Self-reported medication use as an alternate phenotyping method for anxiety and depression in the UK Biobank

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Abstract
The requirement for large sample sizes for psychiatric genetic analyses necessitates novel approaches to derive cases. Anxiety and depression show substantial genetic overlap and share pharmacological treatments. Data on prescribed medication could be effective for inferring case status when other indicators of mental health are unavailable. We investigated self-reported current medication use in UK Biobank participants of European ancestry. Medication Status cases reported using antidepressant or anxiolytic medication (n = 22,218), controls did not report psychotropic medication use (n = 168,959). A subset, “Medication Only,” additionally did not meet criteria for any other mental health indicator (case n = 2,643, control n = 107,029). We assessed genetic overlap between these phenotypes and two published genetic association studies of anxiety and depression, and an internalizing disorder trait derived from symptom-based questionnaires in UK Biobank. Genetic correlations between Medication Status and the three anxiety and depression phenotypes were significant (r̂g = 0.60–0.73). In the Medication Only subset, the genetic correlation with depression was significant (r̂g = 0.51). The three polygenic scores explained 0.33% – 0.80% of the variance in Medication Status and 0.07% – 0.19% of the variance in Medication Only. This study provides evidence that self-reported current medication use offers an alternate or supplementary anxiety or depression phenotype in genetic studies where diagnostic information is sparse or unavailable.

KEYWORDS
 genetic correlation, internalizing, polygenic score, UK Biobank

1 | INTRODUCTION

Anxiety and depression are commonly comorbid (Kendler, Neale, Kessler, Heath, & Eaves, 1992; Moffitt et al., 2007), have notable symptom overlap (American Psychiatric Association, 2013), and share first-line pharmaceutical treatments (National Institute of Health and Care Excellence, 2011). Anxiety and depression are heritable (twin h²: 20–60% (Hettema, Neale, & Kendler, 2001; McIntosh, Sullivan, & Lewis, 2019; Meier & Deckert, 2019; Sullivan, Neale, & Kendler, 2000). SNP-based h²: 10–28% (Hettema et al., 2001; McIntosh et al., 2019;
Meier & Deckert, 2019; Sullivan et al., 2000). They also share much of their underlying genetic influences (twin $r_g \sim 1.00$ (Kendler et al., 1992; Purves et al., 2020; Roy, Neale, Pedersen, Mathé, & Kendler, 1995), SNP-based $r_g \sim 0.8$ (Kendler et al., 1992; Purves et al., 2020; Roy et al., 1995)). Decades of work have demonstrated that liability to anxiety and depression is influenced by numerous individual genetic variants, each associated with a very small effect. To detect these effects, genetic association studies of complex disorders require extremely large sample sizes. The difficulty of ensuring adequate statistical power is compounded by the clinical heterogeneity of internalizing disorders, and their high lifetime prevalence whereby the mean difference in phenotypic liability between cases and controls is smaller than for a rare disorder such as schizophrenia (Mullins & Lewis, 2017; Wray et al., 2018).

One approach to increase statistical power in genetic association studies is to focus participant ascertainment on more clinically and demographically homogeneous individuals (Cai et al., 2015). However, collecting high-quality diagnostic information such as that from structured clinical interviews is resource-intensive and thus data are rarely available on the required scale. Another approach is to use less in-depth phenotyping methods to produce very large samples which can outweigh the noise introduced by phenotypic heterogeneity. For example, brief self-report symptom-based questionnaires with scoring criteria can indicate current or lifetime diagnoses in genetic studies (Coleman et al., 2020; Direk et al., 2017; Purves et al., 2020). Medical records of diagnoses, admissions, and treatments have also shown utility (Hall et al., 2018; Howard et al., 2018). Another method is “broad” or “minimal” phenotyping, whereby case status is determined using single data points, such as self-report of having received a diagnosis from a clinician (Howard et al., 2019; Hyde et al., 2016; Purves et al., 2020; Wray et al., 2018). Broad depression phenotypes demonstrate significant genetic correlations ($r_g = 0.64–0.79$) with clinically defined major depressive disorder (Howard et al., 2018). The availability of multiple phenotyping methods presents the opportunity for combination and triangulation, which can maximize the likelihood of reliably identifying cases (Glanville et al., 2021). Combining indicators of mental health status is also useful in the presence of missing data on more in-depth measures and in meta-analyses of studies that used different phenotyping methods. This has facilitated the identification of numerous novel genetic variants associated with anxiety and depression (Howard et al., 2019; Purves et al., 2020).

An additional indicator of anxiety or depression case status that has not yet been thoroughly investigated for genetic studies is reported use of antidepressant or anxiolytic medication. Medication data could supplement existing symptom-based and broad phenotyping measures by identifying probable cases who are not otherwise captured, perhaps due to missing data or low sensitivity to specific diagnoses. In support of this, 11% of the UK Biobank participants who responded to a follow-up mental health questionnaire reported using antidepressant medication but did not meet case criteria for anxiety or depression in the symptom questionnaires, hospital records or self-reported diagnoses (Davis et al., 2019). As well as supplementing other mental health indicators, medication data could function as a proxy for anxiety and depression when alternate sources of information are unavailable due to study design. For example, in cohort studies where mental health was not of primary interest during study development, records of reported medication use could be used to infer a diagnosis. It may also be a practical phenotyping solution for studies using big data from electronic health records. There is some support for the use of medication data as an alternate phenotype in genetic analyses. One study reported an odds ratio of 1.7 for taking antidepressants in individuals in the top decile of a depression polygenic score, compared with the lowest decile (Wu et al., 2019), and another found high genetic correlations between depression and self-reported antidepressant use in common genetic variants (SNP-based $r_g = 1$) and pedigree associated variants (rare and common variants; kinship-based $r_g = 0.9$) (Wigmore et al., 2019). While these previous studies are indicative of the potential for antidepressants as a proxy phenotype for depression, they did not investigate whether there could be a gain in sample size from using medication data in addition to other commonly used phenotypes. Furthermore, it is unclear whether the same is true for anxiolytics and anxiety. It is pertinent to note that the same class of drugs, selective serotonin reuptake inhibitors, is prescribed as a first-line pharmaceutical treatment for both depression and anxiety, despite being categorized as antidepressants (National Institute of Health and Care Excellence, 2011). By combining reports of antidepressants and anxiolytics, we can create a single internalizing disorder phenotype and examine overlap with existing anxiety and depression phenotypes. The genetic overlap between anxiety and depression supports the study of these two disorders as a combined phenotype (Hetta, 2008), indeed, this has been shown to increase agreement between self-report and symptom-based indicators of mental health status (Davis et al., 2019). While knowledge of the genetic influences on specific phenotypes is required to investigate how symptoms and diagnostic subtypes are related, there are advantages to studying psychiatric genetics at the broader level of internalizing disorders (Slade & Watson, 2006). One benefit could be the identification of genetic influences on factors of general distress or negative affect that act transdiagnostically and are clear therapeutic targets (Clark & Watson, 1991). This is particularly relevant in the context of mixed anxiety and depressive disorder, characterized by the presence of symptoms of anxiety and of depression that do not meet diagnostic criteria for either diagnosis. Although a controversial diagnosis, mixed anxiety and depressive disorder is highly prevalent in primary care and is associated with pronounced distress and impairment (Möller et al., 2016).

### 1.1 Current study

We used data on current medication use reported by participants from the UK Biobank population cohort in an interview with a nurse. This is hereafter referred to as “Medication Status.” Our aim was to explore use of antidepressant and anxiolytic drugs as an alternate phenotyping method to identify anxiety and depression cases where data about diagnoses or symptoms are absent. To test the utility of our Medication Status phenotype, we determined the extent to which common genetic variants associated with Medication Status overlap with those of anxiety and depression cases identified using other measures.
We further tested this question using multiple indicators of mental health status available in the UK Biobank. Specifically, we identified a subset of Medication Status cases who did not meet case status on any other indicator and were thus referred to as “Medication Only.” This subset might represent individuals who were experiencing internalizing disorders but have not previously been identified with other commonly used methods in genetic studies of anxiety and depression. If so, we would expect this group to confer reliable genetic signal similar to that of anxiety and depression cases phenotyped using other measures, demonstrated by high genetic overlap. This would indicate that leveraging medication data alongside symptom-based and diagnostic measures can provide a useful gain in sample size, even in samples well characterized for psychiatric disorders. Alternatively, Medication Only cases could be a particularly heterogeneous group of individuals, a substantial proportion of whom were prescribed medication for reasons other than anxiety or depression diagnoses. We would then expect this group to show low genetic overlap with internalizing disorder cases. As such, caution would be required using this phenotyping approach; the heterogeneity would reduce statistical power, and any genetic signal identified could be nonspecific to internalizing disorders.

2 | MATERIALS AND METHODS

2.1 | Sample

The UK Biobank is a health research resource of more than 500,000 volunteers from the UK population, aged between approximately 40 and 70 years old at recruitment. Between 2006 and 2010, participants provided biological samples and responded to a range of health and lifestyle questionnaires, including an interview with a nurse about medication use. In each of two follow-up visits, approximately 20,000 participants completed additional measurements and could update information from their initial session (Sudlow et al., 2015), resulting in up to three measurement time points. An online Mental Health Questionnaire (MHQ), which asked more detailed information about psychiatric diagnoses and symptoms, was completed by almost one third of the cohort in 2016 (Davis et al., 2020). In the current study, we limited our analyses to participants of European ancestry who passed genetic quality control and had complete data on the phenotypes and covariates.

2.2 | Phenotype definitions

2.2.1 | Medication Status

Medication Status was obtained via a verbal interview item requesting the names of regular prescription medications that the participants were currently taking (UK Biobank Data Field 20003). The nurses conducting the interviews did not record medications that were short-term (e.g., 1-week course of antibiotics), historical, or prescribed but not being taken. We excluded individuals who responded to the MHQ to prevent sample overlap in polygenic comparisons with selected phenotypes that had been derived using MHQ responders (further details in Section 2.4). The sample for analysis consisted of individuals who supplied the name of any medication in the interview, at any of the three data collection time points. The medication interview field had 6,745 unique response values, which were mapped to psychotropic medication classes of antidepressant, anxiolytic, antipsychotic, and mood stabilizer using an existing list of codes (Davis et al., 2019: see Data S1, Supporting Information). Medication Status cases were individuals who reported taking a medication at the time of interview that was classified as an anxiolytic or antidepressant. Note that participants themselves did not need to report, or even know, that the medication was an antidepressant or anxiolytic. This variable thus had the potential to capture individuals who were prescribed medication for reasons other than core symptoms of anxiety or depression, such as sleep difficulties. Controls were defined as individuals who did not report taking any psychotropic medication but who reported taking at least one medication and therefore had a nonblank response (as per a previous UK Biobank study; Wu et al., 2019). As there was not a negative option for this item, we chose not to infer control status from a blank response. Although some blank responses would represent controls, we could not distinguish these from individuals who did not wish to share the information (i.e., possible cases or exclusions). There was a preceding binary question regarding the use of any medications, which could have helped to identify controls, but it had low agreement with the more detailed item in which participants named a medication. Case and control definitions and screening were performed solely using the medication data, so that the same sample would be drawn if only these data were available. We excluded individuals who reported using antipsychotics or mood stabilizers indicative of potential psychosis or bipolar disorder. These disorders are highly heritable and demonstrate strong genetic correlations with other psychiatric disorders, thus potentially producing misleading relationships if included in our analyses. It is worth noting that this may have excluded some of the more severe depression cases who were receiving adjunct antipsychotics. This could lead to decreased observed genetic overlap with other internalizing phenotypes, as more severe symptoms are associated with greater genetic liability (Wray et al., 2018); however, we chose to be conservative.

We also identified a subset of the Medication Status cases and controls for analysis who we will refer to as “Medication Only.” Whereas Medication Status cases and controls were defined solely using the interview item regarding medication use, Medication Only incorporated information from other indicators of mental health. Cases were therefore defined in the same way as for Medication Status but additionally did not meet case criteria (i.e., were controls or missing sufficient information) for anxiety, depression, or other psychiatric conditions, on any other indicator of mental health status in the UK Biobank data. These diagnostic indicators included hospital records (primary and secondary International Classification of Diseases [ICD] 10 “F” codes), self-reported diagnosis in a nurse interview, and treatment seeking (see Data S2 for details and Tables S1 and S2 for data completeness and case overlap between indicators). Medication Only cases therefore represented a group of individuals who, across all these indicators of mental health, were only identified as anxiety or depression cases by their reported
medication use. Medication Only controls were participants who were not taking an antidepressant or anxiolytic (defined as per Medication Status controls) and furthermore did not meet case criteria for any other indicator of mental health status.

Medications can be prescribed for conditions other than those for which they are licensed. Therefore, we created versions of the Medication Status and Medication Only phenotypes excluding individuals with evidence of physical conditions for which antidepressants or anxiolytics are commonly prescribed (see Data S3 and Table S3 for details, including sample sizes).

2.2.2 | Lifetime Internalizing Disorder

To provide data for comparison with Medication Status, we used the anxiety and depression modules of the Composite International Diagnostic Interview Short Form (CIDI-SF) from the MHQ to derive a symptom-based case-control phenotype. This is closest to a “gold-standard” diagnostic approach available in UK Biobank (Cai et al., 2020). To ensure a comparable internalizing disorder phenotype, cases met criteria for either or both of the lifetime anxiety and lifetime depression modules and controls did not fulfill case criteria for either. We refer to this as the “Lifetime Internalizing” disorder diagnosis (see Data S2 for further details).

Phenotype derivation and descriptive analyses were performed in R version 3.6.0 (R Core Team, 2019).

2.3 | Genotyping and quality control

Genetic data were centrally processed as per the UK Biobank pipeline (Bycroft et al., 2018) and variants were limited to those genotyped or imputed (INFO score > 0.4 [Zheng et al., 2015]) to the Haplotype Reference Consortium reference panel and the UK10K Consortium reference panel. Individuals of European ancestry were identified using four-means clustering on the first two genomic principal components available from UK Biobank. Single nucleotide polymorphisms (SNPs) were included in the analyses if they were common (minor allele frequency > 0.01), had low missingness (≤ 0.02), and a nonsignificant Hardy-Weinberg equilibrium test result (p > 1 × 10^{-8}). Individuals were unrelated (more distant than third-degree relatives; KING < 0.044 as reported by UK Biobank), had low SNP missingness (≤ 0.02) and concordant chromosomal and phenotypic sex. SNPs were further filtered to INFO > 0.9 for analyses conducted with linkage disequilibrium score regression (LDSC; Bulik-Sullivan et al., 2015) and PRSice-2 (Choi & O'Reilly, 2019).

2.4 | Statistical analysis

2.5 | Genome-wide association

A genome-wide association study (GWAS) was performed for Medication Status in the full sample and in the Medication Only subset, as well as for the Lifetime Internalizing phenotype, using BGENIE software (version 1.2; Bycroft et al., 2018). GWAS were a necessary step to perform the main investigation of genetic overlap between self-reported medication data and other anxiety and depression phenotypes; see Data S4 and Figures S1 and S2 for GWAS details and results.

To determine how self-reported medication data compared to existing definitions of anxiety and depression, we selected two published genetic studies in addition to the UK Biobank Lifetime Internalizing phenotype. These were a lifetime anxiety GWAS (Purves et al., 2020) (“UKB-anxiety”) and the Psychiatric Genomics Consortium’s second major depressive disorder GWAS (Wray et al., 2018) (“PGC-depression”); see Table 1 for details. Of note, the medication phenotypes had been created in UK Biobank participants who did not complete the MHQ. UKB-anxiety and Lifetime Internalizing phenotypes were derived exclusively from MHQ responders, and we selected summary statistics from a GWAS of the PGC-depression data which excluded the UK Biobank sample. As such, known sample overlap was eliminated.

2.6 | Heritability and genetic correlations

The proportion of phenotypic variance explained by common genetic variants, defined as SNP-based heritability, was estimated using LDSC (Bulik-Sullivan, Loh, et al., 2015) of the GWAS summary statistics. For conversion to the liability scale, we assumed that the sample prevalence represented the true population prevalence, with calculations using ±10% of this value also performed.

We estimated genetic correlations using LDSC (Bulik-Sullivan et al., 2015; Bulik-Sullivan, Loh, et al., 2015). These were calculated between our medication phenotypes with each of UKB-anxiety (Purves et al., 2020), PGC-depression (Wray et al., 2018), and the Lifetime Internalizing phenotype. We used block jackknifing to determine if the correlations between Medication Status and the three comparison phenotypes were significantly different to those estimated with Medication Only. This method divides the summary statistics into a number of blocks (default in LDSC is 200) of contiguous SNPs and performs multiple estimations of the genetic correlation, omitting one block at a time. This provides SEs with which to determine statistically significant differences between pairs of genetic correlations.

2.7 | Polygenic scores

Genetic overlap between self-reported medication use and previously defined anxiety and depression was also assessed via polygenic scoring. GWAS summary statistics from UKB-anxiety (Purves et al., 2020), PGC-depression (Wray et al., 2018), and Lifetime Internalizing were used to compute polygenic scores for each participant in our sample. An individual’s polygenic score is the sum of trait-associated variants they carry, weighted by the GWAS effect size. Polygenic scores were calculated across a range of p-value thresholds, with increasingly lenient thresholds capturing a greater number of the variants that
TABLE 1  Summary statistics from genome-wide association studies (GWAS) selected for comparison with self-reported current antidepressant or anxiolytic medication use in the UK Biobank (European ancestry, excluding Mental Health Questionnaire (MHQ) responders)

| GWAS                              | Sample                      | N cases | N controls | Phenotyping methods                                      |
|-----------------------------------|-----------------------------|---------|------------|---------------------------------------------------------|
| UKB-anxiety (Purves et al., 2020) | UK Biobank MHQ responders   | 25,453  | 58,113     | Lifetime anxiety symptom-based questionnaire             |
|                                   |                             |         |            | Self-report of anxiety diagnosis from a clinician        |
| PGC-depression (Wray et al., 2018)| Meta-analysis, excluding    | 116,404 | 314,990    | Various, including:                                      |
|                                   | UK Biobank                  |         |            | Structured diagnostic interviews                         |
|                                   |                             |         |            | Self-report of depression diagnosis from a clinician     |
|                                   |                             |         |            | Depression symptom-based questionnaire                    |
|                                   |                             |         |            | Depression diagnoses in medical records                  |
| Lifetime Internalizing            | UK Biobank MHQ responders   | 32,160  | 91,732     | Lifetime anxiety and depression symptom-based questionnaires |

Note: To eliminate known overlap between the analytical sample and the comparison GWAS, MHQ responders were excluded from the medication phenotypes, and we selected summary statistics from a GWAS of PGC-depression which did not include UK Biobank data.

were tested in the GWAS. For each of the three trait polygenic scores, logistic regressions were performed with Medication Status and with Medication Only. Age, sex, genotyping batch, assessment center, and the first six genetic principal components were included as covariates. We previously determined that this number of principal components, alongside assessment center, is sufficient to control for the majority of genome-wide inflation associated with geographic location in UK Biobank. The optimum p-value threshold was defined as the one where the proportion of variance (Nagelkerke’s R²) explained in the medication phenotype was highest, as this is likely to represent the maximal amount of true variance explained (in addition to noise). Nagelkerke’s R² is subject to bias when the sample prevalence does not reflect the population prevalence and therefore the variance explained was converted to the liability scale using a range of prevalence values (Lee, Goddard, Wray, & Visscher, 2012). To gain an empirical p-value, 10,000 permutations were performed. Polygenic score analyses were performed in PRSice version 2.3.1 (Choi & O’Reilly, 2019).

2.8  | Sensitivity analyses

The Medication Status and Medication Only GWAS and subsequent analyses were repeated excluding individuals with evidence of physical conditions, such as epilepsy and chronic pain, for which antidepressants or anxiolytics are commonly prescribed (see Data S3 and Table S3 for further details).

2.9  | Ethics

UK Biobank has Research Ethics Committee approval (11/NW/0382) and Research Tissue Bank approval. Participants provided written informed consent which included permission to access their medical records. The current study was performed under UK Biobank application 18177.

3  | RESULTS

3.1  | Sample and phenotype distribution

The genetic quality-control criteria resulted in a sample of 385,645 UK Biobank participants of European ancestry. Of these, 283,662 individuals supplied the name of any medication in response to the Medication Status verbal interview item. After excluding participants who completed the MHQ (n = 89,801) and who reported taking antipsychotic or mood stabilizer medication (n = 2,684), 191,177 participants remained for analysis. Of the 22,218 Medication Status cases, 20,399 (92%) reported taking an antidepressant and 3,047 (14%) reported taking an anxiolytic, with 1,228 (6%) reporting taking both. This left 168,959 controls who had responded to the medication interview item but had not named an antidepressant, anxiolytic, antipsychotic, or mood stabilizer. Following exclusion of individuals who met case criteria for any other indicator of mental health status, there were 2,643 Medication Only cases and 107,029 controls. Of the Medication Only cases, 2,083 (79%) reported taking an antidepressant drug, 618 (23%), an anxiolytic, and 58 (2%) reported taking both.

The majority of Medication Status cases were female (68%), with a mean age of 57 years (SD = 7.8), while 53% of controls were female, and had a mean age of 58 years (SD = 8.0). Medication Only cases were also predominantly female (67%), with a mean age of 60 years (SD = 7.3), and 49% of controls were female, mean age 58 years (SD = 8.0). Further descriptives about these groups and the Lifetime Internalizing phenotype are available in Table S4. Details of the overlap between these groups and other mental health indicators in UK Biobank are available in Tables S1 and S2.

3.2  | Genetic correlations

Results from genetic correlations are displayed in Figure 1. These were performed for Medication Status and the Medication Only subset with the comparison phenotypes; UKB-anxiety, PGC-depression,
FIGURE 1 Genetic correlations between self-reported current antidepressant or anxiolytic medication use in the UK Biobank (European ancestry, excluding Mental Health Questionnaire (MHQ) responders) and anxiety and depression phenotyped using existing methods. Medication Status was defined using self-reported current use of antidepressant or anxiolytic medication in individuals who did not complete the MHQ (N = 191,177, cases = 22,218). Medication Only were a subset who additionally did not meet case criteria for any other indicators of mental health condition in UK Biobank (N = 109,672, cases = 2,643). UKB-anxiety is the Purves et al. (2020) study, which used data from the UK Biobank MHQ. PGC-depression is Wray et al. (2018), an international meta-analysis, excluding the UK Biobank sample. Lifetime Internalizing was created in the present study using lifetime anxiety and depression symptom-based questionnaires in UK Biobank MHQ responders. Standard errors are represented by error bars. * indicates significance at the Bonferroni-adjusted significance level of 8.3 * 10^{-3} used for the six independent tests performed. Liability scale SNP-based r² assuming sample prevalence equals population prevalence: Medication Status 0.074 (SE = 0.004), Medication Only 0.053 (SE = 0.010)

Note: Proportion explained is presented on the liability scale, assuming population prevalence is equal to sample prevalence. Medication Status was defined using self-reported current use of antidepressant or anxiolytic medication in individuals who did not complete the MHQ (to provide independent discovery and target samples) (N = 191,177, cases = 22,218). Medication Only were a subset who additionally did not meet case criteria for any other indicators of mental health condition in UK Biobank (N = 109,672, cases = 2,643). p = empirical p-value resulting from 10,000 permutations.

Abbreviations: p ≠ p-value threshold at which Nagelkerke’s R² was highest; SNPs, single nucleotide polymorphisms.

3.3 Polygenic scores

The proportion of variance explained in the Medication Status and Medication Only phenotypes by polygenic scores created from the UKB-anxiety and PGC-depression studies, as well as the Lifetime Internalizing phenotype, are displayed in Table 2. For both medication use phenotypes, the PGC-depression polygenic score explained the greatest proportion of variance. For bar plots showing the proportion of variance explained across each p-value threshold tested, see Figure S3.

3.4 Sensitivity analyses

The sensitivity analysis excluded individuals with evidence of physical conditions that are commonly treated with antidepressants or anxiolytics. Of the Medication Status cases, 4% had evidence of one of these physical conditions, and 3.5% of the Medication Only cases (see Table S3 for sample size details). The sensitivity analysis for Medication Status and for Medication Only did not substantially change the results for the genetic correlations or polygenic scores (see Data S5, Figure S4, and Tables S5 and S6).

4 Discussion

4.1 Overview

Using genetic correlations and polygenic score analysis, this study demonstrated that self-reported, current antidepressant, and
anxiolytic medication use can serve as an alternate phenotyping method for anxiety or depression. A substantial proportion of the UK Biobank European ancestry sample for genetic analysis had answered the medication verbal interview item (73%) and therefore had data to inform our Medication Status phenotype. We observed genetic overlap between Medication Status and anxiety and depression phenotypes (UKB-anxiety, PGC-depression, and UK Biobank Lifetime Internalizing) that were defined using other methods such as self-report of a diagnosis, symptom-based questionnaires, and clinical interviews.

The existence of multiple indicators of anxiety and depression in the UK Biobank allowed us to further explore the utility of this alternate phenotyping method for identifying anxiety and depression cases. The majority of Medication Status cases were the same individuals that would be identified if we had used other UK Biobank measures, such as reported treatment seeking or hospital codes. However, we did identify approximately 10% of the Medication Status cases who reported antidepressant or anxiolytic use but did not meet case criteria for any of the other indicators of a mental health condition. We named this subset “Medication Only.” This group appeared to be more heterogeneous, demonstrating lower genetic overlap with the comparison phenotypes.

4.2 Genetic correlations

The SNP-based genetic correlations between Medication Status and UKB-anxiety (Purves et al., 2020), PGC-depression (Wray et al., 2018), and Lifetime Internalizing ranged between 0.60 and 0.73. This indicates substantial common variant overlap between individuals who reported taking antidepressant or anxiolytic medication and participants who were identified using other indicators, such as symptom-based questionnaires or clinical interviews.

The correlations were comparable to those from the PGC-depression study, which reported a weighted mean genetic correlation of 0.76 between the seven contributing cohorts (Wray et al., 2018), and also to those reported for depression phenotypes from multiple indicators in a previous UK Biobank study (0.85–0.87; Howard et al., 2018). This is despite the potential presence of individuals with a broader range of psychiatric disorders in the medication phenotype than these depression studies. Antidepressant medication is used to treat generalized anxiety disorder as well as fear disorders, such as agoraphobia, but fear disorders are less genetically similar to depression than generalized anxiety disorder is (Mineka, Watson, & Clark, 1998; Morneau-Vaillancourt et al., 2020). The inclusion of individuals with fear disorders could therefore result in lower genetic correlations with the comparison depression phenotype, but also with UKB-anxiety and Lifetime Internalizing, as the anxiety module of the CIDI-SF questionnaire is most sensitive to generalized anxiety disorder.

We performed analyses in the Medication Only subset to further assess the utility and pitfalls of this approach to identifying cases. An issue we encountered was that, while representing 10% of the Medication Status cases, the Medication Only case group was just approximately 3,000 individuals, which meant that statistical power was attenuated for genetic correlations. The genetic correlation with PGC-depression in this subsample was lower than in the full analysis sample and had a large SE ($r_s = 0.51 \pm 0.16$). The block jackknife analysis revealed that this correlation was not significantly different compared to the Medication Status correlation with PGC-depression. The Medication Only genetic correlations with UKB-anxiety ($r_s = 0.13 \pm 0.13$) and with Lifetime Internalizing ($r_s = 0.19 \pm 0.17$) were not statistically significant. The block jackknife demonstrated that these correlations were significantly lower than the respective correlations with the Medication Status phenotype. The significant correlation with the depression phenotype but not anxiety and internalizing phenotypes could be due to the design of the PGC-depression study, which was a large meta-analysis of numerous cohorts. As such, it may capture a more heterogeneous, negative affect phenotype, than the UK Biobank MHQ derived anxiety and internalizing phenotypes. The higher, significant, genetic correlation may also be explained by the majority of the Medication Only sample taking medications for depression (79% reported an antidepressant, 23% an anxiolytic). However, the use of antidepressants for anxiety disorders renders this unknown. Due to the lack of power, we cannot be certain whether Medication Only cases represent previously unidentified true cases, or a group with noise introduced by heterogeneity due to individuals taking medications for other reasons.

The results of the sensitivity analyses excluding physical conditions known to be treated with antidepressants and anxiolytics were largely the same, with fewer than 4% of cases removed from Medication Status and Medication Only phenotypes. However, it is likely that some individuals’ physical conditions were not recorded in the dataset.

4.3 Polygenic scores

To further explore the genetic overlap of our self-reported medication use phenotypes with the other definitions of anxiety and depression, particularly in the Medication Only subset, we tested for polygenic associations. Polygenic scores created from the UKB-anxiety, PGC-depression, and Lifetime Internalizing GWAS significantly explained 0.33–0.80% of variance (Nagelkerke’s $R^2$) in Medication Status in the full sample and 0.07–0.19% of variance (Nagelkerke’s $R^2$) in the Medication Only subset.

Polygenic scores rarely account for large proportions of variance in psychiatric phenotypes. For example, with over 115,000 cases, the PGC-depression study reported that 1.9% of the variance in case status was explained by the polygenic score out-of-sample (Wray et al., 2018), and the UKB-anxiety polygenic score explained 0.5% of the variance using a within-sample leave-one-out approach (Purves et al., 2020). Our results therefore provide further evidence that to some extent Medication Status functioned as an alternate phenotype for anxiety or depression case status, although evidence was stronger for the latter. As well as previous reasons discussed, such as the
potentially present other anxiety subtypes in the medication phenotype, this may be because the discovery sample for the depression polygenic score was larger and better powered than the anxiety discovery GWAS. It is worth noting that polygenic scoring methods are constantly advancing. As such, if researchers were to use this phenotyping approach in a predictive polygenic score analysis they might see predictive gains, in comparison to what we have reported here, by using alternative methods (Pain et al., 2021).

4.4 | Limitations

There are several limitations to the current study. Primarily, the verbal interview question from which the medication phenotypes were created was self-reported and included only current medication being taken. Medication Status cases and controls were defined solely using this item, and as such individuals with historical use of medications for anxiety or depression are likely to be included as controls, reducing the power of the GWAS. Furthermore, only a fraction of those with mental health conditions seek and receive treatment (McManus, Bebington, Jenkins, & Brugha, 2016; Rayner et al., 2020) and other, nonpharmacological treatments are available. Similar to other methods of phenotyping mental health conditions, perceived stigma could also impact the reliability of this self-report data, assuming that the individual is aware that their medication is primarily prescribed for anxiety or depression. Recall bias is an additional concern, although somewhat mitigated as only current prescriptions were requested. However, these issues appear to be more relevant for some medications than others; self-report of antidepressants shows high agreement with medical records, whereas for mood stabilizers agreement is poor to moderate (Gnjidic, Du, Pearson, Hilmer, & Banks, 2017; Hafferty et al., 2018).

A further limitation is that the dataset did not contain data on the reason for prescription, or consistent information on duration or dosage with which to infer it, which would have enabled refinement of the sample (Wigmore et al., 2019). As mentioned previously, noise in the medication phenotype may have been introduced by including individuals who were prescribed medication for reasons other than anxiety or depression. This could result in the identification of non-specific genetic variants in addition to variants associated with internalizing disorders, consistent with criticisms of the broad phenotyping approach (Cai et al., 2020). However, it is worth noting that high genetic correlations are often not observed even between samples that have similarly been assessed by a clinician using a DSM-based interview or checklist (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013).

UK Biobank participants significantly differ from the general population with regard to both socioeconomic status and long-term illnesses (Davis et al., 2020). The majority (85%) of UK Biobank participants were from urban areas (Fry et al., 2017) and geographical differences in prescription rates, due to factors such as the availability of psychological therapies, may have further impacted the utility of our phenotyping method. However, it has been illustrated that common mental health conditions in UK Biobank are reported at a similar prevalence as national surveys, suggesting that studies focusing on mental health have some generalizability (Davis et al., 2020).

4.5 | Future directions and conclusion

These findings suggest that self-reported current use of antidepressant and anxiolytic medications can offer a reasonable alternate approach to identifying clinical cases of anxiety and depression, where more detailed measures, such as diagnoses or questionnaires, are not available. However, the lower variance explained by the Medication Only group suggests that when other measures of anxiety or depression are present in a dataset, they should be preferentially used. The gain in sample size from using this additional information will not contribute a substantial amount of signal to analyses.

It is likely that prescription data from medical records will better approximate clinically diagnostic measures of anxiety and depression. As medical record linkage has recently become available in the UK Biobank cohort, this presents a future avenue of investigation. With increasing electronic health record data analysis, the use of medication data as an additional or alternate anxiety or depression phenotype could lead to unparalleled sample sizes. In conclusion, this study provides evidence that phenotyping anxiety and depression using medication data may be a useful and pragmatic approach when higher-quality diagnostic information is unavailable.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.
AUTHOR CONTRIBUTIONS
M.S., K.L.P., G.B., and T.C.E. were responsible for conceptualizing and designing the study. M.S. performed the data analysis with technical input from C.R., J.R.I.C., and K.L.P. K.P.G., J.R.I.C., C.H., and H.A.G. performed data preparation and quality control. M.S. wrote the original draft, and all other authors provided a critical review and edits to the draft, including interpretation of the results. All authors reviewed and approved the final manuscript prior to submission. T.C.E. and G.B. provided supervision of the study.

DATA AVAILABILITY STATEMENT
This research was conducted using the UK Biobank Resource, under application number 18177. UK Biobank data is available to researchers conducting health-related research, who register with UK Biobank.

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