbidity (Coombes et al., 2022). Relative to prior analyses of epidemiological samples of non-elderly individuals, aged 15–54 years (Kessler et al., 2008, 1996), our sample was also older, with a median age of 66.4 years. Some studies of older individuals have described both decreasing rates of depression and anxiety with increasing age and decreasing rates of comorbidity (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010; Schuurmans & van Balkom, 2011). Presenting symptoms of depression and anxiety change with increasing age, reflecting cohort factors such as healthy survivor bias, social factors such as reactions to a loss of physical independence or social connections, and biological factors such as psychiatric symptoms of age-related cognitive decline (Byers et al., 2010; Lenze et al., 2001; Schuurmans & van Balkom, 2011; Welzel et al., 2019). Our study results may reflect the evolving heterogeneity of depression and anxiety across the adult lifespan.

Limitations

This study has several limitations. First, our analysis was based on data from the Mayo Clinic Biobank, which represents a selective population of older adults of primarily European descent with higher-than-average levels of education (Olson et al., 2019). This limits our ability to analyze subgroup effects exploring, for instance, variation across race/ethnicity or age. Second, this analysis, which examines phenotypes from the EHR, is limited by length of record, selection into treatment, socioeconomic status, and factors related to working with EHR data. This limits the examination of depression/anxiety onset, which often occurs at ages younger than those captured in our EHR. Socioeconomic factors may influence treatment seeking, comorbidities, and diagnoses received. Furthermore, clinical monitoring and diagnostic patterns may vary by clinical setting. Because we did not have access to standardized diagnostic metrics across clinical settings, we are limited in our ability to address differences arising from true phenotypic differences between groups compared to clinical recording. Similarly, we cannot fully ascertain that patients we characterize as isolated depression or isolated anxiety do not possess any features of the other disorder aside from clinically recorded diagnoses. Third, although our total sample included 14 994 patients, we were restricted by sample size to investigating associations between relatively prevalent conditions. As such, we cannot comment on granular relationships between specific diagnoses including distinctions between depression or anxiety disorders, among depression or anxiety phenotypes, or among patients who may have more than one anxiety disorder (Davies et al., 2023; Klein Hofmeijer-Sevink et al., 2012). Fourth, our analyses focused on differences between depression and anxiety and did not include a control group. For example, a phenotype that is similarly common in depression and controls, but less frequent in anxiety would be reported as associated with depression. Fifth, the analysis was limited to associations between phenotypes. Although we attempted to elucidate temporal clinical presentations within patients and to reduce dimensionality using LASSO, these findings cannot be used to draw direct causal inferences and therefore, we view the results as exploratory.

Conclusions

PheWAS approaches, which invert the idea of genome-wide association studies, have been successful in demonstrating that specific genetic variations are associated with multiple clinical conditions derived from the EHR (Bastarache et al., 2022). Here, we leveraged this approach to instead examine differences in the associations between diagnostic phenotypes of depression and anxiety with multiple clinical conditions derived from the EHR (Phe^{2}WAS). The current results provide several interesting perspectives on the clinical landscape of depression and anxiety. Learning from broad descriptive cohorts across service settings could help us better understand clinical heterogeneity, improve generalizability of diagnostic characterizations, and inform clinical assessment of patients with these common psychiatric disorders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001745.

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Competing interest. The authors have no COI to declare.

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